CURRENT NEUROLOGY

VOLUME 7

Edited by

Stanley H. Appel

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Preface

Neurology continues to benefit from advances in neurosciences and our increasing understanding of brain function. Ultimately such advances bring us closer to devising rational therapy for previously untreatable disorders. The continuing goal of the *Current Neurology* series is to provide the clinician with an understanding of how basic neurosciences can be applied in a clinical context to improve the quality of neurological care.

This year we emphasize advances in our understanding of complex partial seizures as well as movement disorders. Biochemical disturbances of the nervous system as manifest in peroxisomal disorders in children, hereditary ataxias in adults, and metabolic myopathies are also addressed with in-depth reviews. The latest advances in approaches to multiple sclerosis, amyotrophic lateral sclerosis, diabetic peripheral neuropathy, cerebrovascular disease, and aphasic syndromes are also presented. The increasing importance of neuropeptides is also stressed. All of these chapters should help the clinical neurologist formulate appropriate strategies for the care of patients with neurologic disease.

STANLEY H. APPEL, M.D.

Erratum

Current Neurology, Volume 7

Edited by Stanley H. Appel, M.D.

In Chapter 1, "Diabetic Peripheral Neuropathies," written by Yadollah Harati, M.D., an incorrect dosage was inadvertently given. On page 18, paragraph 3, line 8, a recommended dosage of 0.1 to 3.0 mg per day of 9 - α - fluorohydrocortisone **should have been** 0.1 to 0.3 mg per day.

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CHAPTER 1

Diabetic Peripheral Neuropathies

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According to estimates of the American Diabetes Association, there are 5.7 million known diabetics in the United States and another 5 million undiagnosed.[1] The incidence of long-term diverse complications of diabetes has increased in recent years, due largely to increased survival rates. Contrary to the initial optimism, the advent of insulin did not eliminate diabetic complications, just as penicillin did not eliminate infection. The fact that complications continue to develop, despite good plasma glucose control, suggests that mechanisms other than hyperglycemia are involved in the pathogenesis of diabetic complications.

Estimates of the incidence of neuropathy among diabetics range from 5% to 60%,[2] a disparity that is due largely to difficulties in making a definitive diagnosis of neuropathy and to disagreement regarding the definition and classification of neuropathy. It is estimated that 8% of diabetic patients have neuropathy at the time of diagnosis, and 50% develop neuropathies by 25 years.[3] A recent ongoing study entitled "Diabetes Control and Complications Trial," involving 278 patients with Type I diabetes, suggests that females and adolescents are relatively protected from developing peripheral neuropathy as compared with males.[4] A variety of classification systems for diabetic neuropathies has been proposed during the past 100 years, reflecting expanding recognition of the different manifestations of diabetic peripheral neuropathy. Therefore, one should speak of diabetic "neuro-

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pathies," rather than diabetic "neuropathy," to reflect the heterogeneity of the problem, which implies a multifactorial basis involving a number of interacting mechanisms.

CLINICAL ASPECTS

Basically, three major neuropathic syndromes occur[5, 6]: (1) distal symmetric polyneuropathies, (2) proximal motor neuropathies, and (3) focal neuropathies. The same patient may have two or more of these neuropathies. In most cases of polyneuropathies, a combined involvement of sensory, motor, and autonomic nerves is present. Asbury[7] has proposed that the symmetric diabetic neuropathies are caused by yet-unidentified metabolic disturbances of peripheral nerve, while mononeuropathies or multiple mononeuropathies are most likely the result of vascular pathology.

Of the distal symmetric polyneuropathies, clinical manifestations vary, depending on the predominance of the nerve fiber type involved. With predominantly large-fiber involvement, loss of ankle reflexes, decreased position and vibratory sense, and sensory ataxia are seen, while in small-fiber type neuropathy, pain and paresthesia, most commonly of the lower extremities, are the characteristic symptoms. The pain may be dull, aching and cramp-like, burning, lancinating, or crushing, and, occasionally, may be limited to a single nerve root distribution. Paresthesia may be described as coldness, numbness, tingling, or burning. The calves may be tender. Pain and temperature perception in the lower extremities are diminished in a stocking distribution, while position, vibratory sensation, and reflexes are less involved. Autonomic dysfunction is more prevalent in small-fiber type neuropathies. It is not common, however, to find patients belonging to one of the two poles of the spectrum; most patients fall in between. Furthermore, not all painful neuropathies are of the small-fiber type. For example, the syndrome of "acute painful diabetic neuropathy" described by Archer et al.,[8] associated with profound weight loss and depression resembling "diabetic neuropathic cachexia,"[9] is characterized pathologically by acute axonal breakdown involving fibers of all sizes. This form of neuropathy occurs at any age, in Type I and Type II diabetes of variable duration, often without other diabetic complications, and is much more common in males than in females. The pain usually resolves spontaneously in approximately 1 year. Similarly, "diabetic neuropathic cachexia" occurs primarily in males in the sixth decade of life in whom diabetes is mild and easily controlled; it is a self-limiting condition, with weight gain and resolution of painful symptoms in 1–2 years.[9] Young et al.,[9a] however, have recently demonstrated that in the sural nerve biopsy of patients with painful or painless (foot-ulcerating) symmetrical sensory diabetic polyneuropathy, degeneration and regeneration occur in all types of nerve fibers, but the involvement of large myelinated fiber is more pronounced in painless than painful neuropathy.

Selective nerve fiber involvement may also present with a picture of pseudosyringomyelia. Said et al.[10] described five such patients who exhibited a dissociation of sensory loss, mainly affecting pain and temperature sensibility, leading to painless burns, foot ulcers, neuropathic joint degeneration, or spontaneous pain and severe autonomic disturbances. The pathologic changes observed in sural nerve biopsies of these patients included an early and severe loss of unmyelinated and small myelinated axons in a progressive centripetal distribution. Such length-dependent distal axonal degeneration was also apparent in the anterior aspect of the lower trunk of one patient, who had sensory loss in the anterior lower trunk, but none in the back. The anterior trunk sensory loss was due to distal axonal degeneration of truncal nerves. This false sensory level may be misdiagnosed as a myelopathy if examination of the back is omitted, because the sensory level should be present in both front and back in a true myelopathy.

The mechanism of pain in diabetic neuropathy is not understood, although the two most plausible explanations are spontaneous nerve impulses from regenerating small and unmyelinated fibers,[11] and increased pain intensity caused by hyperglycemia.[12] In their study of the effects of glucose on pain perception, Morley et al.[12] demonstrated reduction in maximum pain tolerance in nondiabetic subjects after glucose infusion. Diabetic patients had lower pain tolerance than controls. These findings are supported by reports of increased sensitivity to morphine in hypoglycemic animals and/or reduced response in streptozocin-induced diabetes in rats.[13] It is possible that glucose plays a role in the modulation of opioid receptors.[12] Other supportive evidence for a possible effect of hyperglycemia on painful diabetic neuropathies comes from the demonstration of striking improvement in painful symptoms seen in some patients following control of diabetes,[8, 14] and a higher level of glycosylated hemoglobin in patients with painful diabetic neuropathies than in non-neuropathic diabetic controls.[15] Although provocative, these reports do not explain why the onset of painful neuropathic symptoms occurs soon after institution of diabetic control in some patients.[16] Such effects of blood sugar fluctuation on pain perception, however, are important to recognize, because they may influence the effect of analgesics and/or investigational drugs used in the treatment of symptomatic neuropathy.

The reason for selective nerve fiber involvement in some patients with diabetic neuropathy is not known, although factors such as differential susceptibility of these fibers to variation of endoneurial fluid composition has been considered.[10]

The sensory polyneuropathies may give rise to several complications, including neuropathic arthropathy, or Charcot's joint, and the diabetic foot. Because trauma may not be sensed by the patient, subluxation, degeneration of joint surfaces, and resorption can result. While tabes dorsalis was formerly the leading cause of Charcot's joints, diabetes now is. In tabes, the knee is most commonly involved, while in diabetes, the distal articular surfaces of the feet or ankles are involved. This complication usually occurs in the fifth or sixth decade of life.

The diabetic foot slowly swells and becomes shorter, wider, everted, and externally rotated, with loss of the arch. The combination of small vessel disease,

sensorineural neuropathy, and secondary infection are the three important factors in the pathophysiology of the diabetic foot. However, in the presence of a normal arterial system, the neuropathy is the primary cause of foot lesions. Because of the neuropathy, unrecognized trauma occurs, and because of atrophy of intrinsic muscles, the plantar areas, not suited for weight-bearing, are exposed. Thus, ulcers susceptible to secondary infection may develop at these sites. Ulcers may also be initiated by cuts and punctures from foreign bodies (e.g., needles, glass, etc.), and frequently patients are unaware of these objects in soft tissues. For this reason, all patients with foot ulcers should have x-ray films of the feet to detect foreign bodies. It should be noted that despite the presence of sensory neuropathy, and contrary to one's expectation, there is increased blood flow to the diabetic foot, thought to be the result of dilation of denervated arteriovenous shunts normally controlled by sympathetic nerves.[17, 18] Such increased blood flow may lead to excessive bone resorption, susceptibility to fracture, and finally the development of neuropathic osteoarthropathy.

A predominant motor neuropathy in diabetes is rare, although a pure motor neuropathy may be due to spinal motor neuron loss from repeated episodes of hypoglycemia, as shown in patients with hypoglycemia secondary to insulinoma.[19] In this condition, the hands are usually more severely affected, with muscle wasting to a degree that causes impairment of fine movements. Bilateral foot-drop may also be present. Paresthesia, without objective manifestation of sensory impairment, usually precedes the muscle weakness. In an acute and severe motor neuropathy, the possibility of coincidental Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, or the syndrome of painful lumbosacral plexopathy as described by Bradley et al.[20] must be considered.

Mononeuropathy or multiple mononeuropathies (i.e., mononeuritis multiplex) may affect any cranial or peripheral nerve. Some authors have reported a higher-than-expected incidence of Bell's palsy, hearing loss, and laryngeal palsy in diabetics, while other studies have not shown a relation.[2] Extraocular muscle palsies, usually occurring over age 50 years and rarely in children, are most commonly due to involvement of cranial nerve III, followed in frequency by nerves VI and IV, respectively. The palsy may be bilateral and recurrent. In third cranial nerve mononeuropathy, severe ipsilateral pain precedes paralysis by 3–7 days in approximately 50% of cases. The pain, which may be aching and extremely intense, may follow the distribution of the ophthalmic branch of cranial nerve V, and is often retro-orbital. The cause of pain is uncertain, but could be due to involvement of the fifth cranial nerve in the cavernous sinus, or perhaps involvement of pain-sensitive fibers within oculomotor nerves. The pupil is usually spared,[21] and recovery generally occurs within 6–12 weeks.

Any peripheral nerve may be affected in diabetes mellitus. In one study,[22] the median, ulnar, and common peroneal nerves were more commonly involved in mononeuropathies or multiple mononeuropathies. There was no consistent relationship between the onset of mononeuropathy and the age or sex of the patient, the form of diabetic treatment or degree of control, duration of disease, or other

diabetic complications. Diabetic nerves are considered to be more susceptible to compression, such as the peroneal nerve at the fibular head, the ulnar nerve at the elbow, the radial nerve in the upper arm, and the median nerve in the carpal tunnel. Cutaneous nerve involvement, such as the lateral cutaneous nerve of the thigh (meralgia paresthetica), may be associated with diabetes, especially in obese patients. There is a good correlation between involvement of the femoral nerve and diabetes.[23]

An interesting and increasingly recognized entity among diabetic mononeuropathies is "painful diabetic thoracoabdominal neuropathy."[24–28] The correct diagnosis of this syndrome is of utmost importance, because the clinical presentation of abdominal and/or thoracic pain may lead to diagnostic confusion and unnecessary invasive procedures. This syndrome occurs more commonly than had been previously thought. I have seen 11 such cases among 150 diabetic patients evaluated over 2 years. Most patients are in the fifth or sixth decade of life, with a variable duration of diabetes, and present with the gradual onset of increasing, persistent burning pain of the lower anterior part of the chest and/or upper abdomen. The affected areas are often sensitive to touch, and pain may radiate to other parts of the chest or abdomen. If multiple thoracic nerves are involved, especially those innervating abdominal wall muscles, weakness and denervation changes of these muscles occur.[26, 27] In five of the 11 cases seen by me, and in most of those reported by others, there is a significant associated weight loss, often beginning with the onset of pain. Such weight loss heightens the clinician's suspicion of underlying malignancy, leading to extensive noninvasive and invasive investigations. Physical examination of these patients, however, reveals an area of hypesthesia and/or hyperesthesia in the appropriate thoracic segment(s). Denervation in paraspinal muscles may be present on electromyography (EMG), suggesting that the lesion is very proximal, either in the nerve roots or in the spinal nerves. Exclusion of spinal cord compression may be required. The prognosis of thoracoabdominal neuropathy is good, with spontaneous recovery usually occurring within a few months to 2 years. As with other mononeuropathies or multiple mononeuropathies, it is not known whether thoracoabdominal neuropathy is caused by ischemic infarction of nerve, because no pathologic evaluations of involved intercostal nerves have been reported.

Symmetric proximal motor neuropathy (diabetic amyotrophy) occurs primarily in middle-aged or elderly patients with Type II diabetes. Confusion over this heterogeneous entity has arisen because of at least two clinical subtypes: the subacute proximal diabetic neuropathy of insidious onset, and the ischemic mononeuropathy multiplex of acute onset. The subacute proximal diabetic neuropathy[29] manifests with progressive weakness of hip and thigh muscles, sometimes associated with aching thigh muscles. On occasion, the proximal upper extremities may also be involved, causing confusion by suggesting a myopathic disorder. Electromyography and muscle biopsy of affected muscles show no evidence of myopathy, but rather evidence of denervation and reinnervation. Muscles outside the pelvifemoral group may also show signs of denervation. Mild degrees of asymmetry may

be detected on muscle testing, and reflexes are usually diminished. Spontaneous recovery often occurs from within a few months to up to 3 years. In ischemic mononeuropathy multiplex, a sudden, usually asymmetric weakness of pelvic girdle muscles occurs, often associated with pain.[30] A multitude of small infarctive lesions of proximal major nerve trunks of the leg and lumbosacral plexus may be seen.[30] Recovery usually occurs within 1 year. Asbury[7] hypothesized that proximal motor diabetic neuropathies appear to be a clinical continuum, one pole represented by asymmetric weakness of rapid evolution on an ischemic basis, and the opposite pole marked by slowly evolving symmetric weakness resulting from metabolic factors.

Dysfunction of the autonomic nervous system[31] is reported to occur at an incidence of 20–40% in diabetics.[32, 33] It is generally believed that autonomic neuropathy accompanies peripheral neuropathy and does not become apparent until the later stages of diabetes. While this may hold true in some instances (e.g., orthostatic hypotension, diabetic diarrhea, and other visceral dysfunctions), such is not the case with impotence, possibly the most common complaint present in diabetic autonomic neuropathy. The widely held belief that the problems associated with autonomic neuropathy are not life-threatening has been refuted by Ewing et al.,[34] who reported in a 5-year prospective study of 73 diabetic patients that any symptoms of autonomic neuropathy combined with abnormal tests of autonomic cardiovascular function suggest a poor prognosis. Sudden death, silent myocardial infarction, and renal failure are more common among diabetic patients with autonomic neuropathy.[35–37]

The most common cardiovascular abnormalities in diabetic autonomic neuropathy are postural hypotension, resting tachycardia, and painless myocardial infarction.[38] Orthostatic hypotension, which is probably due to damage to sympathetic vasoconstrictor fibers in skeletal muscles[39] and the splanchnic circulation,[40] is the most common cardiovascular involvement, and is often asymptomatic. The fall in pressure involves both systolic and diastolic values.[41] Insulin, which can cause peripheral vasodilatation, may worsen the symptoms of hypotension.[42, 43]

Patients with autonomic neuropathy may have resting tachycardia as a result of parasympathetic dysfunction.[38, 44] Indeed, 24-hour ambulatory heart rate monitoring shows high mean waking and sleeping heart rates among these patients.[44]

There is an increased incidence of myocardial infarction (MI) in patients with diabetic autonomic neuropathy.[34, 36, 37, 45] Because of lesions of afferent visceral nerves that conduct pain from heart muscle, myocardial infarctions may not be associated with typical cardiac pain.[36, 37, 45] The diagnosis of MI is thus more difficult, its treatment often delayed, and the mortality rate higher than in cases of symptomatic myocardial infarction.[46] A recent study by Hume et al.[46a] suggests that middle-aged diabetic men with neuropathy but without cardiac symptoms have the same incidence of abnormal exercise electrocardiography as those without neuropathy. Their data, however, indicate that 5 of 14 patients with autonomic neuropathy had abnormal exercise electrocardiography, while only 3 of 16 patients without autonomic neuropathy showed such abnormalities.

We evaluated 73 consecutive diabetic adults with symptomatic peripheral neuropathy for the presence of cardiovascular autonomic neuropathy and electrocardiographic evidence of MI.[47] Twenty-five (34.2%) patients demonstrated cardiovascular autonomic neuropathy, as documented by an abnormal Valsalva ratio. Ten (13.7%) patients had electrocardiographic evidence of a previous MI, seven of which were asymptomatic by history. Five of the 25 (20%) patients with cardiovascular autonomic neuropathy had had a silent MI, as opposed to only two of the 48 (4.2%) patients with normal Valsalva ratios, suggesting a high incidence of silent MI in patients with cardiovascular autonomic neuropathy. An expansion of this study is currently in progress. Sudden death may also occur because of impaired respiratory reflexes secondary to autonomic neuropathy.[48]

Assessment of cardiovascular reflex involvement in diabetic autonomic neuropathy is possible by utilization of five simple noninvasive, quantitative tests.[31, 49] These include heart rate response of Valsalva maneuver, heart rate response to standing, heart rate response to deep breathing, blood pressure response to standing, and blood pressure response to sustained hand grip. One or several of these tests may be abnormal early in the course of diabetes mellitus.

Beat-to-beat (R-R interval) variation of heart rate in response to deep breathing, heart rate changes during Valsalva maneuver, and heart rate response to position changes mostly assess the integrity of parasympathetic pathways, while the other two tests evaluate sympathetic pathways. It has been suggested that parasympathetic neuropathy may emerge earlier than sympathetic neuropathy in diabetics.[35, 38, 50] Therefore, tests that check the integrity of parasympathetic pathways may be more sensitive for the early detection of autonomic neuropathy.[51, 52] Both the Valsalva maneuver test and beat-to-beat variation to deep breathing, however, correlate well with other electrophysiologic tests, such as sympathetic skin responses designed to detect dysfunction of sympathetic skin nerve fibers,[53–55] suggesting that in most cases the autonomic dysfunction involves both parasympathetic and sympathetic systems. The ease of performing these tests and the useful information provided by them indicate the necessity of their addition to the routine battery of electrophysiologic tests used for evaluation of patients with peripheral neuropathies.

Routine electrophysiologic studies in diabetics have revealed a variety of abnormalities. Nerve conduction velocities are slower in diabetics with signs of neuropathy than in those without clinical signs, and the evoked potential is reduced in size early.[56, 57]

There is a good correlation between clinical signs of neuropathy and the degree of slowing of nerve conduction. In young patients with Type I diabetes, motor and sensory peripheral somatic nerve conductions and autonomic nerve function tests deteriorate at a rate that is linearly related to the prevailing level of glycemia and duration of illness.[58, 59] These abnormalities may exist even among patients asymptomatic of neuropathy.[51] The involvement of nerves is diffuse, but more pronounced in distal than proximal segments.[60] Although one report[56] claimed that in symmetric sensory neuropathy the most consistent abnormality was in the pe-