Increased Prevalence of Impaired Glucose Tolerance in Patients With Painful Sensory Neuropathy

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OBJECTIVE — To characterize a cohort of patients with neuropathy and impaired glucose tolerance (IGT) but no other identifiable cause of neuropathy. Of patients with diabetes, 10% have peripheral neuropathy at the time of their diagnosis, suggesting that axonal injury may occur early in the course of glucose intolerance. The American Diabetes Association (ADA) revised diagnostic criteria to recognize IGT (a serum glucose between 140 and 200 mg/dl in a 2-h oral glucose tolerance test [OGTT]) as a risk factor for cardiovascular disease independent of development of diabetes.

RESEARCH DESIGN AND METHODS — Using revised ADA criteria for diabetes and IGT, we prospectively evaluated 107 sequential patients with idiopathic neuropathy.

RESULTS — A total of 13 of the 107 patients had diabetes, whereas 36 (34%) had IGT, nearly three times the prevalence in age-matched control subjects ($P < 0.01$). OGTT was often elevated, whereas both fasting plasma glucose and HbA_{1c} were normal. Comparing patients with diabetes, IGT, or normal OGTT, age and BMI were similar. However, painful sensory symptoms were more common in patients with IGT and diabetes, and family history of neuropathy was significantly more common in normoglycemic patients. Electrodiagnostic findings of axonal injury were less severe in patients with IGT and were more likely to be confined to sensory fibers than in patients with diabetes.

CONCLUSIONS — Our results suggest that IGT may cause or contribute to small-fiber neuropathy, which is similar in phenotype to the painful sensory neuropathy commonly encountered in diabetes. Two-hour OGTT is more sensitive than other measures of glucose handling in screening these patients.

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In developed countries, type 2 diabetes is the most common defined cause of axonal neuropathy in middle and old age. As a consequence, early and aggressive screening for diabetes is appropriate in evaluating patients with idiopathic neuropathy. Revised American Diabetes Association (ADA) recommendations for diabetic screening (1) endorse fasting plasma glucose (FPG) as the primary test for glucose handling. FPG levels >126 mg/dl constitute diabetes, whereas an intermediate designation "impaired fasting glucose" (IFG) is established for FPG >110 but <126 mg/dl. A glucose level ≥140 but <200 mg/dl 2 h after a 75-g oral glucose tolerance test (OGTT) is defined as impaired glucose tolerance (IGT), and OGTT ≥200 mg/dl indicates frank diabetes. The intermediate designations for IFG and IGT have been shown to be largely equivalent in their correlation with insulin resistance (2).

Despite careful evaluation, the cause of neuropathy remains obscure in 20–60% of patients. Recent series have examined the cause and clinical, electrodiagnostic, and histologic features of idiopathic neuropathy (3–6). However, none has systematically used current ADA criteria for diabetes screening or examined the prevalence of IGT in this population. We have prospectively screened patients with idiopathic neuropathy as well FPG and OGTT and report here on a large cohort who have IFG and/or IGT but no other identifiable cause of neuropathy.

RESEARCH DESIGN AND METHODS

We followed a uniform clinical protocol to prospectively evaluate 107 sequential patients with idiopathic, symmetric distal neuropathy between July 1997 and June 2000. Patients were referred from within the Department of Neurology of the University Medical Center and by community doctors across a four-state cachement area. In this context, "idiopathic" means that no obvious cause of neuropathy had been identified before referral and that our initial clinical and electrodiagnostic evaluation did not identify an obvious cause, such as inflammatory demyelinating polyradiculoneuropathy. Patients in whom distal neuropathy was discovered in the course of evaluation for another focal complaint are included in this report.

Clinical history was obtained with special attention to childhood illness or foot deformities and family history of neuropathy, sensory loss, foot pain, walking difficulties, foot deformities, and diabetes. Medical history was obtained with attention to medications such as thiazide diuretics, glucocorticoids, and adrenergic agonists, which might alter glucose tolerance. Height and weight were measured for determination of BMI, calculated as weight (in kilograms) divided by height

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Abbreviations: ADA, American Diabetes Association; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCS/EMG, nerve conduction studies and needle electromyography; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(in meters) squared. The neurologic examination focused on manual testing of distal muscles, reflexes, and sensory perception to pin, vibration, and joint position sense. A general medical examination was performed with attention to distal atrophy and skin changes. Based on our clinical assessment, patients with neuropathy were assigned to one of four categories: *1*) sensory exclusive; *2*) sensory exclusive with neuropathic pain, if strength was normal and no distal atrophy, high arches, or hammer toes were obvious; *3*) sensorimotor; or *4*) sensorimotor with neuropathic pain.

Nerve conduction studies and needle electromyography (NCS/EMG) were performed unless the patient refused or if studies had been performed within 6 months and deemed technically adequate. Minimal NCS/EMG data included sural sensory, tibial motor with F-response, peroneal motor response with proximal conduction and F-response, and electromyography of distal muscles of the lower extremity. Electromyography was considered consistent with distal motor involvement if abnormal spontaneous activity (positive waves or fibrillation potentials) or a clear decrease in recruitment was found in the anterior tibialis or medial gastrocnemius muscles.

Tests for thyroid-stimulating hormone, vitamin B_{12} level, serum protein electrophoresis, and serum immunofixation electrophoresis were performed, reviewed, or requested for each patient. Methylmalonic acid levels were measured in patients with vitamin B_{12} levels <250 mg/dl. These uniform screening tests were chosen based on their reported high yield in previous prospective series of idiopathic neuropathy (5,6). We performed or recommended 2-h OGTT for each patient. Because OGTT requires an overnight fast and could not be performed at the time of the clinic visit, not all patients returned for this additional blood testing. In patients who did not live nearby, OGTT was performed by the primary care physician, increasing compliance. Many patients had extensive laboratory testing before referral to our clinic, including various combinations of tests for random plasma glucose, FPG, and HbA_{1c} in evaluation of possible diabetes. Of our 107 patients, FPG was measured in 105 patients, and 72 patients underwent OGTT in accordance with ADA guidelines. HbA_{1c} level was recorded in 33 patients. Random blood glucose results were not considered reliable because relationship to meals could not be ascertained. Other blood tests were obtained for selected patients with symptoms or signs suggesting a specific cause of neuropathy but were not routinely performed.

Statistical analysis of epidemiological and NCS/EMG data were performed using χ^2 analysis for nonparametric data.

Table 1—*Clinical characteristics of 72 idiopathic neuropathy patients evaluated with OGTT*

	Diagnosis		
	Diabetes	IGT	Normal
n	13	36	23
Age	65 (46–82)	62 (49–80)	63 (44–79)
BMI			
Median	29	29	29
≥ 30 kg/m^2	5/13 (38)	15/36 (41)	11/23 (48)
Family history			
Neuropathy	2/13 (15)	7/36 (19)	10/23 (43)*
Diabetes	8/13 (62)	11/36 (30)	6/23 (26)
Clinical phenotype			
S	1	2	4
SP	11	29†	14
MS	1	1	4
MSP	0	4	1

Data are median (range) and n (%). *Family history of possible neuropathy was significantly more common ($P < 0.05$) for patients with normal OGTT than for those with either IGT or diabetes; †complaints of neuropathic pain (SP plus USP) were significantly more common in patients with IGT than in neuropathy patients whose OGTT was normal ($P < 0.025$). S, sensory exclusive; SP, sensory exclusive with neuropathic pain; MS, motor and sensory; MSP, motor and sensory with neuropathic pain.

RESULTS — The median age for the 107 unselected patients with idiopathic neuropathy patients was 64 ± 10.8 years (range 46–92), and 59 (55%) of these patients were women. Most patients (88) had exclusively sensory symptoms and signs; 76 reported neuropathic pain, and 12 reported no significant pain. The remaining 19 patients had symptoms and signs of distal weakness in addition to sensory symptoms.

As part of our assessment, 2-h OGTT was recommended for each patient and was performed in 72. Of these 72 patients with neuropathy, 36 (50%) had IGT. Considering all 107 sequential patients regardless of testing, IGT was discovered in 34%. Four additional neuropathy patients had IFG (4%), and 14 of 107 patients (13%) met ADA criteria for frank diabetes.

Clinical features of the 72 patients with neuropathy who underwent OGTT are summarized in Table 1. Demographic data in the 72 OGTT patients were not significantly different from the patient cohort as a whole with regard to mean age, sex, BMI, and frequency of sensory symptoms or neuropathic pain. Using ADA criteria for OGTT, patients were diagnosed with frank diabetes, IGT, or normal glucose handling. Median age and BMI were similar for all three groups. Patients with neuropathy and IGT were significantly less likely to have a family history suggestive of neuropathy than neuropathy patients without a defect in glucose handling, whereas (not surprisingly) family history of diabetes was more common in patients who were found to have diabetes. Patients in whom IGT was discovered overwhelmingly had a sensory or painful sensory neuropathy. A total of 29 of 36 patients (81%) had exclusively sensory complaints, and 33 of 36 patients (92%) recognized neuropathic pain as a dominant symptom of their neuropathy. Patients with normal IGT were significantly less likely to complain of pain in association with their neuropathy ($P < 0.025$). In patients who reported neuropathic pain, mean (and median) duration of pain symptoms before evaluation was similar in those found to have IGT (54 months, median 35) or normoglycemia (65 months, median 42) but longer in those who had diabetes (92 months, median 71).

As assessed by NCS/EMG, in patients with IGT, neuropathy was less severe than in patients with frank diabetes and was

Table 2—*Laboratory studies performed in evaluation of neuropathy in 36 patients with IGT*

Laboratory test performed*	Normal range	*n*	Abnormal results
Vitamin B_{12}†	210–911 pg/ml	36	217 in one patient, methylmalonic acid level normal
Thyroid-stimulating hormone†	0.4–5.0 mU/l	35	none
Serum protein electrophoresis and immunofixation†	various	35	IgG kappa in one patient
Anti-nuclear antibody titer	≤1:40	27	titer 1:160 in one patient
HbA_{1c}	4.1–6.5%‡	20	none
Folate	7.8–17.8 ng/ml	19	none
Thiamine	0.2–2.0 μg/dl	12	none
Rapid plasma antigen	negative	8	none
Methylmalonic acid	<0.4 μmol/l	7	none
Rheumatoid factor	<20 IU/ml	6	none
Extractable nuclear Ab screen (Smith, RNP, SSA, SSB, sclero)	<20 U	6	none
24-h urine lead	0–31 μg/day	6	none
24-h urine mercury	0–15 μg/day	5	none
24-h urine arsenic	0–63.9 μg/day	4	none
Vitamin B_6	5–30 ng/ml	4	none

Data are *n*. *Two or fewer patients underwent the following tests, all of which were normal: anti–double-standard DNA titer, anti-Hu titer, anti-sulfatide antigen titer, anti-MAG titer, human immunodeficiency virus 2 titer, Lyme titer, vitamin E, and cryoglobulins. Many tests listed were performed before referral; †tests recommended for all patients evaluated; ‡highest HbA_{1c} value obtained for these patients was 6.1%.

more likely to be confined to sensory fibers. Sural sensory amplitude was reduced in 20 of 33 patients (61%) with IGT and 9 of 12 patients (75%) with diabetes, indicating sensory nerve axonal injury in a substantial fraction of both groups. However, patients with diabetes were significantly more likely ($P < 0.05$) to have a low-amplitude peroneal response (7 of 12 patients, 58%) than those with IGT (6 of 29 patients, 21%). As a group, patients with IGT were also significantly less likely to show evidence of previous or active denervation on needle electromyography of distal leg muscles.

Other potential causes of neuropathy were excluded in patients with IGT (Table 2). Vitamin B_{12} level, thyroid-stimulating hormone level, and serum protein electrophoresis or immunofixation were each obtained in 35 of 36 patients. One patient had a borderline low B_{12} level, but methylmalonic acid level was normal. One patient >60 years of age had a coexistent monoclonal gammopathy, and one patient had an elevated anti-nuclear antibody titer of 1:160 with normal sedimentation rate, extractable nuclear antibodies, and rheumatoid factor. No other alternate cause of neuropathy was discovered by laboratory testing in these 36 patients. Five of the 36 patients with IGT had chronic hypothyroidism, for which they took supplementation. Thyroid-stimulating hormone level was normal in all five patients, suggesting adequate replacement therapy. Hereditary neuropathy has been reported as an important and often overlooked cause in idiopathic patients (3), prompting us to carefully elicit family history. Six patients had first-degree relatives with foot sensory loss, weakness, or deformities unassociated with diabetes. Three of these patients had a sensorimotor neuropathy, raising the possibility of a hereditary motor and sensory neuropathy, but none demonstrated significant nerve conduction slowing. Many patients were referred after lengthy evaluations; other tests that were performed with normal results are shown in Table 2.

Hypertension as a comorbid condition was significantly more common ($P < 0.05$) in patients found to have diabetes (8 of 13 patients, 61%) and in patients with IGT or IFG (21 of 40 patients, 52%) than in patients with normoglycemia (18 of 54 patients, 33%). A total of 15–20% of patients in each group were taking thiazide diuretics at the time of their evaluation. Two patients with IGT and two with normoglycemia were taking prednisone at a low dose. Other drugs likely to alter glucose tolerance were prescribed to <5% of patients in each group.

Two-hour OGTT was a more sensitive measure of abnormal glucose metabolism than testing for either FPG or HbA_{1c}. A total of 72 patients underwent both FPG and OGTT, whereas 33 underwent both OGTT and HbA_{1c}. Figure 1 shows values for 2-h OGTT plotted against respective values for FPG or HbA_{1c} for patients in whom both tests were performed. Both plots demonstrate the large population of patients found by OGTT to have IGT or frank diabetes for whom FPG or HbA_{1c} level was within normal limits.

CONCLUSIONS — Neuropathy is a common complication of chronic hyperglycemia: overall prevalence in patients with diabetes is 45–60%, and in more than half of patients followed longitudinally, clinical symptoms of neuropathy develop within 25 years of diagnosis (7,8). Routine NCS/EMG demonstrates diffuse peripheral nerve axonal injury in 10–18% of patients at the time of diabetes diagnosis (9,10), suggesting that nerve injury can predate development of other diabetic symptoms. The concept that peripheral neuropathy may be the first clinical sign of prolonged hyperglycemia was proposed more than 40 years ago but remains controversial (11). We report here the first methodical prospective screening of patients with idiopathic neuropathy by 2-h OGTT. Using the 1997 ADA criteria, we found that 34% of patients evaluated (and 50% of those tested with OGTT) have IGT but no other identifiable cause of neuropathy. By compari-

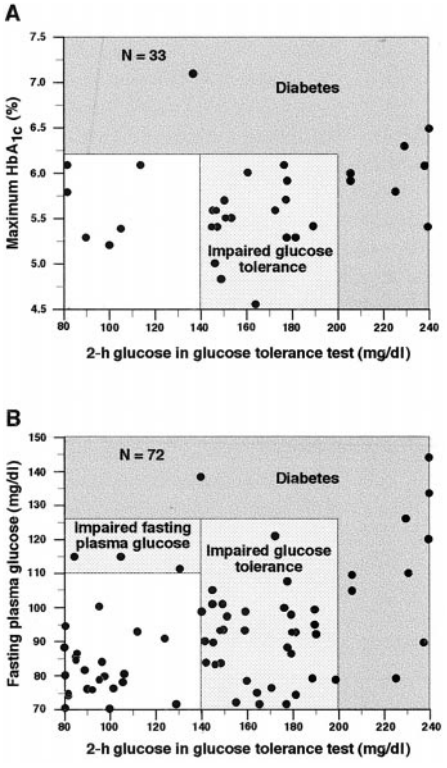

Figure 1—*Two-hour OGTT is more likely than other measures of glucose metabolism to detect IGT or diabetes in patients with idiopathic neuropathy. Comparison of OGTT with either HbA_{1c} (A) or FPG (B) for patients with idiopathic neuropathy using 1997 ADA criteria. Stipled areas of the graphs indicate values of OGTT designated as impaired glucose tolerance or, in the case of fasting plasma glucose, impaired fasting glucose, by ADA guidelines. Darkly shades areas indicate values of FPG, HbA_{1c}, or OGTT diagnostic of frank diabetes. When more than one HbA_{1c} or FPG test was performed, the highest level is shown. Data points in which one measure lies beyond the boundary of the plot are depicted on its appropriate margin.*

son, in the largest screening study in an unselected population, the prevalence of IGT is 11.2% for individuals aged 50–59 years, peaks at 14.2% for individuals aged 60−75 years, and declines in individuals >75 years of age (12). Smaller studies report similar IGT prevalence (12). Therefore, our results establish a robust statistical association between IGT and neuropathy. Most patients with IGT have distal sensory neuropathy with prominent neuropathic pain, linking this cohort syndromically to the typical phenotype of early diabetic neuropathy. Together, these findings suggest a possible causative association between a modest defect in glucose metabolism and sensory neuropathy, which can be identified best by 2-h OGTT.

Additional epidemiological data support an association between IGT and neuropathy. A cross-sectional study using a combination of physical examination and focused history, and validated with vibration threshold measurement, found neuropathy in 26% of 279 patients with diabetes, 11.2% of 89 patients with IGT, and only 3.9% of 577 age-matched normal control subjects (13). Similarly, a small study found vagal dysautonomia in a statistically greater fraction of patients with IGT than in age-matched normal control subjects (14). However, other small studies using older criteria for IGT and diabetes reported no increased association between IGT and peripheral neuropathy compared with control subjects (15,16).

IGT and frank diabetes form a continuum of deranged glucose regulation, and accumulating evidence supports the concept of IGT as a disease entity in its own right (17). IGT is associated with the syndrome of insulin resistance, hyperinsulinemia, hyperlipidemia, and hypertension and is a potent risk factor for cardiovascular and peripheral vascular occlusive disease, independent of IGT risk for diabetes (18–20). Progression of IGT is slow; frank diabetes develops in only 20–35% of patients with IGT during 5-year follow-up (21). The ongoing Diabetes Prevention Project, a large prospective, placebo-controlled trial of the oral hypoglycemic metformin in patients with IGT, will give more precise data on the prognosis of IGT, but it is clear that patients may experience many years of occult insulin resistance and postprandial hyperglycemia before developing typical symptoms of diabetes (15,22).

Previous prospective series report diabetes as an uncommon cause of sensory or painful sensory neuropathy but have not routinely used OGTT or current ADA criteria for diabetes in their analysis. As summarized in Fig. 1, our results indicate that OGTT is more sensitive in detecting abnormalities of glucose handling than either FPG or HbA_{1c}. Only 4 of 105 patients had IFG, whereas 36 of 72 patients had IGT. Diagnosis of more than half of patients with frank diabetes by ADA criteria would have been missed if HbA_{1c} or FPG alone was used for screening. These results mirror large prospective studies in which results of OGTT in older patients are often consistent with diabetes but normal FPG (23), and asymptomatic patients with IGT have normal HbA_{1c} (24). Use of HbA_{1c} for screening purposes is discouraged by the 1997 ADA guidelines (1). We suggest that measurement of HbA_{1c} using typical thresholds is inappropriate when evaluating the cause of neuropathy.

Diagnostic levels for FPG are predicted to be only slightly less sensitive than OGTT for screening and equivalent in their correlation with microvascular complications of diabetes (1). IGT has recently been reported as more likely to predict cardiovascular morbidity than IFG (20). OGTT may be more sensitive than FPG in the evaluation of patients with neuropathy because OGTT is a dynamic measure of peak glycemic control. Experiments in laboratory animals and human subjects indicate that transient hyperglycemia increases spontaneous discharge from small-diameter nociceptive afferent C fibers and is clinically associated with increased neuropathic pain (25). The greater sensitivity of OGTT for patients with neuropathy may offer insight into the pathogenesis of early onset diabetic neuropathy. Specifically, elevated peak serum glucose level may be a more potent pathogen for peripheral nerves than modestly elevated trough glucose levels. However, OGTT is criticized as being more variable than FPG in sequential tests of normal subjects and is often snubbed by clinicians for screening because of its relative inconvenience (26).

Our results establish a syndromic link between neuropathy associated with IGT and the sensory-predominant neuropathy commonly observed in early diabetes. In a survey of 669 patients with early diabetic polyneuropathy, sensory symptoms were present in >60%, impotence was present in nearly 40%, and other autonomic involvement was present in 33%, but evidence of motor involvement was present in only 12% of patients (27). These clinical findings suggest prominent early involvement of the small unmyelinated nerve fibers that carry pain, temperature, and autonomic function. Additional evidence that small fibers are damaged first in diabetes comes from quantitative sensory studies in which cold sensation (mediated by small fibers) is frequently affected before vibration sense (mediated by large myelinated sensory fibers) in diabetic patients, whereas the

reverse scenario is rare (28). We have preliminary data indicating that in patients with IGT and symptoms of sensory neuropathy, skin biopsy often demonstrates loss of intraepidermal unmyelinated axons at a time when results of nerve conduction studies are normal (29).

Careful questioning disclosed possible family history in 6 of 36 patients with IGT. Rare causes of neuropathy were not screened for in most patients because other large prospective series suggest that a more exhaustive panel of laboratory tests yields little incremental value in establishing a diagnosis in idiopathic neuropathy (5,6,30).

In summary, three aspects of our data support the concept that the modest changes of glucose homeostasis identified by IGT are sufficient to cause peripheral neuropathy: *1*) IGT is found at a rate three times higher in patients with otherwise idiopathic sensory neuropathy than in the age-matched general population; *2*) the painful sensory neuropathy common to these patients is indistinguishable from symptoms typically encountered in early diabetic neuropathy; and *3*) no alternative cause of neuropathy has been identified for most of these patients.

Almost all patients with IGT report significant neuropathic pain. Therefore, an alternative hypothesis consistent with our epidemiological data is that chronic pain causes glucose dysregulation, either through adrenal stimulation of cortisol, by limitation of exercise with resultant obesity, or by some other mechanism. However, median and mean duration of neuropathic pain was similar in patients with normoglycemia and IGT. There was not a significant correlation between pain duration and either FPG or 2-h glucose on OGTT. Pain severity was not quantified using formal instruments in this study, but the percentage of patients using medications for neuropathic pain at the time of their evaluation was quite similar in the three groups. BMI was nearly identical for patients with neuropathy and normal or abnormal OGTT. Preliminary data in our IGT patients who have been followed since diagnosis suggest that adequate treatment of neuropathic pain has not reversed IGT. No published reports link chronic pain to IGT or increased risk for diabetes, although the Diabetes Prevention Project (22) may assess whether pain hastens progression from IGT to diabetes.

Conclusive proof that IGT can cause or contribute to neuropathy will be difficult. We are in the process of evaluating this cohort for evidence of retinal microvascular injury. Longitudinal follow-up will be necessary to determine whether frank diabetes develops in these patients in association with progression of neuropathy and whether exercise, altered diet, or hypoglycemic therapy can alter the course of the neuropathy. In the interim, early recognition of IGT in patients with neuropathy should be regarded as an opportunity for intervention to forestall the recognized cardiovascular complications of insulin resistance (17).

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