糖尿病多発神経障害の Up-to-date

2. 糖尿病多発神経障害の臨床診断・診療の実際 Up-to-date

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〔糖尿病 53(2)：79～81，2010〕

糖尿病多発神経障害とは

米国糖尿病学会のステートメントにおいて，糖尿病神経障害は「糖尿病患者にみられ，他の原因を除外できる自覚的あるいは他覚的末梢神経障害」と定義されている．主要な病型は，糖尿病多発神経障害(diabetic polyneuropathy：DPN) であるが，動眼神経麻痺などの脳神経麻痺，手根管症候群などの絞扼性神経障害，下肢近位部の脱力・疼痛を主徴とする糖尿病筋萎縮症，胸・腹部に帯状の疼痛を生じる体幹根神経障害なども糖尿病神経障害に含まれる．

DPN は糖尿病特有の左右対称性，末梢側優位の多発神経障害であり，成因として高血糖による代謝異常と細小血管症による虚血が考えられている．日常診療で最も高頻度にみられる慢性合併症で，糖尿病 3 大合併症のひとつに数えられている．病理学的には dying-back 型の軸策障害であり，走行距離の長い神経の先端部から障害がおこり，極めて緩徐に進行する．人体で最も長い神経は足先・足底を支配する神経であるので，同部の感覚障害（しびれ，紙が張り付いているような異常感覚）は早期からみられる自覚症状である．また，自覚的には無症状でもアキレス腱反射の低下や振動覚・痛覚などの感覚鈍麻で診断されることも多い．DPN が重症化すると，感覚神経障害では耐えがたい疼痛，足潰瘍・壊疽の原因となる感覚脱失が生じ，自律神経障害では，高度の立ちくらみ，難治性の便秘・下痢，嘔吐などさまざまな不快な症状が QOL を著しく低下させるほか突然死の危険性も増大する．

1. 糖尿病多発神経障害（DPN）の臨床診断

DPN に関して世界共通の診断基準はなく，欧米ではベッドサイドの診断法として Michigan Neuropathy Screening Instrument（MNSI：両下肢の感覚・外観に関する問診表）と Michigan Diabetic Neuropathy Score(足外観異常，潰瘍，アキレス腱反射低下，第一趾の振動覚低下を評価）を用いた報告が多い．

わが国では DPN をベッドサイドで簡便かつ的確に診断できる方法として，「糖尿病性神経障害を考える会」から，糖尿病性多発神経障害（distal symmetric polyneuropathy）の簡易診断基準（Fig. 1，以下簡易診断基準とする）が提案され[1]，普及しつつある．簡易診断基準では必須条件である“糖尿病の存在と DPN 以外の末梢神経障害の否定”を満たす患者で，条件項目の① DPN に基づくと思われる自覚症状，②両側アキレス腱反射の低下・消失，③両側内踝の振動覚低下のうち 2 項目以上を満たす場合に“神経障害あり”と診断される．この自覚症状は“両側性の足趾先及び足裏の「しびれ」「疼痛」「感覚異常」”に限定され，手袋・靴下型ではなく短靴・足袋型の感覚障害と規定している点が特徴である．注意事項には，“上肢の症状のみ”および“冷感のみ”の場合は含まないこと，アキレス腱反射は膝立位で確認すること，振動覚検査は C128 音叉を使用し，両側内踝で 10 秒以下を低下の目安とするが，老化による影響を考慮すべきであることが明記されている．また，閉塞性動脈硬化症でも足の感覚障害がみられるので，足背動脈，後脛骨動脈の拍動を触診するなど，常に他疾患の除外を念頭におくことが重要

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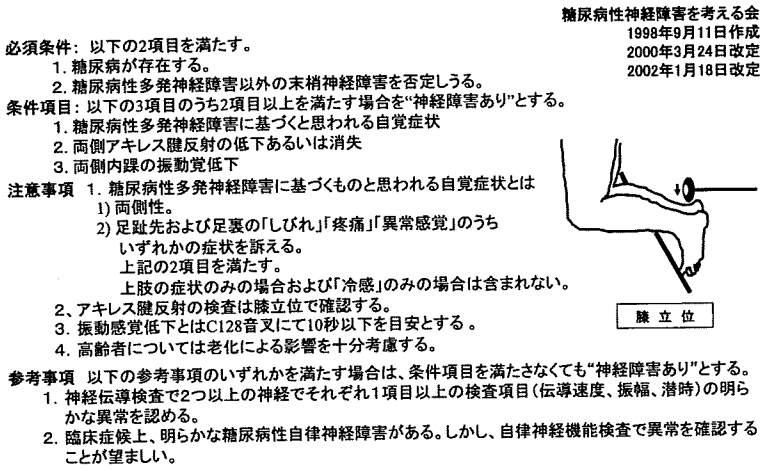

Fig. 1　糖尿病性多発神経障害の簡易診断基準

Table 1　糖尿病多発神経障害およびIGT関連神経障害の頻度

報告	耐糖能（例数）	多発神経障害の診断法	多発神経障害の頻度
佐藤　譲 他 糖尿病 50：799, 2007	糖尿病 約 15,000	簡易診断基準	35.8%
日本糖尿病対策推進会議 平成 20 年 3 月	糖尿病 約 67,000	簡易診断基準を参考に診断	47.1%
後藤由夫 他 日臨内会誌 16：167, 2001	糖尿病 約 13,000	アキレス腱反射などで主治医が診断	36.7%
Young MJ et al Diabetologia 36：150, 1993 英国	糖尿病 6,437	自覚症状と下肢神経学的所見	28.5%
Fedele D et al Diabetes Care 20：836, 1997 イタリア	糖尿病 8,757	足の外観，アキレス腱反射，振動覚	32.3%
迫　康博 他 Diabetologia 2：(Suppl1), S80, 2009	正常 176 IGT 150	簡易診断基準	正常 3.9% IGT 18.0%
Ziegler D et al Diabetes Care 31：464, 2008 ドイツ	正常 81 IFG 71 IGT 46 糖尿病 195	MNSI（Michigan Neuropathy Screening Instrument）	正常 7.4% IFG 11.3% IGT 13.0% 糖尿病 28.0%
Bruce SG et al Diabetes Care 31：1837, 2008 カナダ	正常 300 IFG＋新規 DM 66 既知 DM 101	10g モノフィラメントで診断	正常 5.0% IFG＋新規 DM 8.0% 既知 DM 15.0%

である．

佐藤らの東北地方の実態調査（15,000例），日本糖尿病対策推進会議の全国調査（67,000例）における簡易診断基準によるDPN有病率はそれぞれ35.8%，47.1%であり，前者では53.5%，後者では40.3%が無症候性であった．これらの報告により，わが国のDPN有病率が非常に高いこと，DPNを見逃さないためには積極的なアキレス腱反射，振動覚検査が重要であることが明らかとなった．

DPNの病期分類についても確立したものはない．「糖尿病性神経障害を考える会」は，"糖尿病性多発神経障害が進行性の神経線維脱落を臨床病理学的な基盤として，症候学的に感覚，自律，さらには運動神経障害へと進展する．"との自然史の概念に基づいて病期分類を提案，検証するための全国規模の観察研究を遂行中である．糖尿病患者では，①神経伝導速度，②感覚神経機能（振動覚・触覚閾値，アキレス腱反射），③自律神経機能（心拍変動検査，起立試験など），④運動神経機能（足の筋力，複合筋活動電位など）の順に神経機能障害が進行するとの報告[2]は，病期分類の自然史の概念の妥当性を支持するものである．

2. 糖尿病多発神経障害（DPN）の予防と治療

(1) 予防・進展防止

血糖コントロールと合併症の関係を検討したDCCTおよびその追跡調査であるEDIC研究により，良好な血糖コントロールがDPN発症を防止し，その効果は血糖コントロールに差が無くなっても8年間は持続することが報告され，厳格な血糖コントロールの重要性が再確認された[3]．DPNの進展抑制効果を有する薬剤としては，アルドース還元酵素阻害薬（ARI）のエパルレスタットがあり，多施設共同無作為化比較試験（ADCT）において，エパルレスタット投与は非投与群でみられた下肢振動覚域値，神経伝導速度の悪化を有意に抑制し，DPN進展抑制効果を示した[4]．また，DPN予防・進展防止には高血圧治療，多量の飲酒，喫煙を禁止することも必要である．

(2) 治療

軽度のDPNでは，更なる血糖コントロールに努め，ARIやビタミンB12製剤については十分に情報を提供して患者と相談して使用する．進行したDPNでは治療に難渋することが多く，耐え難い痛み（神経因性疼痛）と多彩な自律神経症状に対する対症療法が必要となる．神経因性疼痛には，ガバペンチン（保険適用外）やデュロキセチン（承認申請中）など新しい薬剤が使用可能となると思われるが，自律神経障害治療も含めて病状に応じた注意深い薬剤選択が重要である．

3. IGT関連神経障害（IGT-associated neuropathy）と新たなDPNの徴候

IGT関連神経障害には2つの概念がある．ひとつは，IGT患者に疼痛を中心とする小径神経線維優位の多発神経障害が多発するという概念である．端緒となったのは原因不明の疼痛を主徴とする多発神経障害の半数以上に未診断糖尿病や耐糖能異常（IGT）がみられ，皮膚生検で表皮内神経線維脱落が認められたという報告である[5]．その後，欧米からは同様の報告が散見されるが，わが国ではそのような報告はない．同様の小径線維優位の神経障害は高血糖よりも肥満や脂質異常症などメタボリックシンドロームの要素との関連性が強いとの報告もある．

もうひとつは，IGT患者にDPN類似の多発神経障害が高頻度にみられるという概念である．Table 1に糖尿病およびIGTでの多発神経障害の有病率に関する最近の報告を示す．わが国のDPN有病率は欧米よりわずかに高い数字を示している．一方，IGTでの多発神経障害有病率に関して，迫らの報告（正常3.9%，IGT 18.0%），Zieglerらの報告（正常7.4%，IFG 11.3%，IGT 13.0%，糖尿病28.0%），Bruceらの報告（正常5.0%，IFG＋新規診断糖尿病8.0%，既知の糖尿病15.0%）があり，糖尿病の約半分の有病率であった．多発神経障害が糖尿病発症前から，患者のQOLを低下させる合併症として発症しうることを念頭において診療することが必要であろう．

最近，新たなDPNの徴候として，“短趾伸筋の萎縮”と“原因が明らかでない体幹部掻痒感”が報告された．短趾伸筋は足趾を背屈させた時に外踝前下方に盛り上がる筋肉で，DPNではこれが萎縮して不明瞭になり，早期の運動神経障害を反映すると考えられている．原因が明らかでない体幹部掻痒感は，糖尿病患者で有意に多く，神経症状および自律神経機能と有意に相関することよりDPNの症状と考えられている[6]．これらは，DPNを見落とさないために銘記しておくべき事項と考えられる．

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Truncal Pruritus of Unknown Origin May Be a Symptom of Diabetic Polyneuropathy

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OBJECTIVE — Our goal was to ascertain the prevalence of pruritus in diabetic and nondiabetic subjects and the relevance of symptoms, signs, and nerve functions of diabetic polyneuropathy (DPN) of pruritus.

RESEARCH DESIGN AND METHODS — A large-scale survey of 2,656 diabetic outpatients and 499 nondiabetic subjects was performed. In diabetic subjects, the relationship between pruritus and age, sex, diabetic duration, A1C, Achilles tendon reflex (ATR), and abnormal sensation in legs was evaluated. In 105 diabetic subjects, nerve conduction studies, quantitative vibratory threshold (QVT), heart rate variability, and a fall of systolic blood pressure at a head-up tilt test (ΔBP) were performed, and the relationships between pruritus and nerve functions were evaluated.

RESULTS — Although the prevalence of truncal pruritus of unknown origin (TPUO) in diabetic subjects was significantly higher than that in age-matched nondiabetic subjects (11.3 vs. 2.9%, $P = 0.0001$), the prevalence of other pruritus was not different between the two groups. Multiple logistic regression analysis revealed that abnormal sensation and ATR areflexia were independent risk factors for TPUO in age, sex, duration of diabetes, and A1C. ΔBP in diabetic subjects with TPUO was significantly impaired compared with that in those without TPUO. Larger ΔBP was identified as a significant risk factor of TPUO independent of other nerve dysfunctions by multiple logistic regression analysis.

CONCLUSIONS — TPUO is significantly more frequent in diabetic than in nondiabetic individuals. TPUO is significantly associated with symptoms and signs of DPN, including impaired blood pressure response in a head-up tilt test. TPUO, therefore, might be a newly recognized symptom of DPN.

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We have an unproven idea that diabetic patients complain of pruritus more frequently than the general population does. A textbook of diabetology also describes this uncertainty as follows, "The frequency of generalized pruritus in diabetes is unknown; however, many believe that it is increased in diabetes" (1). As an itching sensation is thought to be transmitted by small unmyelinated sensory c-fibers (2), pruritus may reflect some abnormality of the peripheral nerve. In this study, we sought to clarify the prevalence of pruritus in diabetic and nondiabetic subjects and the relevance of pruritus to the symptoms and signs of diabetic polyneuropathy (DPN) using a large-scale questionnaire survey. Furthermore, the relationships between pruritus and quantitatively assessed nerve functions were also examined.

RESEARCH DESIGN AND METHODS

— The study comprised two investigations. The first investigation consisted of a questionnaire to assess the prevalence of pruritus and its relevance to neuropathic symptoms and signs. The second investigation was performed using quantitative neurological function tests to determine what kind of nerve dysfunction is related to pruritus.

Prevalence of pruritus and its relevance to symptoms and signs of DPN

A large-scale survey of diabetic subjects was performed with the cooperation of the physicians of the Wakayama medical association. Between November 2006 and August 2007, questionnaires were sent to 48 medical practitioners and hospital physicians in Wakayama Prefecture, Japan. The questionnaires consisted of patient- and physician-completed portions, and both were returned to our department for analysis. A survey of nondiabetic subjects was performed with the cooperation of the health examination division of Wakayama Rosai Hospital. Between September 2006 and August 2007, the same questionnaires were used for nondiabetic subjects who had received annual medical examinations at their workplace. Participation was voluntary, and data that could identify individuals was not collected.

Items in questionnaire

Age (expressed as decade), sex, height, and body weight were obtained from all participants. Duration of diabetes, most recent A1C measurement, and Achilles tendon reflex (ATR) were provided by the physicians treating the diabetic participants. Subjective sensory symptoms were examined in diabetic and nondiabetic participants using four criteria: "numbness in toes and soles," "dysesthesia in toes and soles," "pain in feet," and "painful leg cramp." In this study, "numbness" was defined as an abnormal sensation with the absence of stimulation, and "dysesthesia" was defined as an abnormal sensation produced by ordinary stimuli. Final questions to diabetic and nondiabetic subjects concerned "pruritus" and its distribution in the body and the suspected cause of itching. Prevalence of pruritus and abnormal sensations were compared between diabetic and nondiabetic participants. The relations between pruritus and neurological symptoms, signs, and other clinical factors described above were also evaluated in diabetic participants.

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See accompanying editorial, p. 210.

Nerve dysfunctions associated with pruritus

A total of 105 diabetic subjects (58 men and 47 women) aged <70 years who received medical interviews and quantitative nerve function tests were enrolled in this study. Forty-four patients were outpatients and 61 were inpatients of the Wakayama Medical University Hospital. Numbers of patients receiving insulin therapy with or without additional oral agents, oral hypoglycemic agents, and only diet/exercise therapy were 73, 29, and 3, respectively. Their mean ± SD age, duration of diabetes, BMI, and recent A1C were 55.7 ± 9.6 years, 11.6 ± 8.8 years, 24.8 ± 4.3 kg/m^2, and 8.6 ± 2.1%, respectively. Prevalence of proteinuria (intermittent and persistent proteinuria) and retinopathy (simple preproliferative and proliferative retinopathy) was 29.1 and 45.9%, respectively. Subjects with systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg or those receiving antihypertensive treatment were defined as hypertensive. Subjects with total cholesterol >5.69 mmol/l (220 mg/dl) and/or triglycerides >1.70 mmol/l (150 mg/dl) or those receiving antihyperlipidemia medication were defined as hyperlipidemic. The prevalence of hypertension and hyperlipidemia was 46.7 and 48.5%, respectively.

Nerve function tests

Four objective and quantitative tests (nerve conduction study, quantitative vibratory perception test, head-up tilt test, and heart rate variability test) were performed to evaluate the relationships between pruritus and various somatic and autonomic nerve functions. All examinations were conducted in a temperature-controlled room at 25°C. Methods for each examination are described only briefly in the following because they were described in our previous report (3).

Nerve conduction study. Motor nerve conduction velocity (MCV) between the wrist and elbow, compound muscle action potential (CMAP) of the ulnar nerve, sensory nerve conduction velocity (SCV) between the wrist and elbow, and sensory nerve action potential (SNAP) of the median nerve were measured using standard methods. Examinations were performed bilaterally, and an average value was used for analysis.

Quantitative vibratory perception threshold test. The quantitative vibratory perception threshold (QVT) at 125 Hz was semiquantitatively assessed at the tips of big toes using a vibratory sensation meter (AU02A; RION, Tokyo, Japan).

Autonomic nerve function tests (head-up tilt test and heart rate variability test). Sympathetic vasomotor function was evaluated by a head-up tilt test. Orthostasis-induced decreases in brachial systolic blood pressure after passive standing in a 70° head-up position (ΔBP) were examined. Parasympathetic cardiovagal function was evaluated by the heart rate variability test. Coefficients of variation of RR intervals on the electrocardiogram during deep breathing (CV-DB) were determined.

Comparisons between pruritus and neurological functions

Actual data from neurological examinations and the prevalence of impaired values were compared between patients with and without pruritus. Because nerve conduction data (MCV, SCV, CMAP, and SNAP) and vibratory thresholds (QVT) were distributed normally, values exceeding the range of means ± 2 SD of the healthy subjects in our institute (4) were judged as impaired. CV-DB results that were converted into logarithms were distributed normally, and data that were more than the means −2 SD of logarithms of healthy subjects (5) was considered impaired. Because ΔBP values in the head-up tilt test were not distributed normally, decisions regarding impairment were judged according to the criteria of the American Autonomic Society (6): a decrease in upright systolic blood pressure of at least 20 mmHg.

Table 1—*Comparison of the prevalence of neurological symptoms, pruritus, and subclassified pruritus between age-matched diabetic and nondiabetic subjects and the relevance of TPUO with the signs and symptoms of DPN*

	Influence of diabetes		Influence of TPUO	
	Nondiabetic	Diabetic	TPUO(−)	TPUO(+)
n	391	391	2,172	316
Sex (male/female)	239/144	229/162	1,186/943	160/151
Age (years)	NE	NC	60.2 ± 12.0	63.1 ± 12.3*
Duration (years)	NE	8.4 ± 7.1	10.9 ± 8.5	13.5 ± 9.5*
BMI (kg/m^2)	22.5 ± 3.3	25.1 ± 4.8†	24.0 ± 4.3	24.0 ± 5.0
A1C (%)	NE	7.3 ± 1.5	7.0 ± 1.4	7.1 ± 1.2
Numbness in toes and soles (%)	8.0	27.5†	27.6	41.3*
Dysesthesia in toes and soles (%)	4.4	16.6†	17.9	28.6*
Pain in feet (%)	4.4	9.6‡	8.7	16.6*
Painful leg cramp (%)	36.1	31.8	34.0	47.4*
Bilateral areflexia in ATR (%)	NE	16.7	18.1	34.3*
Pruritus (%)	14.6	26.3†	14.9	100*
TPUO (%)	2.9	11.3†	0	100*
Head and neck pruritus of unknown origin (%)	0.8	0	NC	NC
Leg pruritus of unknown origin (%)	1.1	1.6	NC	NC
Pruritus due to dermatitis (%)	4.1	4.1	NC	NC
Pruritus due to athlete's foot (%)	1.5	3.8‡	NC	NC

Data are means ± SD or %. Statistical analyses were made by unpaired *t* test and χ^2 test. *$P < 0.001$ vs. TPUO(−). †$P < 0.001$ vs. nondiabetic subjects. ‡$P < 0.05$ vs. nondiabetic subjects. NC, not calculated; NE, not examined.

Statistical analysis

Data are expressed as means ± SD. Statistical analyses were performed by χ^2 test, unpaired *t* test, and multiple logistic regression analysis using statistical software (Statview-J5.0TM; Hulinks, Tokyo, Japan). $P < 0.05$ was considered significant.

RESULTS

Prevalence of pruritus and its relevance to symptoms and signs of DPN

Questionnaires were collected from a total of 3,042 diabetic patients, with an average of 64 per clinic or hospital. The data for 386 diabetic subjects who did not reply to the questions concerning pruritus were excluded from analysis, and the data

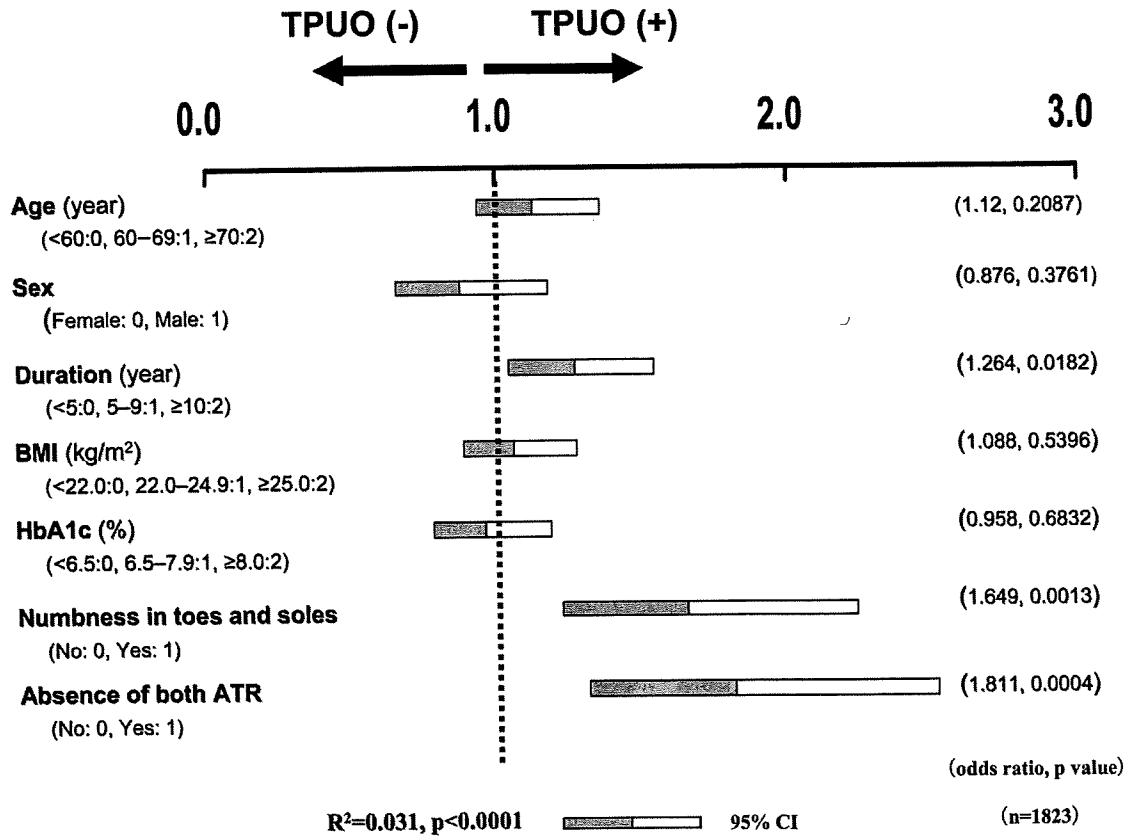

Figure 1—*Multiple logistic regression analysis with TPUO as an independent variable revealed that dysesthesia, ATR areflexia, and duration were significant risk factors for TPUO with odds ratios of 1.649, 1.811, and 1.264, respectively. Horizontal columns show the 95% CIs of each independent factor.*

of the remaining 2,656 diabetic subjects (1,440 men, 1,161 women, and 55 not specified) were included. Their ages were distributed from 20 to 80 years. Half of the subjects included were aged 60 or 70 years. Average ± SD duration of diabetes was 11.4 ± 8.8 years, and A1C was 7.05 ± 1.34%. Questionnaires were collected from 499 nondiabetic subjects (307 men, 170 women, and 22 not specified). Although their age distribution was also from 20 to 80 years, half of those included were aged 40 and 50 years and were significantly younger than the diabetic subjects.

Prevalence of pruritus and symptoms and signs of DPN

Because of the significant difference in the age distribution between diabetic and nondiabetic subjects, the prevalence of pruritus, abnormal sensations, and painful leg cramp was calculated in age-matched diabetic and nondiabetic samples and compared between the two groups. The same numbers of diabetic and nondiabetic subjects for the analysis were randomly selected for each decade of age using a stratified sampling method. Therefore, the data from 391 participants from each group (aged 20–29 years, n = 9; 30–39 years, n = 62; 40–49 years, n = 121; 50–59 years, n = 122; 60–69 years, n = 57; 70–79 years, n = 16; and ≥80 years, n = 4) were evaluated. Pruritus was subclassified by itching site and cause into five categories: truncal pruritus of unknown origin (TPUO), head and neck pruritus of unknown origin, leg pruritus of unknown origin, pruritus caused by dermatitis, and pruritus due to athlete's foot. Frequency was also examined.

The prevalence of numbness in toes and soles, dysesthesia in toes and soles, pain in feet, and pruritus in diabetic subjects was significantly higher than that in nondiabetic subjects. The prevalence of painful leg cramps was not different between the two groups. The prevalence of total pruritus in diabetic subjects was significantly higher than that in nondiabetic subjects (26.3 vs. 14.6%, $P < 0.001$). In subclassified pruritus, TPUO occurred more frequently in diabetic than in nondiabetic subjects (11.3 vs. 2.9%, $P < 0.001$), and the prevalence of pruritus due to athlete's foot was higher than that in nondiabetic subjects ($P = 0.047$). However, the prevalence of pruritus in other sites and that due to dermatitis was not different between the two groups. Therefore, the characteristic pruritus in diabetic subjects seemed to be TPUO. TPUO was seen in 12.7% (316 of 2,488) of the total diabetes group. In the patients with DPN judged by bilateral ATR areflexia, the prevalence of TPUO was 20.5% (84 of 410). In the asymptomatic patients with DPN who complained of no abnormal sensation, TPUO was observed in 15.2% (31 of 204). There was no significant sex difference in the prevalence of TPOU in diabetic and nondiabetic subjects.

Relevance of pruritus to signs and symptoms of DPN

The age of patients with TPUO and duration of DPN were significantly higher than those of patients without TPUO. The prevalence of all symptoms of DPN (numbness in toes and soles, dysesthesia in toes and soles, pain in feet, and painful leg cramps) and bilateral areflexia of ATR

in the patients with TPUO was significantly higher than those in the patients without TPUO (Table 1). Thus, multiple logistic regression analysis was performed to confirm the risk factors for TPUO. Seven clinical factors were correlated into scores (age: <60 years, 0, 60–69 years, 1, and ≥70 years, 2; sex: female, 0 and male, 1; duration of diabetes: <5 years, 0, 5–9 years, 1, and ≥10 years, 2; BMI: <22.0 kg/m^2, 0, 22.0–24.9 kg/m^2, 1, and ≥25.0 kg/m^2, 2; A1C: <6.5%, 0, 6.5–7.9%, 1, and ≥8.0%, 2; dysesthesia: no, 0 and yes, 1; and absence of both ATR: no, 0 and yes,1) and adopted as independent valuables. As a result, numbness in toes and soles, ATR areflexia, and longer duration of diabetes were identified as the independent risk factors of TPUO (Fig. 1).

Nerve dysfunctions associated with pruritus

The prevalence of total pruritus and TPUO in 105 diabetic patients was 32 and 19%, respectively. There was no significant difference in all clinical background data between TPUO(+) and TPUO(−) groups (Table 2). In the comparison of actual neurological data, only ΔBP in the TPUO(+) group was significantly higher than that in the TPUO(−) group. In the comparison of prevalence of impaired nerve functions, impaired ΔBP and CV-DB occurred in a significantly higher frequency in the TPUO(+) group than in the TPOU(−) group (Table 2). Multiple logistic regression analysis was also performed to examine neurological function, which is closely related to TPUO. Seven clinical and neurological factors were converted into scores (age: <50 years, 0, 50–59 years, 1, and ≥60 years, 2; sex: female, 0 and male, 1; duration of diabetes, <5 years, 0; 5–9 years, 1, and ≥10 years, 2; impaired SCV: no, 0 and yes, 1; impaired CV-DB: no, 0 and yes, 1; impaired ΔBP: no, 0 and yes, 1; and impaired QVT: no, 0 and yes, 1), and they were adopted as independent variables, respectively. As a result, impaired ΔBP was identified as a significant risk factor of TPUO (Fig. 2).

Table 2—*Clinical characteristics and neurological data of diabetic patients divided into two groups based on TPUO*

	TPUO(+)	TPUO(−)	*P*
n (%)	20 (19.0)	85 (81.0)	
Age (year)	58.0 ± 11.3 (20)	55.2 ± 9.1 (85)	0.238
Sex (male/female)	11/94	7/38	0.981
BMI (kg/m^2)	24.2 ± 4.5 (19)	24.9 ± 4.3 (83)	0.487
A1C (%)	8.5 ± 1.8 (18)	8.7 ± 2.1 (83)	0.774
Duration of diabetes (years)	12.8 ± 8.2 (20)	11.4 ± 8.9 (85)	0.534
Proteinuria (more than intermittent proteinuria) (%)	8/20 (40.0)	22/83 (26.5)	0.233
Retinopathy (more than SDR) (%)	12/20 (60.0)	32/76 (42.1)	0.153
Dyslipidemia (%)	10/20 (50.0)	41/85 (48.2)	0.887
Hypertension (%)	11/20 (55.0)	38/85 (44.7)	0.406
MCV (m/s)	49.9 ± 5.2 (20)	50.9 ± 5.1 (84)	0.396
Prevalence of impaired MCV (%)	8/20 (40.0)	28/84 (33.3)	0.573
CMAP (mV)	5.92 ± 1.2 (19)	6.35 ± 2.1 (84)	0.384
Prevalence of impaired CMAP (%)	5/20 (25.0)	16/83 (19.3)	0.569
SCV (m/s)	55.4 ± 5.5 (19)	56.6 ± 4.9 (78)	0.355
Prevalence of impaired SCV (%)	11/19 (55.0)	32/81 (39.5)	0.210
SNAP (μV)	24.8 ± 16.4 (20)	25.3 ± 18.7 (79)	0.909
Prevalence of impaired SNAP (%)	4/20 (20.0)	16/80 (20.0)	0.999
QVT (dB)	21.2 ± 9.5 (20)	19.4 ± 9.4 (85)	0.376
Prevalence of impaired QVT (%)	9/20 (45.0)	25/85 (29.4)	0.180
ΔBP (mmHg)	19.2 ± 15.8 (20)	10.4 ± 15.2 (84)	0.014
Prevalence of impaired ΔBP (%)	13/20 (65.0)	17/84 (20.2)	<0.001
CV-DB (%)	4.29 ± 3.56 (19)	4.91 ± 3.99 (83)	0.538
Prevalence of impaired CV-DB (%)	10/20 (50.0)	23/85 (27.1)	0.047

Data are means ± SD (*n*) unless indicated otherwise. $n = 105$. Statistical analyses were made by unpaired *t* test and χ^2 test.

CONCLUSIONS— The first investigation (a large-scale survey) revealed the following three findings: *1*) the prevalence of pruritus, especially TPUO, in diabetic patients was significantly higher than that in age-matched nondiabetic subjects; 2) ~12% of diabetic outpatients of general physicians complained of TPUO, and this prevalence was four times that of nondiabetic subjects; and *3*) bilateral sensory symptoms in the feet and ATR areflexia occurred in a significantly higher frequency in diabetic subjects with TPUO than in diabetic subjects without TPUO, and numbness in toes and soles and ATR areflexia were identified as significant risk factors of TPUO by multivariate analysis. From these findings, TPUO was suspected of being a complication of diabetes, and DPN was suspected of being a possible origin of TPUO.

The second investigation, using several quantitative nerve function tests, revealed the following two findings: *1*) impaired blood pressure response to a head-up tilt test and impaired heart rate variability during deep breathing occurred in a significantly higher frequency in TPUO(+) diabetic subjects than in TPOU(−) diabetic subjects; and 2) only impaired blood pressure responses to head-up tilt were identified as significant risk factors of TPUO by multivariate analysis. These findings suggested that autonomic nerve dysfunction, especially sympathetic nerve dysfunction, might be the most plausible candidate for the origin of TPUO.

Many clinicians may have an impression that pruritus is more frequent in diabetic patients than in nondiabetic individuals. Although pruritus in the feet due to tinea pedis and pudendal pruritus due to candidiasis have been reported to be highly prevalent in diabetic patients (7,8), there is little epidemiological evidence of pruritus with diabetes. In this study, we clearly demonstrated the higher prevalence of TPUO in diabetic than in nondiabetic subjects, and TPUO was observed in ~12% of general diabetic outpatients in a frequency similar to that of the symptom of "pain in feet." On the other hand, the prevalence of pruritus in the head and neck or legs and pruritus caused by dermatitis were not different between diabetic and nondiabetic subjects.

The etiology of TPUO has not been elucidated. Our survey showed that TPUO was significantly associated with sensory disturbance in the legs and areflexia of ATR. These findings were thought to be characteristic for DPN (9). Moreover, detailed neurological evaluation indicated that an impaired blood pressure response to a head-up tilt test

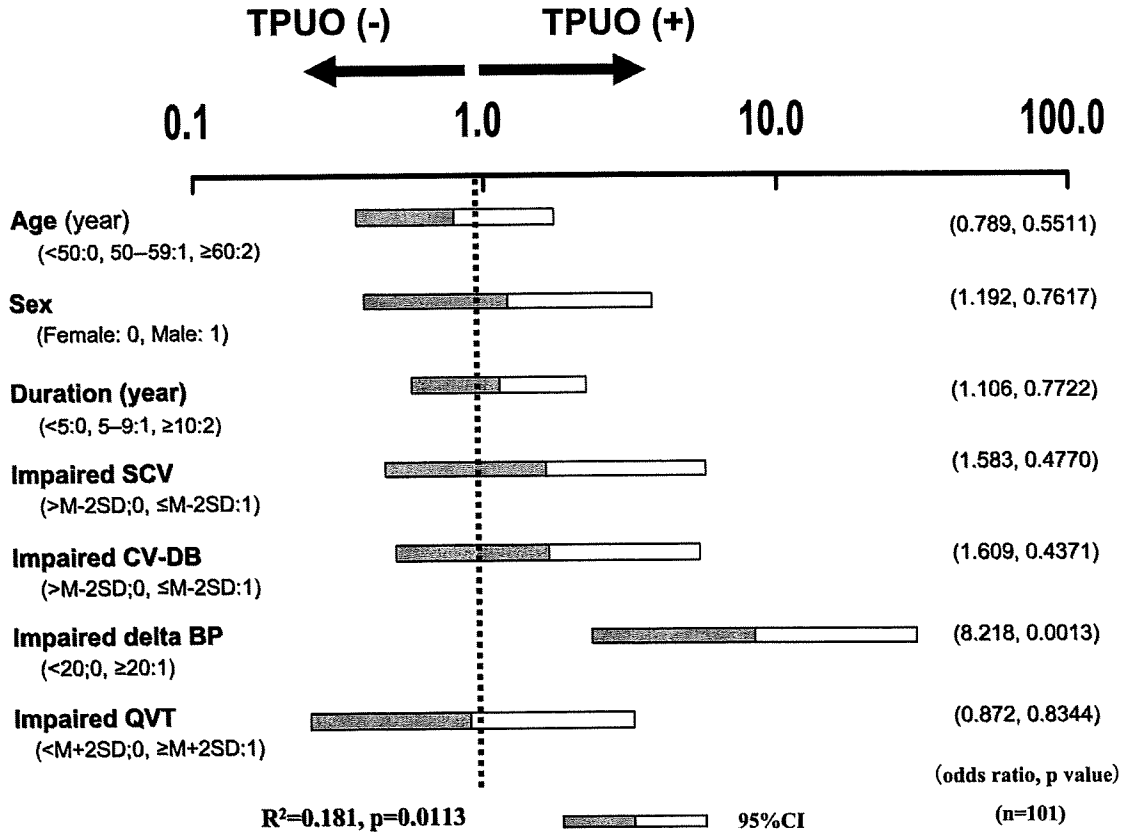

Figure 2—*Multiple logistic regression analysis clarified that the only significant risk factor for TPUO was the impairment of blood pressure response to a head-up tilt test, and the odds ratio was 8.218. Horizontal columns show the 95% CIs.*

was most closely associated with TPUO. This impairment reflected the deterioration of sympathetic nerve function (10). We therefore think that TPUO is a symptom of DPN, especially in sympathetic nerve dysfunction. Two possible mechanisms are proposed as an etiological theory of TPUO. First, because sympathetic nerve function includes the sudomotor function (11), sympathetic dysfunction caused hypohydrosis and resulted in dry skin. It is well known that pruritus occurs frequently with dry skin. In dry skin the barrier function of the skin is decreased, and the threshold for itching is lowered; therefore, TPOU is elicited. In fact, increased numbers of mast cells and histamine content have been reported in experimental dry skin in mice (12). A second possibility is that the damage to sensory c-fibers by DPN causes pruritus directly. Superficial skin pain is considered to be caused by abnormal firing of the pain nerve fiber in patients with DPN (13). Similarly, abnormal firing of the nerve fiber in pruritus may induce TPUO. In fact, hyperplasia of the c-fibers in the epidermis has been reported in dermatitis with strong pruritus (14). The unmyelinated c-fiber that transmits pruritus is a fiber similar to the sympathetic nerve ending in the skin. Thus, a significant association between TPUO and orthostatic intolerance seems to be reasonable. Both of the two etiological factors, the dry skin due to sudomotor hypofunction and direct nerve fiber damage by DPN, may be involved in TPUO. To determine the etiology of TPOU accurately, a skin biopsy and nerve fiber staining with antiprotein gene product 9.5 antibody in patients with TPUO will be necessary (15). Although discussion of treatment of diabetic truncal pruritus is beyond the scope of this study, two kinds of drugs might be useful. One is an antihistaminic agent that may be effective for mild pruritus due to dry skin and the other is a neurotropic agent such as gabapentin that may be effective for severe TPUO such as uremic pruritus (16).

From the viewpoint of clinical practice, TPUO seems to be useful for not misdiagnosing DPN. Some investigators have reported that ~50% of patients with DPN did not complain of sensory disturbance in their legs, which is a symptom typical of DPN (17). It is therefore necessary to do a neurological examination such as vibratory perception threshold and ATR for the diagnosis of DPN. However, it is not feasible to examine ATR and vibratory perception threshold in all diabetic outpatients because of the remarkable increase in the diabetic population. Consequently, it is important to be familiar with the symptoms of DPN other than the sensory disturbance of the legs. By recognizing TPUO as a subjective symptom of DPN, it may be possible to reduce the misdiagnosis of DPN. Indeed, 15% of asymptomatic patients with DPN, who showed bilateral ATR areflexia and no abnormal sensations, complained of TPUO in our questionnaire survey.

In summary, the prevalence of TPUO in diabetic patients is significantly higher than that in nondiabetic individuals, and TPUO is significantly associated with symptoms and signs of DPN, one of which is orthostatic hypotension. TPUO, therefore, may be a newly recognized symptom of DPN.

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特集 糖尿病性神経障害の新しい展開

糖尿病性消化管運動異常の病態と対策

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● key words　糖尿病性自律神経障害／胃食道逆流症／糖尿病性胃不全麻痺／糖尿病性下痢症／便秘症

はじめに

糖尿病患者では嚥下困難，胸やけ，嘔気，嘔吐，腹痛，下痢，便秘，便失禁など上・下部の消化管運動異常に基づくと考えられる多彩な症状がみられる[1)-3)]。これらの症状には高血糖，微小循環障害の関与も推定されるが，主因は自律神経障害と考えられており，血糖コントロールの悪い罹病期間の長い患者によくみられる。**表1**に糖尿病患者における主な消化管症状の頻度を示す[4)]が，調査対象や質問内容の違いによってその頻度はさまざまである。

図には自律神経機能の客観的指標である深呼吸時心電図R-R間隔変動係数（$CV_{R\text{-}R}$）およびヘッドアップティルト試験時の収縮期血圧低下幅（⊿BP）の加齢変化を代表的な消化器症状である便秘・下痢（頑固な便秘また便秘/下痢の交替）の有無別の示したものである。便秘・下痢の有無により$CV_{R\text{-}R}$，⊿BPの平均値は有意に異なるが，分布範囲はほとんど一致している。このように，自覚症状と神経機能障害の重症度との相関は弱く，消化管運動障害を正確に診断・評価するには自覚症状に客観的指標を加えて総合的に判断する必要がある。しかし，簡便に消化管機能を評価できる検査法に乏しいことから，しばしば見逃されるケースや消化管運動異常によらない症状を診断するケースも多いと考えられる。

通常，消化器症状を訴える例の多くは軽症で治療を要さないが，緩下薬で改善しない頑固な便秘，長期間続く嘔気・嘔吐，夜間に頻発する下痢は患者のQOLを大きく損なう重要な合併症である。このような症状は他の慢性合併症の進行している重症例にみられる。また，高度の消化管運動異常，特に胃排出遅延は，血糖コントロールを不安定にする要因として重要である。以下，臓器別の運動機能障害について概説する。

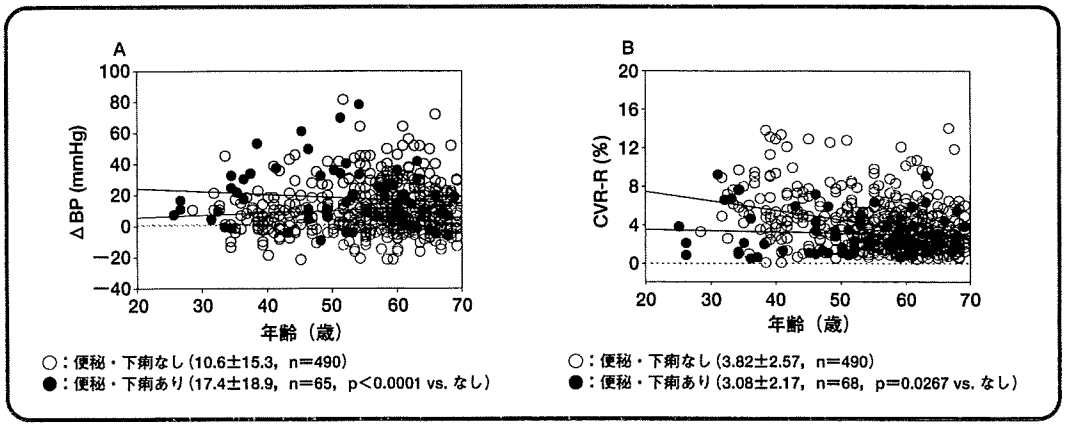
表1．糖尿病患者の消化器症状の頻度

自覚症状	有症状率（%）
嚥下困難	2～27
嘔気・嘔吐	7～29
腹　痛	18～34
下　痢	0～22
便　秘	2～60
便失禁	1～20

（文献3より引用）

Ⅰ．食道運動機能障害

食道機能障害は迷走神経障害から生じるとされており，症状としては嚥下障害や胸やけがみられるが，嚥下障害の頻度は少なく程度は軽く治療を要することはまれである[5)6)]。最近，胸やけの原因となる胃食道逆流症（GERD）の増加が注目され，糖尿病性神経障害との関連を示唆する報告がある[7)8)]。上部消化管内視鏡検査で炎症があれば逆流性食道炎と診断される。また，内視鏡検査の際に食道カンジダ症が見つかることも多い[9)]。食道



図．ヘッドアップティルト試験時収縮期血圧低下幅（Δ BP ： A）および深呼吸時心電図 R-R 間隔変動係数（CV_{R-R} ： B）の加齢変化

数字は平均値±標準偏差を示す。検定は unpaired t-test による。

運動機能は食道内圧測定，食道内 pH モニタリングで診断できるが一般の日常臨床では実施困難である。GERD の治療は非糖尿病者と変わらずプロトンポンプ阻害薬など制酸薬で，食道カンジダ症の治療には抗真菌薬の内服が用いられる。

Ⅱ．胃機能障害

1　糖尿病性胃疾患（ガストロパシー）

糖尿病性自律神経障害により胃酸分泌と胃腸管運動の両方が障害される。胃排出能は主に迷走神経機能に依存しており，糖尿病では重度に障害される。罹病期間の長い糖尿病患者のおよそ 50 %に胃排出の遅延（糖尿病性胃不全麻痺，胃アトニー，ガストロパレーシス）がみられることが報告されている[10]。最近ではカハール間質細胞（interstitial cells of Cajal ： ICC）がペースメーカーとして電気的興奮を生成し，胃の運動性神経伝達を調節していると考えられており，ICC 減少が胃不全麻痺の進展に寄与する可能性が報告されている[11]。

糖尿病性胃不全麻痺は臨床的にはしばしば無症状であるが，重症例では最も QOL を損なう消化管合併症である。胃不全麻痺の典型的症状は早期の満腹感，嘔気，嘔吐，鼓腸，上腹部痛，食欲不振で，数時間あるいは数日前に食べた未消化の食物を嘔吐することがある。嘔気，嘔吐は数日から数ヵ月持続し経静脈栄養を余儀なくされる例や，周期的に起こる例もある[12]。

一方，血糖コントロールの不安定な患者には糖尿病性胃不全麻痺の存在も念頭に置くべきである。たとえそれが軽症であっても，胃不全麻痺では胃内容物の小腸への輸送が損なわれているため，食事による糖の吸収と外因性インスリン注射の効果発現に時間的ずれが生じ，結果的に血糖の変動は大きくなり，予期せぬ食後低血糖や，血糖コントロールの不安定性を惹起する。

2　診断・評価

上部胃腸症状を胃不全麻痺と診断するためには，胃炎，胃潰瘍，十二指腸潰瘍，胃癌などの除外が必要である。早朝空腹時の内視鏡検査で食後 8 ～ 12 時間後の胃内食物残渣を確認すれば胃不全麻痺を診断する。

胃排出能はラジオアイソトープで標識した食事を摂取させた後シンチグラフィーでその分布を計測することで評価できる。しかし，シンチグラフィーの結果は常に症状の重症度と相関するわけではなく，胃排出に遅延がみられるのに無症状の糖尿病患者もいれば，胃排出能は正常にもかかわらず重い症状を呈する糖尿病患者も存在する。胃・十二指腸の消化管内圧測定は，幽門痙攣や胃と十二指腸の協調運動障害の識別に有用で，胃電図も胃運動機能の評価に用いられるが，いずれも日常診療での使用は困難で研究目的に実施されている。

3　治　療

まず行うべきことは，血糖のコントロールである。高血糖状態はそれ自体が胃排出を遅延させるとの報告があり[13]，血糖を正常化することにより胃の運動機能が改善することが知られて

いる[14]。薬物療法としては消化管運動機能改善薬が用いられ，メトクロプラミド，ドンペリドン，モサプリド，イトプリド，エリスロマイシンなどがある[15][16]。重症例には空腸造瘻術も行われることがある。胃の大弯に電極を埋め込み電気刺激することで胃の運動機能を改善する埋め込み式ペースメーカーにより，糖尿病患者の胃腸症状と血糖値が有意に改善したとの報告がある[17]。

Ⅲ．小腸・大腸機能障害(直腸・肛門を含む)

糖尿病性自律神経障害による運動機能低下と内臓知覚鈍麻によって，食物摂取による胃の拡張に伴い結腸の蠕動運動が亢進する胃・結腸反射や，便が直腸に達すると便意をもよおす結腸直腸反射などが障害され，便通異常が生じる。

1　便　秘

便秘は最も頻度の高い糖尿病性消化管合併症である。大腸と直腸の緊張低下に関連があり，時に巨大結腸症を伴う。緩下薬が奏効しにくい便秘が多く，便秘と下痢が交互に出現することもある[18]。

1）診断・評価

甲状腺機能低下症，抗うつ薬やカルシウム拮抗薬などの薬剤の副作用や大腸癌などの除外が必要である。客観的評価法として大腸通過試験(X線不透過性マーカーを飲み込み，経時的にX線撮影し停留位置や量を確認する)や直腸内圧測定が一部の施設で行われている。直腸内圧測定は直腸肛門反射を評価できるので，直腸S状結腸の機能障害と大腸の運動性低下による閉塞症状の鑑別が可能である。器質的疾患の除外には下部消化管内視鏡が有用である。

2）治　療

生活習慣の改善が重要で，規則正しい運動，適切な炭水化物や食物繊維の摂取を続けること，規則的な排便習慣を身につけることが有用である。薬物療法としては，緩下薬を用いることが多く消化管運動機能改善薬も用いられる。

2　下痢・便失禁

下痢は糖尿病患者の1～20％でみられ，自律神経障害の合併する患者では頻度が増す。特徴的な糖尿病性下痢は，便秘との交替性下痢，数日間断続的に続く下痢，夜間に突然起こる下痢であり，無痛性のことが多く便失禁を伴うこともある。下痢の原因には交感神経性抑制の減弱，腸の停滞による腸内細菌の過剰増殖による胆汁酸の脱抱合，膵分泌不全による脂肪の分解障害，脂肪便または胆汁酸塩の吸収障害に起因する腸の運動性の亢進などが考えられている[19]。発作性下痢や便失禁には肛門括約筋の緊張減弱が関連する[20]。

1）診断・評価

ビグアナイド，αグルコシダーゼ阻害薬，胆汁酸製剤などによる薬剤性下痢，乳糖不耐症，過敏性腸症候群や甲状腺機能亢進症，慢性膵炎などを除外する必要がある。絶食で治まる下痢は食物による浸透圧性下痢かもしれない。夜間の下痢など絶食時に続く下痢は分泌性下痢が疑われ，まれではあるが神経内分泌疾患であるWDHA症候群(watery diarrhea, hypokalemia, achlorhydria)，VIPoma(血管作用性小腸ペプチド産生腫瘍)，Zollinger-Ellison症候群(ガストリノーマ)，カルチノイド腫瘍などを除外する必要がある。空腹時血中ホルモン濃度や5HIAA(5-ヒドロキシインドール酢酸)の尿排出量の測定により診断する。器質的疾患除外に下部消化管内視鏡が必要である。

2）治　療

難治性下痢の対症療法は，輸液などで水と電解質を補正し栄養状態を改善することである。下痢止め(たとえばロペラミド)は排便回数を減らすことができるが，中毒性巨大結腸症のおそれがあり，細心の注意をはらって使用すべきである。腸内細菌の異常増殖による下痢には抗菌薬が有効なこともあり，軽症例では乳酸菌製剤を用いる。これらの治療に抵抗する難治性下痢に酢酸オクトレオチドの有効性が報告されている[21]。

おわりに

糖尿病に合併する消化管運動障害と症状，病態生理，診断法，対策・治療をまとめた結果を**表2**に示す。糖尿病性消化管運動異常は胸やけ，嘔気，嘔吐，下痢，便秘，便失禁など患者のQOL低下に直結する消化器症状の原因であると同時に，栄養の吸収遅延により血糖コントロールを乱す原因でもある。血糖コントロールが不安定で糖尿病性神経障害が進行している症例では，本症の存在も疑うことが重要である。糖尿病性消化管運動異常で消化管運動を正常化することは血糖コントロールの安定化をもたらし，それが神経障害など合併症の予防につながることより，見逃してはならない合併症である。

表2．糖尿病に合併する主な消化管運動障害

臓　器	疾患名	症状	病態生理	診断法	対策・治療
食　道	逆流性食道炎	胸やけ，胸痛	胃酸逆流	内視鏡	制酸薬
	（胃食道逆流症：GERD）			内圧，pH測定	
	食道カンジダ症	胸痛	易感染性	内視鏡	抗真菌薬
胃	糖尿病性胃疾患	満腹感，嘔気，嘔吐	胃排出遅延	内視鏡，胃電図	
	糖尿病性胃不全麻痺	鼓腸，上腹部痛	幽門痙攣	内圧検査	血糖制御
		血糖調節不安定化		シンチグラフィー	消化管
					運動促進薬
小腸・大腸	糖尿病性腸疾患		内視鏡検査		血糖制御
（直腸・肛門）	糖尿病性便秘症	難治性便秘	腸管運動低下	大腸通過試験	緩下薬
	糖尿病性下痢症	下痢（夜間，持続性	細菌過剰増殖	直腸内圧測定	止痢薬
		便秘と交替，無痛）	神経反射低下		抗菌薬
		便失禁	括約筋低下		乳酸菌製剤

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Original Article: Complications

Serum VEGF increases in diabetic polyneuropathy, particularly in the neurologically active symptomatic stage

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Abstract

Aim To identify the relationship between vascular endothelial growth factor (VEGF) and diabetic polyneuropathy (DPN).

Methods Two hundred and twenty diabetic patients participated, 113 with DPN and 107 without DPN. All patients were also classified according to the four stages of DPN (no neuropathy: stage 0; asymptomatic neuropathy: stage 1; symptomatic neuropathy: stage 2; disabling neuropathy: stage 3). Serum VEGF concentration was measured using an enzyme-linked immunosorbent assay (ELISA) and levels between the patients with and without DPN and also between the different stages of DPN, were compared.

Results The mean serum VEGF level in all patients was 264.6 ± 218.8 pg/ml. The mean serum VEGF level was higher in patients with DPN (310.1 ± 224.3 pg/ml) than in the patients without DPN (216.5 ± 204.0 pg/ml, $P = 0.0014$). Serum VEGF was higher in the 'symptomatic' stage (stage 2, 364.8 ± 225.9 pg/ml) in comparison with the 'asymptomatic' (stage 1, 256.7 ± 224.4 pg/ml, $P = 0.015$) and 'disabling' (stage 3, 180.3 ± 109.4 pg/ml, $P = 0.042$) stages. The mean serum VEGF level in patients with diabetic retinopathy (261.1 ± 210.6 pg/ml) and in patients with diabetic nephropathy (241.5 ± 185.7 pg/ml) was not increased.

Conclusions The serum VEGF level is increased in patients with DPN, particularly in patients in the neurologically active 'symptomatic' stage.

Diabet. Med. 26, 247–252 (2009)

Keywords diabetes, neuropathy, vascular endothelial growth factor

Abbreviations DPN, diabetic polyneuropathy; HbA_{1c}, glycated haemoglobin; VEGF, vascular endothelial growth factor

Introduction

Vascular endothelial growth factor (VEGF)-A is one of the potent angiogenic and vascular permeability factors induced in ischaemic organs [1]. As VEGF production is stimulated by hypoxia [2], hyperglycaemia, advanced glycation end products and oxidative stress [3–6], VEGF has been recognized as a key cytokine related to the development of complications of diabetes mellitus such as retinopathy [7,8] and nephropathy [9–11]. In diabetic retinopathy, VEGF is increased in the vitreous and aqueous fluids [7] and a recent report has shown that VEGF in the aqueous fluid is increased in both pre-proliferative and proliferative diabetic retinopathy [12]. In nephropathy, urinary VEGF excretion rates are increased and recent reports have focused on the relationship between VEGF and the stage of diabetic nephropathy [9,13,14]. As other reports have identified a significant correlation between VEGF and diabetic microangiopathy [14,15], one might predict a close relationship between VEGF and diabetic polyneuropathy (DPN). There is, however, little clinical evidence available regarding the potential role of VEGF in DPN [16,17].

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Moreover, there are no reports regarding the relationship between VEGF and the stages of DPN. This study, therefore, examined serum VEGF in diabetic polyneuropathy and investigated how it relates to the status of neuropathy.

Patients and methods

Two hundred and twenty diabetic patients (105 men, 115 women, mean age 63.5 ± 12.6 years, 11 with Type 1 and 209 with Type 2 diabetes) were enrolled. All of the patients attended the diabetes outpatient clinic of Kagoshima University hospital and at the Southern-Region hospital from 2001 to 2005. The mean duration of diabetes was 10.4 ± 9.2 years and mean glycated haemoglobin (HbA_{1c}) 8.0 ± 2.1%. One hundred and twenty-one patients had diabetic retinopathy and 99 patients had overt proteinuria. All patients gave their informed consent to participate in this study.

Diagnosis and staging of DPN

The criteria for the diagnosis and staging of DPN were previously proposed by Dyck [18]. Recently in Japan, a new approach to establish abbreviated diagnostic criteria and staging for diabetic polyneuropathy has been developed for daily practice [19]. Thus we modified Dyck's criteria by using the Japanese abbreviated criteria and all patients were classified into four stages; stage 0 (no neuropathy), stage 1 (asymptomatic neuropathy), stage 2 (symptomatic neuropathy) or stage 3 (disabling neuropathy). For the staging of DPN, each patient completed a detailed questionnaire and neurological evaluation. These included inquiries about subjective symptoms and determination of presence or absence of muscle weakness, ankle jerk, vibratory sensation, sensory disturbance, autonomic neuropathy and disorders affecting quality of life. Other causes of neuropathy were excluded by measuring vitamin B12, thyroid-stimulating hormone, anti-nuclear antibody and serum protein electrophoresis. Individuals with a family history of neuropathy or a disease known to cause neuropathy were excluded by taking a detailed history. Laboratory investigations, spinal X-rays and diagnostic imaging systems such as magnetic resonance imaging were performed where appropriate. In addition, patients with diseases known to affect serum VEGF, such as cancer, inflammatory diseases and peripheral vascular disease, were also excluded. The effect of age was taken into consideration when examining elderly patients and symptoms and deficits from entrapment neuropathies or mononeuropathies were not staged. All examinations and questionnaires were performed by two neurologists certified by the Japanese Society of Neurology.

Measurement of serum VEGF

Early morning fasting serum was obtained from each patient. Serum was rapidly cryopreserved. VEGF concentrations were measured in duplicate using a commercial enzyme-linked immunoabsorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) that recognizes the soluble isoforms $VEGF_{121}$ and $VEGF_{165}$ as previously described [20,21]. The assay system used is sensitive to 15.6 pg/ml VEGF and does not cross-react with platelet-derived growth factor (PDGF) or other homologous cytokines. The optical density at 450 nm was measured on the ImmunoMini NJ-2300 (Nippon Inter Med, Tokyo, Japan) and the VEGF concentration was determined by linear regression from a standard curve using the VEGF supplied with the kit as a standard.

Statistical analysis

All data are presented as mean ± SD unless otherwise indicated. Differences between data sets were assessed by analysis of variance (ANOVA), with the Scheffe test *post hoc*. Paired data were compared by paired Student's *t*-test. All statistical analyses were carried out using the STATVIEW J-5.0 software program (SAS Institute, Cary, NC, USA) for Windows; P-value < 0.05 was considered to be statistically significant.

Results

Characteristics of subjects

By the diagnostic criteria and staging of DPN [18,19], 113 of the 220 patients had DPN (males 51, females 62, mean age 65.4 ± 11.3 years, mean duration of diabetes 11.6 ± 7.7 years, mean HbA_{1c} 8.2 ± 2.0%) while 107 did not (males 54, females 53, mean age 61.5 ± 13.6 years, mean duration of diabetes 9.1 ± 10.4 years, mean HbA_{1c} 7.7 ± 2.2%). Patients without DPN were included in stage 0. One hundred and thirteen DPN patients were included in stages 1–3. Thirty-five patients were classified as stage 1, 65 patients were stage 2 and 13 patients were stage 3 and the characteristics of patients in each stage of DPN are shown in Table 1. There was a significant correlation between the stages of DPN and the duration of diabetes, however, no significant correlation was found between the severity of DPN and age or HbA_{1c}.

The number and characteristics of patients with or without other diabetic complications are shown in Table 2. One hundred and twenty of the 211 patients had diabetic retinopathy and 99 of the 211 patients had overt proteinuria. The incidence of diabetic microvascular complications, paticularly retinopathy and nephropathy, significantly increased with age and duration of diabetes; however, there was no relationship with HbA_{1c}.

Comparison of serum VEGF level

There was a significantly higher level of serum VEGF in patients with DPN (310.1 ± 224.3 pg/ml) in comparison with those without DPN (216.5 ± 204.0 pg/ml) (P = 0.0014). In contrast, no significant difference in serum VEGF was found between patients with diabetic retinopathy (261.1 ± 210.6 pg/ml) and those without diabetic retinopathy (268.1 ± 237.3 pg/ml) (P = 0.82). In addition, in the patients with diabetic

Table 1 The characteristics of diabetic patients in each stage of diabetic polyneuropathy

	DPN (−)	DPN (+)		
	Stage 0	Stage 1	Stage 2	Stage 3
n	107	35	65	13
Age (years)	61.5 ± 13.6	66.4 ± 12.1	65.5 ± 11.3	62.3 ± 8.2
Sex (male)	54 (50.7)	18 (51.4)	24 (36.9)	7 (53.8)
Duration of diabetes (years)	9.1 ± 10.4*	8.4 ± 5.2†	11.9 ± 7.8	14.9 ± 12.9*,†
HbA_{1c} (%)	7.7 ± 2.2	7.8 ± 2.1	8.3 ± 2.0	8.5 ± 1.5
Neuropathy (%)‡	0	100	100	100
Subjective symptoms of DPN (%)§	17.8	0	100	100
ATR (−)/(±) (%)	15.0	100	64.6	100
Vibration ↓ (%)	14.8	100	61.7	84.6
Autonomic¶	7.8	5.7	38.8	92.1
Motor**	0.2	0.2	7.7	100
Retinopathy (%)	34.6	51.4	66.2	84.6
Nephropathy (%)	18.7	34.3	52.3	84.6

Data are the means ± SD or number or per cent, unless otherwise indicated. There was a significant dierence in duration of diabetes between stage 0 and stage 3* ($P = 0.008$) and between stage 1 and stage 3† ($P = 0.013$). There was no significant dierence in HbA_{1c} by stage of DPN (Schee's *post hoc* test with ANOVA).
‡Meets the abbreviated diagnostic criteria for DPN.
§Bilateral numbness, spontaneous pain, paraesthesia, decreased sensation, etc.
¶Orthostatic hypotension, abnormal sweating, severe diarrhoea and constipation, etc.
**Weakness and/or atrophy.
ANOVA, analysis of variance; ATR, Achilles tendon reflex; DPN, diabetic polyneuropathy; HbA_{1c}, glycated haemoglobin; SD, standard deviation.

Table 2 The number and the characteristics of patients with diabetic retinopathy and nephropathy

	Retinopathy			Nephropathy		
	(−)	(+)	*P*	(−)	(+)	*P*
n	91	120		112	99	
Age (years)	61.6 ± 14.6	65.0 ± 10.6	0.048	61.0 ± 13.5	66.3 ± 10.9	0.0023
Duration of diabetes (years)	6.9 ± 5.9	13.0 ± 10.3	< 0.0001	8.5 ± 6.9	12.7 ± 11.1	0.0013
HbA_{1c} (%)	7.8 ± 2.5	8.1 ± 1.8	0.29	7.8 ± 2.3	8.2 ± 1.9	0.25

Data are the means ± SD.
The incidence of diabetic retinopathy and diabetic nephropathy increased with age and the duration of diabetes.
There was no significant correlation between diabetic microangiopathies and HbA_{1c}.
HbA_{1c}, glycated haemoglobin; SD, standard deviation.

nephropathy, there was no significant difference of serum VEGF level between patients with overt proteinuria (241.5 ± 185.7 pg/ml) and those without overt proteinuria (284.1 ± 248.8 pg/ml) ($P = 0.16$; Fig. 1).

Serum VEGF level was 216.5 ± 204.0 pg/ml in the 'no neuropathy' stage 0, 256.7 ± 224.4 pg/ml in the 'asymptomatic' stage 1, 364.8 ± 225.9 pg/ml in the 'symptomatic' stage 2 and 180.3 ± 109.4 pg/ml in the 'disabling' stage 3. The serum VEGF level in stage 2 was higher than in stage 0 ($P = 0.0002$) and stage 3 ($P = 0.04$; Fig. 2).

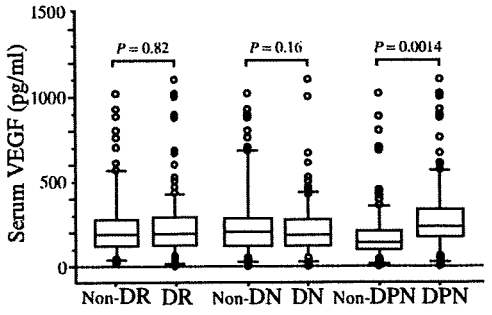

FIGURE 1 Serum vascular endothelial growth factor (VEGF) levels in patients with and without diabetic retinopathy (DR), diabetic nephropathy (DN) and overt proteinuria (DPN).

Discussion

In the present study, serum VEGF levels in the patients with DPN were significantly higher than in the patients without DPN.

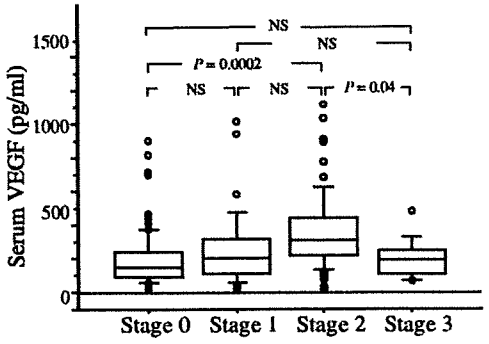

FIGURE 2 Serum vascular endothelial growth factor (VEGF) levels in four stages (stages 0–3) of diabetic polyneuropathy. NS, not significant.

Furthermore, serum VEGF correlated with the neurological staging, in other words, the severity of DPN, rather than with glycaemic control. This is the first report to address the relationship between serum VEGF levels and DPN, particularly in its neurological staging. In a previous report, no correlation was observed between DPN and plasma VEGF concentrations [16], but, unfortunately, the methods for diagnosing DPN were not clearly defined in that study, even although it was observed that DPN occasionally includes a subclinical neuropathy characterized by the disappearance or attenuation of the ankle jerk and dysaesthesia in the absence of subjective symptoms. Therefore, we paid particular note to patients with 'asymptomatic' stage 1 disease, based on the criteria for the diagnosis of DPN [18,19], and the neurological findings were carefully assessed.

In our previous report, the mean serum VEGF levels of healthy control subjects was 214.9 ± 139.3 pg/ml (n = 443) and we found no significant difference in the serum VEGF levels with age [21]. There was a significantly higher level of serum VEGF in patients with diabetes mellitus (264.6 ± 219.3 pg/ml) than in the healthy control subjects (P = 0.0004). In general, VEGF production is stimulated by hyperglycaemia and hypoxia; VEGF has been regarded as a potent cytokine related to the development of diabetic microvascular complications, particularly diabetic retinopathy [2–8]. If VEGF acts to accelerate the progression of DPN as well as diabetic retinopathy, then serum VEGF levels may increase along with the progression of DPN. However, our results suggest that serum VEGF levels fall in the advanced stage of DPN. In addition, these data show that the serum VEGF level of 'symptomatic' stage 2 patients was significantly higher than that of patients in 'asymptomatic' stage 1 and 'disabling' stage 3. Clinically, positive neuropathic symptoms such as dysaesthesia, pain and numbness are frequently seen at stage 2 and negative symptoms such as hypoaesthesia and sensory loss are representative of stage 3. Positive neuropathic symptoms are related to neural hyperactivity and they are thought to arise from the ectopic impulses in damaged nerve fibres or the sprouts of regenerated nerve fibres. In contrast, negative symptoms such as hypoaesthesia and sensory loss are related to a decreased number of nerve fibres or loss of neural function [22,23]. This suggests that VEGF production becomes active in stage 2 because of nerve regeneration and decreases in stage 3 as a result of degeneration and a decreasing number of nerve fibres. A reduction in VEGF expression and loss of intra-epidermal nerve fibres occurs in diabetic patients with increasing neuropathic severity, supporting our speculations [17]. In addition, recent reports showed a marked improvement of nerve blood flow and neurological function by local injection of unmodified VEGF [24] and the herpes simplex virus (HSV)-mediated gene transfer of VEGF to dorsal root ganglia prevents diabetic neuropathy [25]. In other neurological conditions, such as motor neurone disease and cerebrovascular disease, VEGF plays a role in various expedient effects such as axonal extension, random migration, multiplication and angiogenesis of nerve. VEGF also acts as a protector for neurone, Schwann cell, nerve nutrient vessels and other neural component cells [26]. As mentioned above, it is possible that VEGF acts as a survival factor for neuroprotection in the nerve of patients with diabetes mellitus during the neurologically active symptomatic period [27].

The role of VEGF itself in pathological angiogenesis and the transition from a healthy to a diseased state remains unclear. It is well known that, although VEGF is increased in vitreous and aqueous fluids in diabetic retinopathy [7], serum VEGF is not increased [28]. In addition, in the present study, serum VEGF levels were not increased in patients with diabetic retinopathy and nephropathy in comparison with DPN. VEGF has a 'double face' and acts to accelerate or suppress angiopathy, as if it can act as an agonist and an antagonist [29,30]. However, VEGF seems to act as a survival factor, particularly for DPN in contrast to proliferative diabetic retinopathy. The possible relationship between VEGF and nerve regeneration is summarized in Fig. 3. Unfortunately, it

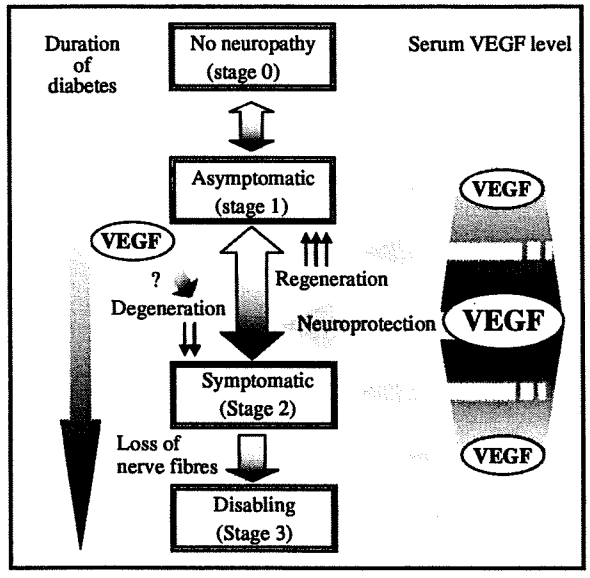

FIGURE 3 Possible relationship between vascular endothelial growth factor (VEGF) and nerve regeneration.

was not possible to recruit a sufficient number of patients with DPN stage 3 and therefore the detailed staging of retinopathy and nephropathy could not be analysed in this study. It is necessary to study a larger number of patients with severe disabling DPN and compare the stages and severity of other microvascular complications. In addition, it is necessary to carry out further detailed investigations, including an animal model of various stages of DPN, to elucidate how VEGF works and acts upon the nervous system in diabetes mellitus.

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Competing interests

Nothing to declare.

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特集 糖尿病性神経障害の新しい展開

糖尿病性神経障害と運動障害

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はじめに

糖尿病性多発ニューロパチー（diabetic polyneuropathy：DPN）において筋力低下や筋萎縮などの運動障害がみられるのは病期が進行してからであり，病期がさほど進行していない患者において運動障害優位の末梢神経障害を伴う場合は，他の病型や疾患との鑑別が必要となる。

運動障害優位の末梢神経障害である慢性炎症性脱髄性多発根ニューロパチー（chronic inflammatory demyelinating polyradiculoneuropathy：CIDP）は，免疫グロブリン大量療法（IVIg）やステロイドにより治療可能な免疫介在性ニューロパチーである。健常人よりも糖尿病患者での頻度が高く，糖尿病性神経障害の1病型と分類する向きもあるので[1]，周知が必要であろう。

臀部・大腿に疼痛を伴う筋力低下や筋萎縮を呈する糖尿病性筋萎縮症（diabetic amyotrophy）は，神経根～神経叢を含む腰仙髄領域の広範囲な末梢神経障害であり，最近は diabetic lumbosacral radiculoplexus neuropathy（DLRPN）と呼ばれる[2]。免疫療法の有効例が報告されており[3][4]，DPNとは異なる病態機序が想定されている。

糖尿病患者にみられる運動障害について，DPNによる病態と，免疫介在性ニューロパチーの側面から自験例をふまえて概説する。

Ⅰ．糖尿病性多発ニューロパチー（DPN）

DPNは，感覚・自律，運動神経障害へと緩徐に進行する対称性ポリニューロパチーである。糖尿病では小径有髄神経や無髄神経で構成される神経線維が最初に侵されるため，感覚，自律神経障害が前景に立って進行する。一方，大径有髄神経で構成される運動神経は予備能が大きいため，病期の進行した患者においてさえもしばしば無症候である。しかしながら，筋力低下を伴わなくとも骨間筋や短趾伸筋など足部小筋群の萎縮を認めることがあり，足部の変形からしばしば足病変の誘因となるので注意が必要である（**図1**）。

DPNは高血糖に伴う代謝異常による進行性の神経線維脱落を臨床病理学的基盤とする。運動障害を伴う病期のDPN患者の腓腹神経では，高度な神経線維の変性・脱落を認め，再生線維はほとんどみられなかった（**図2**）。

Ⅱ．糖尿病に合併するCIDP（DM-CIDP）

CIDPは，末梢神経に多発性の脱髄病変が慢性再発性に形成される運動＞感覚性ポリニューロパチーであり，病態機序として有髄神経髄鞘構成成分に対する自己免疫反応が想定されている。稀な疾患であるが，糖尿病では非糖尿病の約11倍の頻度で好発すると報告され[5]，にわかに注目を集めている。

DM-CIDPの臨床像は，主に大径有髄線維障害による運動神経