Alcoholic Neuropathy Is Clinicopathologically Distinct from Thiamine-Deficiency Neuropathy

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Characteristics of alcoholic neuropathy have been obscured by difficulty in isolating them from features of thiamine-deficiency neuropathy. We assessed 64 patients with alcoholic neuropathy including subgroups without (ALN) and with (ALN-TD) coexisting thiamine deficiency. Thirty-two patients with nonalcoholic thiamine-deficiency neuropathy (TDN) also were investigated for comparison. In ALN, clinical symptoms were sensory-dominant and slowly progressive, predominantly impairing superficial sensation (especially nociception) with pain or painful burning sensation. In TDN, most cases manifested a motor-dominant and acutely progressive pattern, with impairment of both superficial and deep sensation. Small-fiber-predominant axonal loss in sural nerve specimens was characteristic of ALN, especially with a short history of neuropathy; long history was associated with regenerating small fibers. Large-fiber-predominant axonal loss predominated in TDN. Subperineurial edema was more prominent in TDN, whereas segmental de/remyelination resulting from widening of consecutive nodes of Ranvier was more frequent in ALN. Myelin irregularity was greater in ALN. ALN-TD showed a variable mixture of these features in ALN and TDN. We concluded that pure-form of alcoholic neuropathy (ALN) was distinct from pure-form of thiamine-deficiency neuropathy (TDN), supporting the view that alcoholic neuropathy can be caused by direct toxic effect of ethanol or its metabolites. However, features of alcoholic neuropathy is influenced by concomitant thiamine-deficiency state, having so far caused the obscure clinicopathological entity of alcoholic neuropathy.

Ann Neurol 2003;54:19–29

Despite the common occurrence of polyneuropathy associated with chronic alcoholism, its pathogenesis and clinical features are incompletely understood. The relationships of alcoholic neuropathy to commonly associated nutritional deficiencies, especially of thiamine, so-called beriberi neuropathy, have been discussed in terms of apparent clinical and pathological resemblances,[1–3] but clinicopathological features of these neuropathies initially were studied before precise evaluation of thiamine status was possible, leading to confusion. The frequent occurrence of thiamine deficiency together with chronic alcoholism[4] therefore has obscured the picture of alcoholic neuropathy. Clinically, sensory disturbance and weakness, especially in the distal part of the lower extremities, are common features of both alcoholic and thiamine-deficiency neuropathies.[2,5,6] Electrophysiological and histopathological findings of axonal neuropathy also have been considered as a common feature.[7–11] These similarities led to a belief that these conditions were identical, and that polyneuropathy associated with chronic alcoholism most likely was caused by thiamine deficiency.[2,3] Other investigators, however, emphasized differences between these neuropathies in terms of sensory symptoms, particularly painful paresthesias.[12] In previous reports, diagnosis of these neuropathies was mostly made according to dietary history, particularly amount of alcohol intake, as well as clinical manifestations. Reliable assessment of thiamine status still awaited availability of high-performance liquid chromatography in the 1980s.[13–15] More recent studies in both animals and humans suggested a direct neurotoxic effect of ethanol or its metabolites.[16–18] We previously reported painful alcoholic polyneuropathy with normal thiamine status and

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Published online May 14, 2003, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.10550

proposed that neuropathy can occur as a result of a direct toxic effect on peripheral nerves in patients with chronic alcoholism but no thiamine deficiency.[19]

In this study, we compared clinicopathological features of neuropathies associated with chronic alcoholism and thiamine deficiency in a series of consecutive patients who underwent careful determination of thiamine status and assessment of daily alcohol consumption to assess whether neuropathies caused by ethanol and thiamine deficiency were identical, and how thiamine deficiency was related to alcoholic neuropathy.

Patients and Methods

Patients

Consecutive patients with neuropathy who were referred to Nagoya University Hospital and its affiliated institutions between 1990 to 2002 and fulfilled the following criteria were included. Patients were assigned to one of three groups according to cause of neuropathy: pure alcoholic neuropathy without thiamine deficiency (ALN), alcoholic neuropathy with thiamine deficiency (ALN-TD), or pure, nonalcoholic thiamine-deficiency neuropathy (TDN). All patients with "alcoholic neuropathy" (ALN or ALN-TD) had chronic alcoholism, defined by regular intake of more than 100gm of ethanol daily for at least 10 years before onset of neuropathic symptoms. Individuals with lesser but daily consumption of alcohol were excluded from the TDN group. Four subjects not excluded had only occasional intake of alcohol, not exceeding 20gm per occasion. The remaining patients in the TDN group were total abstainers. The ALN group consisted of 36 men ranging from 31 to 70 years of age (mean ± standard deviation [SD], 50.7 ± 10.0); the ALN-TD group, 23 men and 5 women ranging from 27 to 68 years of age (mean ± SD, 51.1 ± 11.2); and the TDN group, 26 men and 6 women ranging from 18 to 81 years of age (mean ± SD, 54.5 ± 15.5; see Table 1). Causes of thiamine deficiency in patients with TDN were dietary imbalance in 12 patients and previous gastrointestinal surgery to treat ulcer or neoplasm in 20 patients.[20–22] Clinicopathological features of 17 patients in the TDN group who had undergone gastrectomy have been reported previously.[22] Of 28 patients in the ALN-TD group, 10 had a history of gastrectomy. Patients who had undergone operations to treat morbid obesity were excluded. A detailed history was obtained from each patient as well as their families concerning lifestyle, occupation, diet, and amount of daily consumption of alcohol. All patients underwent clinical and neurological assessment, routine blood and urine studies, blood thiamine determinations, cranial magnetic resonance imaging or computed tomography, and nerve conduction studies. Sural nerve biopsies were performed in 66 of 96 patients. A major manifestation of thiamine deficiency apart from peripheral neuropathy, Wernicke's encephalopathy, had occurred in 32 and 22% of patients in the ALN-TD and TDN groups, respectively. In the ALN group, no patients manifested this syndrome. Signs of heart failure possibly related to thiamine deficiency (cardiomegaly evident from chest radiographs, or pitting edema in the distal lower limbs) were observed in 50 and 69% of patients in the ALN-TD and TDN groups but no ALN patients. Patients with diabetic neuropathy, chronic inflammatory demyelinating polyneuropathy, Guillain–Barré syndrome, familial amyloid polyneuropathy, or other neuropathies unrelated to alcohol or thiamine deficiency were excluded. Patients' functional status was assessed at the peak phase according to modified Rankin score.[23]

Results of the various assessments in the three neuropathy groups defined above are described in the following order to facilitate comprehension: ALN, TDN, and ALN-TD.

Assessment of Thiamine Status

Thiamine status was determined at the time of the first referral to the hospital in all patients as previously described.[19,22] No patient had received thiamine at the time of

Table 1. Backgrounds of the Patients with Alcoholic Neuropathy and Nonalcoholic Thiamine-Deficiency Neuropathy

Characteristic	Alcoholic Neuropathy		Nonalcoholic Thiamine-Deficiency Neuropathy, n = 32 (%)
	Without Thiamine Deficiency, n = 36 (%)	With Thiamine Deficiency, n = 28 (%)	
Age (yr)	50.7 ± 10.0	51.1 ± 11.2	54.5 ± 15.5
Men/women	36/0	23/5	26/6
Duration of neuropathic symptoms (mo), mean ± SD	26.1 ± 39.3	16.5 ± 32.3	11.4 ± 23.5
Gastrointestinal tract operation			
Gastrectomy	0 (0)	10 (36)	18 (56)
Others	0 (0)	0 (0)	2 (6)
Associated symptoms			
Wernicke's encephalopathy	0 (0)	9 (32)	7 (22)
Heart failure	0 (0)	14 (50)	22 (69)
Total thaimine concentration (ng/ml), mean ± SD	38.5 ± 12.0	12.6 ± 4.0	11.0 ± 4.3

Normal values for whole-blood concentration of total thiamine were established in 100 normal volunteers (mean age ± SD, 29.7 ± 5.0 yr; male/female ratio, 50:50).
Normal thiamine concentration (mean ± 2 SD for normal control) is 20–50ng/ml.

SD = standard deviation.

this determination. Thiamine concentrations were measured by high-performance liquid chromatography as described previously.[13–15] Normal thiamine status was defined by a whole-blood concentration of total thiamine between 20 and 50ng/ml (the mean ± 2 SD for normal control subjects) and normal erythrocyte transketolase activity (between 123.8 and 206.2U/L, representing the mean ± 2 SD for normal controls). Thiamine deficiency was defined as total thiamine concentrations in whole blood below 20ng/ml and decreased erythrocyte transketolase activity less than 123.8U/L. Normal values for total thiamine concentration were established in 100 normal volunteers.[19,22] Normal values for erythrocyte transketolase activity were adopted from previous report.[24]

Electrophysiological Assessment

Motor and sensory conduction was measured in the median, ulnar, tibial, and sural nerves in all patients during their initial clinical assessment at the hospital, using a standard method with surface electrodes for stimulation and recording.[25,26]

Pathological Assessment of Sural Nerve Specimens

Sural nerve biopsy was performed in 29 patients with ALN, 18 patients with ALN-TD, and 19 patients with nonalcoholic thiamine-deficiency neuropathy, as described previously,[27–31] in most cases biopsy was performed before administration of thiamine. Informed consent was obtained beforehand. Specimens were divided into two portions. The first of these was fixed in 2.5% glutaraldehyde in 0.125M cacodylate buffer (pH 7.4) and embedded in epoxy resin for morphometric and ultrastructural study. Density of myelinated fibers was assessed in toluidine blue–stained semithin sections using a computer-assisted image analyzer (Luzex FS; Nikon, Tokyo, Japan), and densities of small and large myelinated fibers were calculated as described previously.[28–31] The extent of subperineurial edema was assessed by measuring total endoneurial area surrounded by perineurial cells and also determining endoneurial area after subtracting the increased subperineurial space representing edema. The latter then was subtracted from the former by the image analysis system.[22,32] Clusters of two or more small myelinated fibers enclosed by one basement membrane were designated as an instance of axonal sprouting.[19,33] Numbers of axonal sprouting were estimated as those of myelinated fibers. Cases with more than 5% of regenerating myelinated fibers (fibers which constitute axonal sprouting) in the total myelinated fibers were designated to be abundant with regenerating fibers.

For electron microscopic study, epoxy resin–embedded specimens were cut into ultrathin transverse sections and stained with uranyl acetate and lead citrate. To assess the density of unmyelinated fibers, we took electron microscopic photographs at a magnification of ×4,000 in a random fashion to cover the area of ultrathin sections as described previously.[28,30,31] Density of unmyelinated fibers was estimated from these electron micrographs. For determination of G-ratios (axon diameter/fiber diameter),[34] electron micrographs of up to 200 randomly selected fibers photographed at a magnification of ×8,000 were used. Numbers of neurofilaments were counted in systematically sampled squares of an overlying transparency placed upon the electron microscopic photographs at a final magnification of ×50,000. The first square was selected using a random table, and subsequent squares were sampled systematically. At least 30% of the axon area was counted, including subaxolemmal and central regions. At least 30 fibers were examined to calculate the mean density of neurofilaments in each case. Cases with abundant regenerating fibers were excluded for determination of the mean G-ratio and neurofilament density. Control values for G-ratio and neurofilament density were obtained from nine normal controls

A fraction of the glutaraldehyde-fixed sample was processed for teased-fiber study, in which at least 100 single fibers were isolated; their pathological condition was assessed microscopically according to criteria described previously.[28,35,36]

The second portion of the specimen was fixed in 10% formalin solution and embedded in paraffin. Sections were cut by routine methods and stained with hematoxylin and eosin as well as by the Klüver–Barrera and Masson trichrome methods.

Statistical Analyses

Quantitative data were presented as the mean ± SD and compared with previously described control values.[19,22,28,32] Statistical analyses were performed using the χ^2 test or the Mann–Whitney *U* test as appropriate. *p* values less than 0.05 were considered to indicate significance.

Results

Alcoholic Neuropathy without Thiamine Deficiency

All patients in this group, as well as in the other two groups, showed symmetric polyneuropathy with greater involvement of the lower than upper limbs. The initial symptom of neuropathy was pain or a painful burning sensation in the toes and/or ankle in all patients (see Table 2). This symptom gradually ascended to include the proximal part of the lower extremities, and occasionally to the lower trunk. In severely affected patients, the distal part of the upper limbs also were involved. Progression was mostly slow, occurring over months to years. Nineteen patients (53%) showed weakness in the lower extremities but with a sensory-dominant pattern; the remaining 17 patients (47%) showed a pure sensory pattern without any weakness in the limbs. Weakness in the upper extremities was seen in six patients (17%). Sensory disturbance was present in the lower limbs in all patients and also present in the upper limbs and trunk in 17 (47%) and 7 (19%) of patients, respectively. Almost all patients (97%) reported a painful sensation in the affected limbs and/or trunk. As for the modalities of sensation affected, loss of superficial sensation, particularly nociception, was predominant. Yet, involvement of all sensory modalities was seen in severely affected patients. Biceps, patellar, and Achilles tendon reflexes were reduced or absent in 10 patients (28%), 17 (47%), and 31 (86%),

Table 2. Neuropathic Symptoms of the Alcoholic Neuropathy and Nonalcoholic Thiamine-Deficiency Neuropathy

	Alcoholic Neuropathy			*p*		
	1. Without Thiamine Deficiency, n = 36 (%)	2. With Thiamine Deficiency, n = 28 (%)	3. Nonalcoholic Thiamine-Deficiency Neuropathy, n = 32 (%)	1 vs 2	2 vs 3	1 vs 3
Initial symptom						
Sensory disturbance	36 (100)	16 (57)	16 (50)	<0.0001	NS	<0.0001
Muscle weakness	0 (0)	12 (43)	16 (50)			
Progression						
<1 mo	2 (6)	11 (39)	18 (56)	0.0006	NS	0.001
1 mo to 1 yr	18 (50)	4 (14)	8 (25)			
>1 yr	16 (44)	13 (46)	6 (19)			
Type						
Motor-dominant	0 (0)	15 (54)	27 (84)	<0.0001	0.02	<0.0001
Sensory-dominant	19 (53)	11 (39)	3 (9)			
Pure sensory	17 (47)	2 (7)	2 (6)			
Presence of weakness						
Upper limbs	6 (17)	14 (50)	26 (81)	0.004	0.01	<0.0001
Lower limbs	19 (53)	26 (93)	30 (94)	0.0002	NS	<0.0001
Presence of sensory disturbance						
Upper limbs	17 (47)	19 (68)	25 (78)	NS	NS	0.03
Trunk	7 (19)	7 (25)	9 (28)	NS	NS	NS
Lower limbs	36 (100)	28 (100)	32 (100)	NS	NS	NS
Painful sensation	35 (97)	16 (57)	7 (22)	0.0001	0.005	<0.0001
Modality of sensory deficit						
Superficial sensation-dominant	22 (61)	7 (25)	3 (9)	0.005	NS	<0.0001
All modalities	13 (36)	15 (54)	20 (63)			
Deep sensation-dominant	1 (3)	6 (21)	9 (28)			
Deep tendon reflexes						
Biceps; reduced or absent	10 (28)	13 (46)	26 (81)	NS	0.005	<0.0001
Patellar; reduced or absent	17 (47)	23 (82)	29 (91)	0.004	NS	0.0001
Achilles; reduced or absent	31 (86)	28 (100)	32 (100)	0.04	NS	0.03
Functional status						
Unable to walk	9 (25)	15 (54)	27 (84)	0.02	0.009	<0.0001
Able to walk	27 (75)	13 (46)	5 (16)			
Modified Rankin score	2.1 ± 0.6	2.8 ± 0.9	3.6 ± 1.0	0.04	0.003	<0.0001

Patients' functional status was assessed at the peak phase according to modified Rankin score.[23] 0, asymptomatic; 1, nondisabling symptoms not interfering with lifestyle; 2, minor disability from symptoms leading to some restriction of lifestyle but not interfering with patients' capacity to look after themselves; 3, moderate disability from symptoms significantly interfering with lifestyle or preventing totally independent existence; 4, moderately severe disability from symptoms clearly precluding independent existence, though not requiring 24-hour attention from a caregiver; and 5, severe disability and total dependence, requiring constant attention day and night.

NS = not significant.

respectively. Plantar responses were flexor in all patients. Autonomic symptoms including urinary retention, constipation, impaired sweating, and orthostatic hypotension were not prominent in patients of this group. In all patients, sensory disturbance compromised activities of daily living significantly, but 27 patients (75%) could walk unaided at the time of first referral to the hospital. Functional status determined by the modified Rankin score was 2.1 ± 0.6.

Nerve conduction studies showed more profound abnormalities in the lower than upper limbs (see Table 3). Moderate reduction of compound muscle action potentials (CMAPs) in the tibial nerves and severe reduction of sensory nerve action potentials in the sural nerves were seen. In contrast, CMAPs in the median nerves were relatively preserved, and sensory nerve action potentials in the median nerves were only moderately decreased. Mild to moderate slowing of motor nerve conduction velocity in the median and tibial nerves and of sensory nerve conduction velocities in the median and sural nerves also was observed. Distal latencies in the median and tibial nerves also were mildly prolonged.

Myelinated fiber density in the sural nerve was significantly reduced (see Table 4). Densities of large myelinated fibers were 1307 ± 864 fibers/mm^2 (43% of normal control); those of small myelinated fibers were 1381 ± 1278 fibers/mm^2 (27% of normal control). In

Table 3. Nerve Conduction Studies, Mean ± SD

	Alcoholic Neuropathy						
	1. Without Thiamine Deficiency, n = 36	2. With Thiamine Deficiency, n = 28	3. Nonalcoholic Thiamine-Deficiency Neuropathy, n = 32	*p* 1 vs 2	*p* 2 vs 3	*p* 1 vs 3	Controls (n = 121 ~ 191)
Median nerve							
MCV (m/sec)	51.2 ± 4.7[a]	50.4 ± 5.2[a]	52.3 ± 5.9[a]	NS	NS	NS	57.8 ± 3.7
DL (msec)	4.2 ± 0.7[a]	4.0 ± 0.6[a]	3.6 ± 0.6	NS	0.02	0.005	3.4 ± 0.4
CMAP (mV)	8.4 ± 4.2[b]	8.7 ± 5.0[a]	6.7 ± 4.5[a]	NS	NS	NS	10.7 ± 3.5
Not elicited	None	None	None				
SCV (m/sec)	48.0 ± 7.2[a]	46.9 ± 8.4[a]	47.9 ± 9.3[a]	NS	NS	NS	57.8 ± 4.7
SNAP (μV)	8.7 ± 6.4[a]	6.8 ± 4.9[a]	7.8 ± 8.4[a]	NS	NS	NS	23.5 ± 8.4
Not elicited	2 cases (6%)	1 case (4%)	8 cases (25%)				
Tibial nerve							
MCV (m/sec)	40.6 ± 4.2[a]	40.8 ± 5.6[a]	42.8 ± 4.5[a]	NS	NS	NS	46.9 ± 3.5
DL (msec)	5.3 ± 0.8[a]	5.3 ± 1.8[c]	4.9 ± 1.0[c]	NS	NS	NS	4.5 ± 0.8
CMAPs (mV)	4.6 ± 3.5[a]	5.4 ± 5.1[a]	2.6 ± 2.4[a]	NS	0.045	0.002	10.9 ± 3.8
Not elicited	None	3 cases (11%)	3 cases (10%)				
Sural nerve							
SCV (m/sec)	38.8 ± 6.9[a]	40.5 ± 6.3[a]	41.0 ± 11.8[c]	NS	NS	NS	51.0 ± 5.1
SNAP (μV)	2.4 ± 3.3[a]	1.5 ± 2.3[a]	2.0 ± 3.5[a]	NS	NS	NS	11.5 ± 4.7
Not elicited	14 cases (39%)	17 cases (61%)	21 cases (66%)				

[a] $p < 0.001$, [b] $p < 0.005$, and [c] $p < 0.05$ (Mann–Whitney *U* test) for the control values.

SD = standard deviation; MCV = motor nerve conduction velocity; DL = distal latency; CMAP = compound muscle action potential; SCV = sensory nerve conduction velocity; SNAP = sensory nerve action potential; NS = not significant.
Control values are based on previously published reports.[19,22]

Table 4. Pathology of the Sural Nerves, Mean ± SD

	Alcoholic Neuropathy						
	1. Without Thiamine Deficiency, n = 29	2. With Thiamine Deficiency, n = 18	3. Nonalcoholic Thiamine-Deficiency Neuropathy, n = 19	*p* 1 vs 2	*p* 2 vs 3	*p* 1 vs 3	Controls (n = 9)
Total MFD (no./mm^2)	2,687 ± 1,875[a]	2,727 ± 1,649[a]	2,367 ± 1,868[a]	NS	NS	NS	8,190 ± 511
Large MFD (no./mm^2)	1,307 ± 864[a]	928 ± 764[a]	663 ± 693[a]	NS	NS	0.005	3,068 ± 294
Small MFD (no./mm^2)	1,381 ± 1,278[a]	1,800 ± 1,245[a]	1,704 ± 1,310[a]	NS	NS	NS	5,122 ± 438
Axonal sprouting (no./mm^2)	137.6 ± 264.8	157.3 ± 271.4	2.8 ± 9.5	NS	0.01	0.046	
Small/large							
All cases	1.8 ± 2.9 (n = 29)	4.4 ± 8.0 (n = 18)	13.6 ± 27.0 (n = 19)	NS	0.02	<0.0001	1.7 ± 0.2
Cases with abundant RMFs are excluded	0.7 ± 0.3[a] (n = 20)	4.7 ± 9.6 (n = 12)	13.6 ± 27.0 (n = 19)	0.03	0.02	<0.0001	1.7 ± 0.2
G-ratio	0.58 ± 0.07[a]	0.54 ± 0.06[a]	0.56 ± 0.06[a]	NS	NS	NS	0.73 ± 0.03
Neurofilamant density (no./μm^2)	187.0 ± 44.1[a]	188.2 ± 41.2[a]	193.5 ± 43.8[a]	NS	NS	NS	108.3 ± 25.9
UMFD (no./mm^2)	7,029 ± 4,153[a]	11,194 ± 4,386[a]	10,585 ± 4,867[a]	0.004	NS	0.006	29,913 ± 3,457
Subperineurial edema (%)	6.6 ± 2.9[b]	7.3 ± 4.2[c]	10.3 ± 4.5[a]	NS	0.02	0.002	4.6 ± 1.0
Teased fiber study							
Myelin irregularity (%)	17.3 ± 11.3	9.2 ± 7.7	5.7 ± 5.2	0.01	NS	0.0003	
De/remyelination (%)	9.0 ± 5.2	10.3 ± 8.2	3.4 ± 4.8	NS	0.003	0.001	9.5 ± 8.8
Axonal degeneration (%)	30.9 ± 19.7[a]	45.3 ± 30.7[a]	57.8 ± 25.3[a]	NS	NS	0.001	1.7 ± 1.4

[a] $p < 0.001$, [b] $p < 0.005$, and [c] $p < 0.05$ (Mann–Whitney *U* test) for the control values.

SD = standard deviation; MFD = myelinated fiber density; small/large = ratio of small myelinated fibers to large myelinated fibers; UMFD = unmyelinated fiber density; RMFs = regenerating myelinated fibers, NS = not significant.
Cases with abundant regenerating fibers were excluded for determination of the mean *G*-ratio and neurofilament density.
Control values are based on previously published reports,[28,32] and control values for *G*-ratio and neurofilament density are obtained from nine normal volunteers.

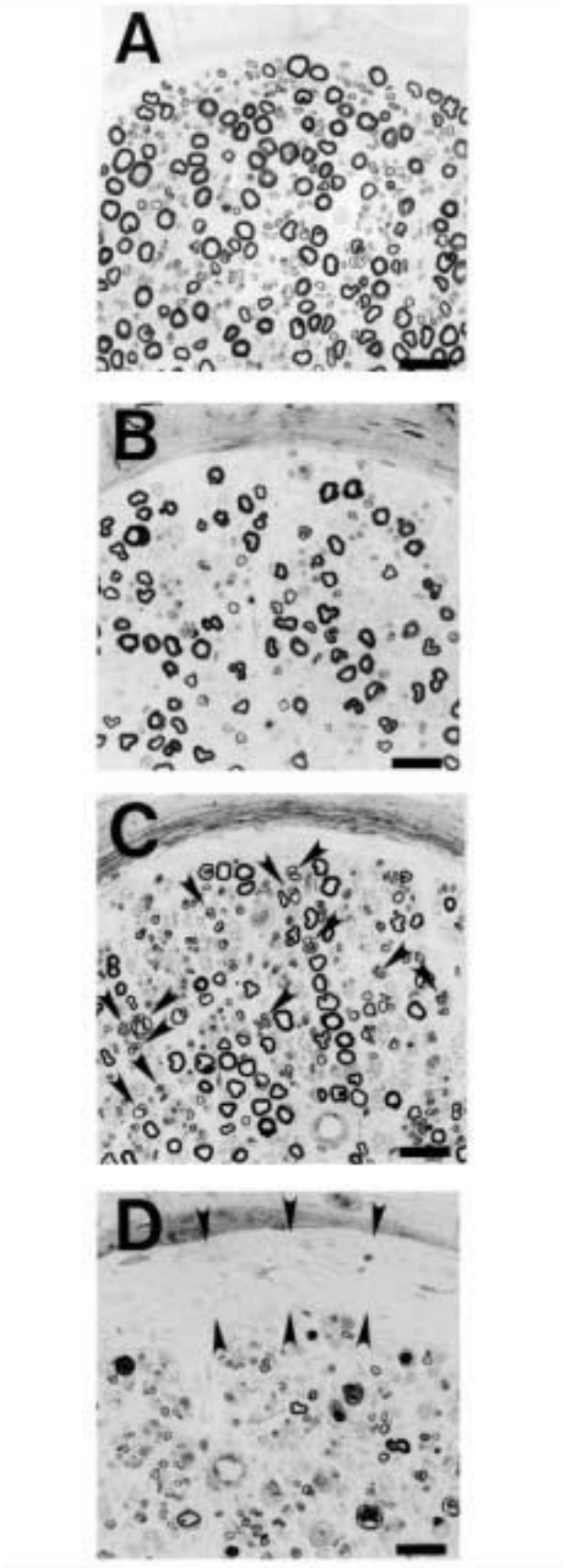
nine cases (31%) axonal sprouting was abundant (more than 5% of regenerating fibers in the total myelinated fibers; see Fig 1C). The duration of neuropathic symptoms of these nine cases was extremely long (70.5 ± 49.5 months), and the regenerating myelinated fibers increased the proportion of small myelinated fibers (small/large, 4.3 ± 4.4; control, 1.7 ± 0.2). In the remaining 20 cases (69%), duration of neuropathic symptoms was much shorter (9.7 ± 11.6 months). Reduction of small myelinated fibers in these 20 cases was more profound than reduction of large myelinated fibers (small/large, 0.7 ± 0.3), hence small-fiber-predominant loss was clearly evident (see Figs 1B and 2). Axonal shrinkage with increased neurofilament density accompanied by a redundant loop of myelin was observed in some myelinated fibers. Decreased G-ratio (0.58 ± 0.07; control, 0.73 ± 0.03) and increased neurofilament density (187.0 ± 44.1 filaments/μm^2; control, 108.3 ± 25.9) indicated axonal atrophy. Reduction of unmyelinated fiber density also was profound (7029 ± 4153 fibers/mm^2). Clusters of small unmyelinated fibers, suggestive of regenerating fibers, were seen in cases with abundant axonal sprouting of myelinated fibers. Varying degrees of subperineurial edema was seen. In teased-fiber preparations, the frequency of axonal degeneration was prominent (30.9 ± 19.7%), and myelin irregularity was conspicuous in the remaining fibers (17.3 ± 11.3%). The proportion of segmental de/remyelination was 9.0 ± 5.2%. This demyelination consisted of widening of consecutive nodes of Ranvier resulting from attenuation of the internodes of the myelin sheath (see Fig 3).

Nonalcoholic Thiamine Deficiency Neuropathy

All patients manifested symmetric polyneuropathy with more involvement in the lower than upper limbs, showing a centripetal pattern of progression. The initial symptom of neuropathy was variable, in contrast with alcoholic neuropathy without thiamine deficiency (ALN); this was weakness in the lower extremities in 16 patients (50%) and numbness in the distal lower limbs in 16 patients (50%; see Table 2). Progression rate also varied; acute progression within 1 month was seen in 18 patients (56%), whereas slow progression over more than 1 year was seen in 6 patients (19%). On average, progression was more rapid than in ALN ($p = 0.001$). Impairment usually was motor dominant, as in 27 patients (84%), which contrasted to the sensory-dominant pattern characteristic of ALN. Some patients whose motor weakness progressed over days initially were thought to have Guillain–Barré syndrome. Motor symptoms were more predominant in the lower than upper extremities; even so, 26 patients (81%) showed weakness in the upper limbs. Sensory disturbance was present in the lower limbs in all patients and also was present in the upper limbs and trunk in 25 patients (78%) and 9 patients (28%), respectively. Varying degrees of numbness with or without painful sensations were noted in all patients, but painful sensations were reported by only 7 patients (22%). Involvement of all sensory modalities was a common feature in TDN, in contrast with predominant affection of nociception in ALN; superficial sensation was most affected in only 3 patients (9%), deep sensation was most involved in 9 patients (28%), and both modalities were equally affected in 20 patients (63%). Biceps, patellar, and Achilles tendon reflexes were reduced or absent in most patients. Plantar responses were flexor in all patients. Autonomic symptoms were absent or only mildly present in most patients, but six patients who had severe thiamine deficiency manifested flaccid bladder requiring urethral catheterization or severe intestinal gas retention that mimicked ileus. Activities of daily living were significantly more impaired than in ALN ($p < 0.0001$) mainly because of rapid progression of muscle weakness. Only five patients (16%) could walk unaided at the time of initial examination. Functional status determined by modified Rankin score was 3.6 ± 1.0.

Findings of nerve conduction studies were similar to those in ALN (see Table 3). Only distal latency of the median nerve was significantly prolonged ($p = 0.005$), whereas CMAPs in the tibial nerves were significantly smaller ($p = 0.002$) in ALN than in TDN.

Myelinated fiber density was significantly reduced (see Table 4). Reduction of large meylinated fibers was greater than in ALN ($p = 0.005$). Densities of large myelinated fibers were 663 ± 693 fibers/mm^2 (22% of normal control), whereas those of small myelinated fibers were 1704 ± 1310 fibers/mm^2 (33% of normal control). The mean ratio of small to large myelinated fibers was 13.6 ± 27.0 (control, 1.7 ± 0.2), significantly higher than in ALN ($p < 0.0001$). Axonal sprouting was scarce in all cases. In contrast with ALN, all cases showed more loss of large myelinated fibers than loss of small mylinated fibers except one (see Figs 1D and 2). The mean G-ratio was 0.56 ± 0.06 (control, 0.73 ± 0.03) and the density of neurofilaments was 193.5 ± 43.8 filaments/μm^2 (control, 108.3 ± 25.9), not differing significantly from those in ALN. Reduction of unmyelinated fibers also was seen but was less profound than in ALN ($p = 0.006$). Regeneration of unmyelinated fibers was scarce. Subperineurial edema was more severe than in ALN ($p = 0.002$). In teased-fiber preparations, significantly more axonal degeneration was seen than in ALN ($p = 0.001$). The proportion of fibers showing segmental de/remyelination was small compared to ALN ($p = 0.001$). Myelin irregularity was observed in 5.7 ± 5.2% of fibers, significantly less often than in ALN ($p = 0.0003$).



Alcoholic Neuropathy with Thiamine Deficiency

Neuropathic symptoms in alcoholic neuropathy with thiamine deficiency (ALN-TD) were variable, showing characteristics of both ALN and TDN (see Table 2). The initial symptom was numbness or painful paresthesias in the lower limbs in 16 patients (57%) but was weakness in 12 others (43%). Progression varied from acute (within 1 month) in 11 patients (39%) to chronic (occurring over 1 year) in 13 (46%). Relative degrees of motor and sensory deficits also were variable; 15 patients (54%) showed a motor-dominant pattern, whereas the remaining 13 (46%) showed a sensory-dominant or purely sensory pattern. Muscle weakness was present in the lower limbs in 26 patients (93%) and in the upper limbs in 14 (50%). Sensory disturbance was present in the lower extremities in all patients extending to the trunk and distal portion of the upper extremities in 7 patients (25%) and 19 patients (68%), respectively. Painful paresthesias were reported by 16 patients (57%), significantly less often than in ALN ($p = 0.005$). Modaliy of sensory deficit also was variable; superficial and deep sensations were affected equally in 15 patients (54%), deep sensation predominated slightly in 6 (21%), and predominant involvement of nociception associated with painful paresthesias as in ALN was seen in 7 (25%). Deep tendon reflexes were reduced in the biceps, patellar, and Achilles tendons in 13 patients (46%), 23 (82%), and 28 (100%), respectively. Plantar responses were flexor in all patients. The modified Rankin score was 2.8 ± 0.9, intermediate between ALN and TDN scores.

Findings of nerve conduction studies were similar to those in ALN and TDN (see Table 3).

Sural nerve biopsy specimen findings also were variable occupying a range between ALN and TDN (see Table 4). Densities of large myelinated fibers were 928 ± 764 fibers/mm^2 (30% of normal control) and those of small myelinated fibers were $1{,}800 \pm 1{,}245$ fibers/mm^2 (35% of normal control). The mean ratio of small to large myelinated fibers was 4.4 ± 8.0,

Fig 1. Light microscopic observations of the sural nerve. (A) Transverse section of a sural nerve specimen from a control case. (B) A specimen from a patient with a 4-month history of alcoholic neuropathy without thiamine deficiency. Small myelinated fibers show more loss than large myelinated fibers. Subperineurial edema is slight. (C) A specimen from a patient with a 5-year history of alcoholic neuropathy without thiamine deficiency does not show small-fiber-predominant axon loss as in B, because of the presence of abundant axonal sprouting (arrowheads)*, which indicates regeneration of axons. (D) A specimen from a patient with nonalcoholic thiamine-deficiency neuropathy. In contrast with B, large myelinated fibers show more loss than small myelinated fibers, although both types of myelinated fibers are significantly reduced. Subperineurial edema is marked (between* arrowheads*). Bar = 30μm.*

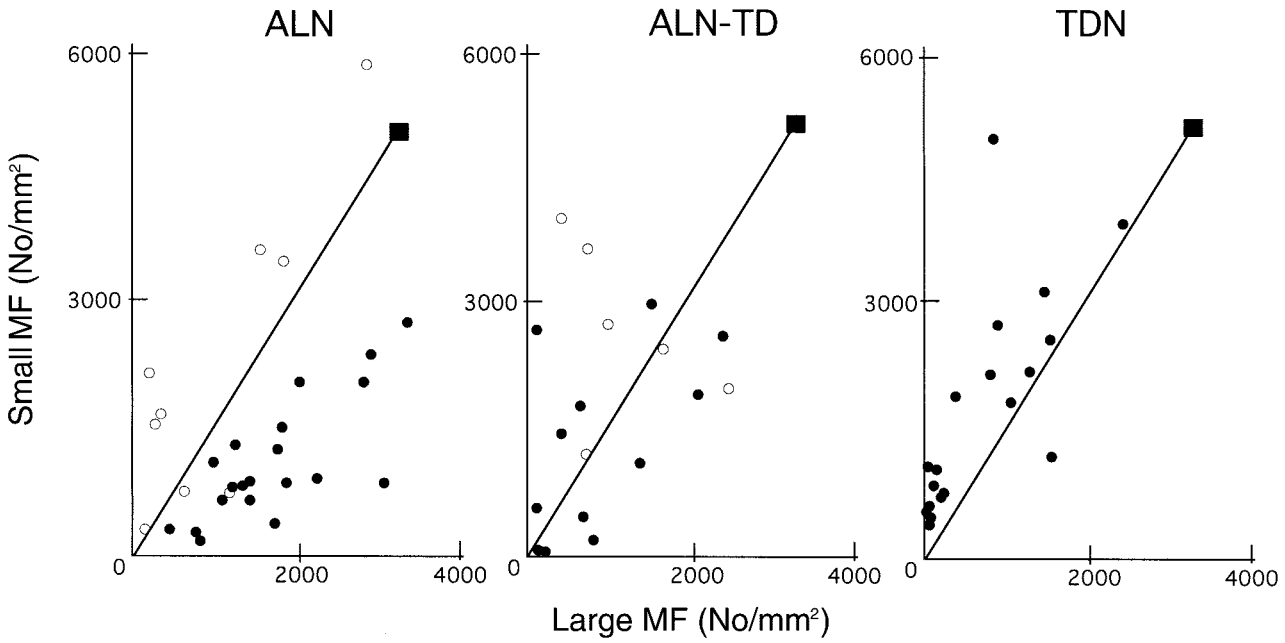


Fig 2. Relationships between large and small myelinated fibers. Boldface lines represent the normal ratio of small to large myelinated fibers (small/large = 1.7). Black boxes indicate the mean value in control cases. Circles located below the boldface lines indicate predominance of large myelinated fibers, whereas those above the boldface lines indicate predominance of small myelinated fibers. Black circles represent cases with few regenerating myelinated fibers (<5% of total myelinated fibers), whereas white circles represent cases with abundant regenerating myelinated fibers (> 5% of total myelinated fibers). Abundant regeneration of myelinated fibers increase the number of small myelinated fibers. In the pure alcoholic neuropathy (ALN) group, all cases with few regenerating fibers showed predominance of large myelinated fibers, reflecting predominantly small-fiber loss; all except one nonalcoholic thiamine-deficiency neuropathy (TDN) cases showed predominance of small myelinated fibers, reflecting predominantly large-fiber loss.

which was intermediate between ratios in ALN and TDN. Axonal sprouting was abundant in six cases (33%). The proportions of large and small myelinated fibers were highly variable between cases (see Fig 2). The mean G-ratio was 0.54 ± 0.06 and the density of neurofilaments was 188.2 ± 41.2 filaments/μm^2, not differing significantly from those in ALN or TDN. In teased-fiber preparations, the frequency of axonal degeneration was 45.3 ± 30.7%. Myelin irregularity was conspicuous in the remaining fibers (9.2 ± 7.7%). The proportion of segmental de/re-myelination was 10.3 ± 8.2%. Values for the teased-fiber preparations were intermediate between the range of ALN and TDN.

Discussion

The pathogenesis of alcoholic neuropathy, especially its relationship to thiamine deficiency, has remained unclear. Recent studies indicated a direct neurotoxic effect of ethanol or its metabolites, involving ethanol-induced glutamate neruotoxicity,[18,37] decreased production of neurofilament protein or its phosphorylated form,[38,39] or impairment of fast axonal transport.[40] Axonal degeneration has been documented in animals receiving ethanol while maintaining normal thiamine status.[41] Human studies also have suggested a direct toxic effect, because a dose-dependent relationship has been observed between severity of neuropathy and amount of ethanol consumed.[17] In addition to this direct toxic effect, thiamine deficiency is closely related to chronic alcoholism[4] and also can induce neuropathy in alcoholic patients. Ethanol diminishes thiamine absorption in the intestine and reduces hepatic stores of thiamine.[42,43] Ethanol also decreases phosphorylation of thiamine, reducing availability of the active form of the vitamin.[44–46] In addition, patients with chronic alcoholism tend to have dietary imbalance. These relationships make chronic alcoholism a risk factor for thiamine-deficiency neuropathy.

Clinicopathological features of alcoholic neuropathy have remained obscure despite its wide prevalence, in large part because of incomplete differentiation from beriberi neuropathy. Although sometimes attributed to inadequate nutritional assessment in reported cases, technical limitations of thiamine status assessment contributed greatly to the problem. Only in the 1960s were assays of erythrocyte transketolase activity intro-

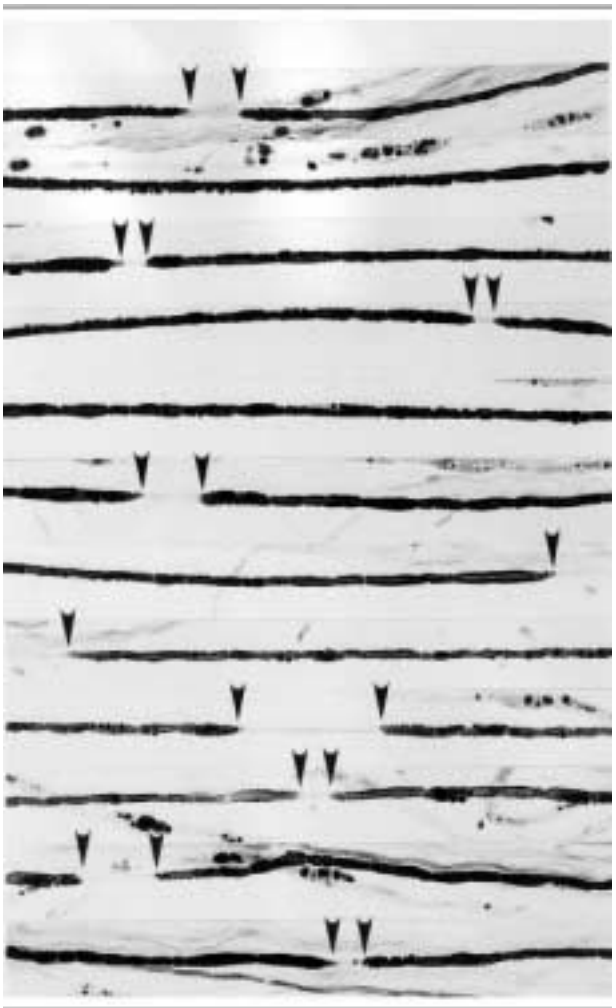


Fig 3. Consecutive portions along the length of a single teased fiber from a patient with alcoholic neuropathy. Note marked irregularity of myelin. Segmental demyelination has resulted from widening of consecutive nodes of Ranvier (arrowheads).

duced,[47] and this method assesses thiamine only indirectly. In the 1980s, a direct, highly sensitive, and convenient high-performance liquid chromatographic assay for thiamine became widely available.[13–15] When we assess clinicopathological features of "alcoholic neuropathy," both direct toxicity of ethanol or its metabolites and concomitant effects of thiamine deficiency need to be considered. In addition, clinicopathological features of pure thiamine-deficiency neuropathy need to be studied in nondrinkers.

In this study, we divided consecutively recruited patients with "alcoholic neuropathy" into two groups based on thiamine status. Alcoholic neuropathy without thiamine deficiency (ALN) was considered to be attributable solely to direct toxicity of ethanol or ethanol metabolites. Characteristics of ALN-TD were considered to reflect combined cause of ethanol toxicity and thiamine deficiency. On the other hand, patients with nonalcoholic (ie, "pure") thiamine-deficiency neuropathy (TDN), identical to previously reported "beriberi neuropathy," were assessed for comparison. We thus were able to differentiate the distinct clinicopathological features of the individual neuropathies and confirm that effects of thiamine deficiency can modify the features of ALN.

As for clinical features, ALN in our series uniformly showed slowly progressive, sensory-dominant symptoms. Painful paresthesias were major complaints and that often limited daily activities in these patients. In pure TDN, in contrast, many patients manifested an acutely progressive, motor-dominant pattern leading to loss of ambulation, although variation including slow progression or sensory-dominant pattern was apparent in some patients. Clinical features of ALN-TD were particularly variable, constituting a spectrum raging from a picture of ALN to that of TDN among individual patients.

Major electrophysiological and histopathological findings in our three groups of patients indicated axonal neuropathy, in agreement with previous descriptions of both alcoholic neuropathy and beriberi neuropathy.[6–11] The electrophysiological features that we observed were similar in ALN and TDN. Like the clinical findings, these studies showed predominant lower limb involvement in both neuropathies. Lower amplitude of CMAPs in TDN than in ALN were reflected by more severe muscle weakness in TDN. Electrophysiological findings commonly associated with myelin damage (slowing of MCV and SCV as well as prolongation of DL) also were observed in patients with ALN and those with TDN, even though axonal damage was dominant histopathologically.

Sural nerve specimens showed more clear-cut differences between these neuropathies than did electrophysiological studies. ALN showed loss of mainly small fibers, less subperineurial edema, and more frequent myelin irregularity and segmental de/remyelination. In contrast, TDN showed predominantly large-fiber loss, more subperineurial edema, and less myelin irregularity and segmental de/remyelination. In ALN, small-fiber-predominant axonal loss (small-fiber axonopathy) was most evident in cases with recent onset. In long-standing cases, abundant regenerating fibers obscured some small-fiber loss. The finding of small-fiber-predominant loss was in accord with previous descriptions of painful alcoholic neuropathy.[19] Relative preservation of deep tendon reflexes in ALN reflected relative sparing of the large fibers that mediate them. ALN-TD showed an extensive range of pathology from small-fiber-predominant loss to large-fiber-predominant loss with features of both ALN and TDN. Axonal sprouting in long-standing cases and large-fiber-predominant loss in some ALN-TD cases may have

obscured the characteristic feature of small-fiber-predominant loss in ALN in some previous reports describing loss of nerve fibers throughout the entire range of fiber diameter.[7,8,10] Axonal atrophy as determined by the G-ratio and the density of neurofilaments did not differ between the three groups, but irregularity of myelin, which also indicates axonal atrophy,[48] was significantly more frequent in ALN than in TDN. Segmental de/remyelination in teased-fiber preparations also was more frequent in ALN than in TDN. This change is consisted of the widening of consecutive nodes of Ranvier. Irregularity of the myelin sheath also was seen in these fibers; so these findings are supposed to reflect axonal atrophy.[48,49] Differences in relative frequency of these changes are supposedly caused by different mechanism of axonal atrophy in ALN from TDN.

Another important characteristic of "alcoholic neuropathy" is a presence of postgastrectomy patients; 36% of ALN-TD patients but no ALN patients. This finding suggests that gastrectomy is a risk factor for thiamine deficiency in patients with chronic alcoholism and establishes thiamine deficiency as a cause of postgastrectomy polyneuropathy.[19]

In conclusion, the nature of "alcoholic neuropathy" has been unclear because of an often undetected or overestimated influence of thiamine deficiency, whereas the clinical picture of thiamine-deficiency neuropathy (ie, beriberi neuropathy) can be distorted by concomitant effects of ethanol. We compared these two neuropathies with careful consideration of interactions, confirming that the two neuropathies are clinically and pathologically distinct. Not only thiamine deficiency but also direct toxic effects of ethanol or its metabolites can cause alcoholic neuropathy. Although clinicopathological features of pure alcoholic neuropathy are remarkably uniform, extensive variation results when thiamine deficiency is present.

This study was supported by grants from the Ministry of Health and Welfare of Japan (G.S.).

We thank Drs Y. Takeuchi, M. Hirayama, and S. Mitake for the provision of clinical data.

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