# Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP

**Abstract**—To identify clinical and electrophysiologic features related to IV immunoglobulin (IVIg) responsiveness in chronic inflammatory demyelinating polyneuropathy (CIDP), the authors conducted a multicenter study on 312 patients with CIDP (199 responders and 113 nonresponders). Muscle atrophy and decreased compound muscle action potential were pronounced in nonresponders of IVIg. Male gender, longer disease duration, and slow progression of symptoms were also associated with IVIg unresponsiveness. Features suggesting axonal dysfunction in peripheral nerves indicated IVIg unresponsiveness in CIDP.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by insidious onset, chronicity with progressive or remittent clinical course, and segmental demyelination in peripheral nerves.[1] Among treatments for CIDP such as corticosteroids, plasmapheresis, and IV immunoglobulin (IVIg), IVIg is commonly used as an initial therapy because of relatively few side effects, immediate therapeutic response, and convenient administration without special equipment. However, some patients fail to show therapeutic response to IVIg,[2,3] and the features related to IVIg responsiveness are not well understood.[2-4] Thus, we investigated the clinical and electrophysiologic correlates of CIDP patients showing a good response or little or no response to IVIg.

**Methods.** We studied CIDP patients from June 2002 to April 2004 as members of the multicenter study group for hereditary neuropathy in Japan, working under the Auspices of the Ministry of Health, Labor, and Welfare of Japan. The Ethics Committee of the Nagoya University Graduate School of Medicine approved the study design in full. All patients fulfilled the diagnostic criteria established by the Ad Hoc Subcommittee of American Academy of Neurology AIDS Task Force.[1] Patients with monoclonal gammopathy of undetermined significance, anti-myelin-associated glycoprotein, and anti-sulfate-3-glucuronyl paragloboside antibodies were excluded, together with patients with severe diabetes mellitus, alcoholism, drug poisoning, hereditary neuropathy, and other diseases causing neuropathy. The subjects of the current investigation were the 312 of 372 patients initially entered, who met diagnostic and inclusion criteria and treated with IVIg (400 mg/kg/day for 5 days). The majority of the patients (90.7%) were treated initially by IVIg without any other prior therapy, whereas some patients (9.3%) who had received other treatments such as plasmapheresis or corticosteroids before IVIg were followed for >4 weeks before IVIg treatment to be sure they were not on some other form of treatment.

Clinical features including motor and sensory impairment and muscle atrophy were assessed. Weakness was estimated according to Medical Research Council criteria in proximal muscles (deltoid, biceps, and triceps muscles in upper limbs, iliopsoas and quadriceps muscles in lower limbs) as well as distal muscles (thenar, interosseous, and finger flexion muscles in upper limbs, ankle dorsiflexor and toe dorsiflexor muscles in lower limbs).[6] Activities of daily living (ADLs) involving upper limbs were evaluated according to the arm disability score of the overall disability sum score (ODSS).[7] ADLs involving lower limbs were evaluated according to the modified Rankin Scale.[8] We assessed ADLs 1 to 14 days before IVIg and reassessed then 4 to 6 weeks after IVIg for evaluation of clinical efficacy. Those patients who improved by ≥1 point in the ODSS or the modified Rankin Scale were termed responders, and those with no change, a minimal improvement of <1 point, or showing a worse score were termed nonresponders.

For electrophysiologic study, the previously described standardized method was adopted.[5,6] Motor nerve conduction was evaluated for the median, ulnar, and tibial nerves, whereas sensory nerve conduction was evaluated for median, ulnar, and sural nerves. Motor nerve conduction velocity (MCV), distal latency, compound muscle action potential (CMAP), and presence of conduction block was also assessed. Sensory nerve conduction velocity and sensory nerve action potential also were assessed. Control values were obtained from normal subjects for median (n = 191; 48.7 ± 16.5 years old), ulnar (n = 166; 48.9 ± 15.8 years old), tibial (n = 121; 49.9 ± 15.0 years old), and sural (n = 133; 50.6 ± 15.6 years old) nerves as previously described.[6] All electrophysiologic data were obtained 1 to 14 days before IVIg was started. For some patients who were assessed 4 to 6 weeks after IVIg, nerve conduction velocity findings were compared before and after IVIg.

The two-tailed Fisher exact test and Mann–Whitney *U* test were used to evaluate relative differences between responders and nonresponders and between data before and after IVIg, using

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***Table 1*** *Clinical findings*

| Clinical features and CSF | Responders | Nonresponders | *p* value* |
|---|---|---|---|
| All patients (responders: n = 199; nonresponders: n = 113) | | | |
| Age, y | 52.5 ± 18.3 | 55.5 ± 16.7 | NS |
| Sex, M/F | 1.8/1.0 | 2.9/1.0 | <0.05 |
| Duration from onset to IVIg, mo | 7.8 ± 4.0 | 9.8 ± 3.5 | <0.0005 |
| Progression after onset,† % | 45.9 | 22.9 | <0.0005 |
| MRC score,‡ 0–5 | | | |
| Upper limb, proximal | 4.1 ± 1.0 | 4.4 ± 0.9 | <0.0005 |
| Upper limb, distal | 3.5 ± 1.0 | 3.8 ± 1.2 | <0.005 |
| Lower limb, proximal | 4.0 ± 1.0 | 4.3 ± 1.1 | <0.01 |
| Lower limb, distal | 3.4 ± 1.1 | 3.3 ± 1.4 | NS |
| Muscle atrophy, % of patients | | | |
| Upper limb | 28.9 | 42.4 | <0.01 |
| Lower limb | 25.9 | 47.8 | <0.0005 |
| ADL score | | | |
| Arm disability score (ODSS) | 2.3 ± 1.5 | 1.5 ± 1.5 | <0.0001 |
| Modified Rankin Scale | 2.6 ± 1.2 | 2.2 ± 1.3 | <0.005 |
| CSF protein, mg/dL | 94 ± 71 | 132 ± 158 | NS |
| Patients with similar duration (<12 mo) (responders: n = 115; nonresponders: n = 29) | | | |
| Age, y | 52.2 ± 9.0 | 50.3 ± 18.0 | NS |
| Sex, M/F | 1.5/1.0 | 2.5/1.0 | <0.05 |
| Duration from onset to IVIg, mo | 4.5 ± 2.1 | 4.8 ± 2.2 | NS |
| Progression after onset,† % | 22.2 | 12.1 | <0.01 |
| MRC score, 0–5 | | | |
| Upper limb, proximal | 4.0 ± 1.0 | 4.4 ± 0.9 | <0.05 |
| Upper limb, distal | 3.5 ± 1.0 | 3.8 ± 1.2 | NS |
| Lower limb, proximal | 3.9 ± 1.1 | 4.2 ± 1.1 | <0.05 |
| Lower limb, distal | 3.4 ± 1.2 | 3.3 ± 1.5 | NS |
| Muscle atrophy, % of patients | | | |
| Upper limb | 20.2 | 48.9 | <0.05 |
| Lower limb | 20.4 | 48.3 | <0.01 |
| ADL score | | | |
| Arm disability score (ODSS) | 2.4 ± 1.5 | 2.0 ± 1.7 | <0.01 |
| Modified Rankin Scale | 2.8 ± 1.2 | 2.6 ± 1.3 | NS |
| CSF protein, mg/dL | 129 ± 202 | 191 ± 206 | NS |

* *p* value indicates a significant difference between responders and nonresponders.
† Rate of patients with disability <3 mo after the onset.
‡ Mean score of the examined muscles.

ODSS (overall disability sum score) = 0, normal; 1, minor symptoms or signs in one or both arms but not affecting any function (dressing upper part of body, washing and brushing hair, turning a key in a lock, using knife and fork, doing/undoing buttons and zips); 2, moderate symptoms or signs in one or both arms affecting but not preventing any function listed; 3, severe symptoms or signs in one or both arms preventing at least one but not all functions listed; 4, severe symptoms or signs in both arms preventing all functions listed but some purposeful movements still possible; 5, severe symptoms and signs in both arms preventing all purposeful movements. Modified Rankin Scale = 0, normal; 1, nondisabling symptoms not interfering with lifestyle; 2, minor disability from symptoms leading to some restrictions of lifestyle but not interfering with patients' capacity to look after themselves; 3, moderate disability from symptoms that significantly interfered with lifestyle or prevented fully independent existence; 4, moderately severe disability from symptoms that clearly precluded independent existence, although patients did not need constant attention day and night; 5, severe disability involving total dependence, including constant care day and night. IVIg = IV immunoglobulin; MRC = Medical Research Council; ADL = activities of daily living.

*Table 2* *Electrophysiologic findings*

| Nerve | Responders | Nonresponders | *p* value* | Control, n = 121–191 |
|---|---|---|---|---|
| All patients | | | | |
| Median (R, n = 191; NR, n = 105) | | | | |
| MCV, m/s | 35.2 ± 13.2 | 39.8 ± 13.8 | <0.01 | 57.8 ± 3.7 |
| DL, ms | 7.4 ± 5.3 | 6.4 ± 4.5 | NS | 3.4 ± 0.4 |
| CMAP, mV | 6.4 ± 4.6 | 5.3 ± 4.5 | <0.05 | 10.7 ± 3.5 |
| CB, % | 45.5 | 27.5 | <0.01 | |
| Ulnar (R, n = 171; NR, n = 93) | | | | |
| MCV, m/s | 35.9 ± 12.7 | 39.0 ± 12.9 | NS | 58.6 ± 4.3 |
| DL, ms | 5.5 ± 5.0 | 5.0 ± 3.4 | NS | 2.7 ± 0.3 |
| CMAP, mV | 6.2 ± 4.2 | 4.8 ± 3.6 | <0.005 | 8.4 ± 2.5 |
| CB, % | 50.9 | 41.3 | NS | |
| Tibial (R, n = 168; NR, n = 81) | | | | |
| MCV, m/s | 33.7 ± 9.2 | 34.0 ± 9.4 | NS | 46.9 ± 3.5 |
| DL, ms | 7.5 ± 4.0 | 7.0 ± 3.0 | NS | 4.5 ± 0.8 |
| CMAP, mV | 5.7 ± 6.5 | 3.5 ± 5.9 | <0.0001 | 10.9 ± 3.8 |
| CB, % | 40.5 | 35.6 | NS | |
| Patients with similar duration (<12 mo) | | | | |
| Median (R, n = 112; NR, n = 36) | | | | |
| MCV, m/s | 34.4 ± 12.5 | 40.5 ± 14.5 | <0.05 | 57.8 ± 3.7 |
| DL, ms | 7.6 ± 4.8 | 8.3 ± 7.0 | NS | 3.4 ± 0.4 |
| CMAP, mV | 6.8 ± 4.6 | 4.2 ± 2.9 | <0.01 | 10.7 ± 3.5 |
| CB, % | 33.0 | 20.0 | <0.05 | |
| Ulnar (R, n = 101; NR, n = 33) | | | | |
| MCV, m/s | 35.6 ± 11.4 | 37.6 ± 15.3 | NS | 58.6 ± 4.3 |
| DL, ms | 5.5 ± 3.6 | 5.5 ± 2.5 | NS | 2.7 ± 0.3 |
| CMAP, mV | 5.9 ± 4.2 | 4.0 ± 3.6 | <0.05 | 8.4 ± 2.5 |
| CB, % | 50.8 | 44.4 | NS | |
| Tibial (R, n = 102; NR, n = 25) | | | | |
| MCV, m/s | 33.5 ± 9.0 | 33.4 ± 8.5 | NS | 46.9 ± 3.5 |
| DL, ms | 7.9 ± 4.0 | 8.0 ± 3.1 | NS | 4.5 ± 0.8 |
| CMAP, mV | 5.2 ± 5.5 | 1.9 ± 2.8 | <0.0005 | 10.9 ± 3.8 |
| CB, % | 48.8 | 44.4 | NS | |

* *p* value indicates a significant difference between responders and nonresponders.

R = responder; NR = nonresponder; MCV = motor nerve conduction velocity; DL = distal latency; CMAP = compound muscle action potential; CB = conduction block.

StatView software for Macintosh (version 4.5; Abacus Concepts, Berkeley, CA).

**Results.** *Clinical findings.* Efficacy of IVIg therapy was 63.8% (table 1 and table E-1 on the *Neurology* Web site at www.neurology.org). The rate of patients whose symptomatic exacerbation stopped 3 months after onset was higher in responders than in nonresponders. Responders showed significantly more severe weakness of the upper and proximal lower limbs, whereas nonresponders showed more marked muscle atrophy in the upper and lower limbs. As the disease duration from onset to IVIg differed significantly between responders and nonresponders in the patients as a whole, we additionally compared the subgroups of responders and nonresponders with disease duration of <12 months, eliminating significant differences about the disease duration.

Efficacy of IVIg in the patients with similar duration was 79.9%. The rate of patients whose symptomatic exacerbation stopped 3 months after onset was still higher in responders. Muscle atrophy of each limb was significantly more prominent in nonresponders, as was true for the patients as a whole.

*Electrophysiologic findings.* Mean CMAP was significantly more reduced in the median, ulnar, and tibial nerves in nonresponders (table 2 and table E-2). Frequency of conduction block showed a tendency to be more pro-

*Table 3* *Electrophysiologic findings before and after IVIg therapy*

| Nerve | Pre IVIg | Post IVIg | *p* value* |
|---|---|---|---|
| Responders, n = 71 | | | |
| Median | | | |
| MCV, m/s | 32.4 ± 13.2 | 35.3 ± 12.4 | <0.05 |
| DL, ms | 6.6 ± 4.0 | 6.7 ± 4.7 | NS |
| CMAP, mV | 5.6 ± 4.1 | 6.7 ± 4.6 | NS |
| CB, % | 45.7 | 38.9 | <0.05 |
| Ulnar | | | |
| MCV, m/s | 33.5 ± 11.3 | 36.7 ± 11.1 | <0.01 |
| DL, ms | 5.3 ± 2.8 | 4.8 ± 2.7 | NS |
| CMAP, mV | 5.3 ± 3.1 | 5.8 ± 3.3 | NS |
| CB, % | 42.2 | 35.7 | <0.05 |
| Tibial | | | |
| MCV, m/s | 31.5 ± 8.3 | 33.3 ± 10.4 | <0.05 |
| DL, ms | 7.1 ± 3.1 | 7.1 ± 4.3 | NS |
| CMAP, mV | 3.5 ± 3.2 | 4.4 ± 4.3 | NS |
| CB, % | 44.8 | 27.6 | <0.01 |
| Nonresponders, n = 51 | | | |
| Median | | | |
| MCV, m/s | 38.5 ± 13.6 | 39.1 ± 13.7 | NS |
| DL, ms | 7.3 ± 4.1 | 7.7 ± 4.8 | NS |
| CMAP, mV | 5.9 ± 5.0 | 5.6 ± 4.7 | NS |
| CB, % | 32.7 | 23.5 | NS |
| Ulnar | | | |
| MCV, m/s | 36.0 ± 14.4 | 34.0 ± 12.5 | NS |
| DL, ms | 5.6 ± 2.4 | 5.5 ± 2.1 | NS |
| CMAP, mV | 4.4 ± 3.3 | 4.2 ± 3.9 | NS |
| CB, % | 40.9 | 35.0 | NS |
| Tibial | | | |
| MCV, m/s | 30.5 ± 9.7 | 32.7 ± 10.3 | NS |
| DL, ms | 7.8 ± 3.6 | 7.5 ± 3.7 | NS |
| CMAP, mV | 3.2 ± 4.1 | 4.1 ± 4.9 | NS |
| CB, % | 46.5 | 46.2 | NS |

* *p* value indicates a significant difference between responders and nonresponders.

IVIg = IV immunoglobulin; MCV = motor nerve conduction velocity; DL = distal latency; CMAP = compound muscle action potential; CB = conduction block.

nounced in responders. In the patients with similar durations, electrophysiologic findings also resembled those for patients as a whole. Mean CMAP was significantly more reduced in nonresponders, and conduction block tended to be more frequent in responders.

*Electrophysiologic findings before and after IVIg therapy.* We assessed electrophysiologic changes before and after IVIg (table 3). Mean MCV in the median, ulnar, and tibial nerves in responders improved significantly after IVIg, whereas mean CMAP in the same nerves did not. In contrast, both mean MCV and mean CMAP in nonresponders did not improve significantly. Conduction block became less frequent after IVIg in responders.

**Discussion.** One cardinal finding was that features related to axonal dysfunction were a major contribution to unresponsiveness to IVIg therapy in CIDP. More severe CMAP amplitude reduction and more severe muscle atrophy were seen in nonresponders than in responders. MCV and distal latency were essentially similar between responder and nonresponder groups, but conduction block was more frequent in responders, suggesting that IVIg responsiveness was linked to demyelinating as opposed to axonal features.

In the previous reports, nonresponsiveness has been suggested to be caused by the longer interval from symptom onset to initiation of IVIg therapy.[9] One possible explanation for the longer duration effect might be that secondary axonal degeneration could follow segmental demyelination in patients with long symptomatic intervals prior to effective therapy, as suggested in primary demyelination. Accordingly, we compared features between subgroups of responders and nonresponders who had similar disease duration from onset, obtaining similar results that axonal dysfunction remained the major determinant of IVIg unresponsiveness. These observations suggest that whereas symptom duration before treatment was one determinant of IVIg ineffectiveness in CIDP, duration-independent axonal dysfunction was another. According to recent reports, demyelination-independent primary axonal damage has been suggested to occur in a subgroup of CIDP cases, termed the axonal variant of CIDP. These findings support our view that duration-independent axonal features can exist in CIDP and thus contribute to treatment failure.[5,9,10]

In addition, electrophysiologic impairment is more reversible in responders than in nonresponders, and demyelinating features are effectively improved by IVIg. Axonal features, less reversible with IVIg, were more prominent in nonresponders. Nonresponders also did not show any improvement in MCV, CMAP, or frequency of conduction block. The current results suggest that the pathologic dysfunction of peripheral nerves differs between responders and nonresponders.

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# Thiamine-deficiency neuropathy in Japan

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**Abstract**

We reviewed the clinicopathologic features of patients with thiamine-deficiency neuropathy. Symmetric sensorimotor polyneurpathy predominantly involving the lower limbs was the typical presentation, while variations were seen in the severity and the distribution of weakness and sensory disturbance. Progression occurred over intervals varying from days to years. Some patients progressed rapidly in a manner resembling Guillain-Barre syndrome. Symptoms of heart failure and Wernicke-Korsakoff syndrome varied among individual patients. Major electrophysiologic findings were those of axonal neuropathy with more marked abnormalities in the lower limbs. Sural nerve biopsy specimens mainly showed predominant loss of large myalinated fibers and marked subperineurial edema. Major etiologies of thiamine deficiency were postgastrectomy state, chronic alcoholism, and dietary imbalance. Patients with chronic alcoholism showed slightly different clinical features in that they were sensory-dominant, slowly progressive, and predominantly impaired superficial sensation with pain or painful burning sensation compared to those of the other two major etiologies. Thiamine adnministration achieved substantial functional recovery within 6 months, irrespective of the initial deficit, but recovery of sensory impairment was incomplete. The variability of thiamine-deficiency neuropathy should be kept in mind, because early diagnosis and treatment facilitates recovery.

## Introduction

Deficiency of thiamine (vitamin B1) causes peripheral neuropathy and heart failure, designated as beriberi. Wernicke-Korsakoff syndrome also may occur.[1] Deficiency may occur in individuals with decreased thiamine intake caused by insufficient consumption of appropriate food, due to high-

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carbohydrate or low-thiamine diets, chronic alcoholism,[2] anorexia nervosa,[3] or hyperemesis gravidarum,[4,5] or alternatively in persons with increased thiamine requirements such as laborers performing heavy outdoor work.[6] Historically, beriberi was an endemic disorder among Asians for whom milled white rice was a dietary staple in the late 19th century.[7] The number of patients with beriberi decreased markedly after the discovery of vitamin B1,[8] and public education regarding the need for a balanced diet. However, in Japan, an epidemic of beriberi occurred in the 1970s when instant foods with low vitamin contents became popular.[6,9,10] The epidemic was resolved by nutritional education and supplementation of food with thiamine as a countermeasure. Since that time, the disorder has been largely forgotten by many physicians, especially those in developed countries. However, recent reports suggest that neuropathy associated with thiamine deficiency is not uncommon among patients with a variety of background factors including chronic alcoholism[11] and prolonged parenteral nutrition.[12] Furthemore, we previously reported 17 patients with postgastrectomy polyneuropathy associated with thiamine deficiency, suggesting gastrectomy as a risk factor for thiamine deficiency.[13]

In this article, we review the clinicopathologic features of thiamine-deficiency neuropathy in Japan.

**Causes of thiamine deficiency**

We reviewed 66 patients with thiamine-deficiency neuropathy who were referred to Nagoya University Graduate School of Medicine and its affiliated institutions from 1990 to 2002. Major factors contributing to thiamine deficiency in these patients were gastrectomy, heavy drinking, and dietary imbalance. Among patients with dietary imbalance, the staple food was milled rice or noodles, without adequate meat and vegetables; also, food intake was irregular. A striking observation was that many of the patients had undergone gastrectomy. Gastrectomy was preformed to treat ulcers or neoplasms. Patients who had undergone gastric restriction surgery for morbid obesity were not present. Among these patients we reported 17 having postgastrectomy polyneuropathy with thiamine deficiency.[13] Gastrectomy had been performed in these patients 2 months to 39 years prior to the onset of neuropathy. Nine patients underwent gastrectomy for carcinoma, one for lymphoma, and 7 for gastric or duodenal ulcer. The method of reconstruction varied, and included Billroth I or Billroth II for subtotal gastrectomy and a Roux-en-Y method or a jejunal poutch interposition for total

gastrectomy. Interestingly, most patients took particular care of dietary balance after surgery. The presence of these patients supports the view that thaimne deficiency can occur in those who undergo gastrectomy. Wernicke's encephalopathy has been reported occasionally in association with operations performed to treat morbid obesity.[14,15] Neuropathy can also occur in some patients following gastric restriction surgery for morbid obesity.[15,16] Thiamine deficiency may occur in patients who undergo operations for morbid obesity, especially those who are prone to vomiting.[17] Roux-en-Y bypass to create a bypass or gastroplasty to produce stenosis of the gastrointestinal tract were the major procedures performed for morbid obesity. Patients undergoing such surgery show extensive weight loss, sometimes with protracted nausea and vomiting, as well as severe malnutrition. In our series, none of the gastric operations were performed for morbid obesity, and our patients underwent total or subtotal gastrectomy. Unlike patients who undergo surgery for morbid obesity, only one of our patients had vomiting and extensive weight loss. Some of our patients had carcinomas, but tumors did not show recurrence or metastasis at the time neuropathic symptoms appeared.

Thiamine is absorbed by the mucosa of the entire intestine, with the highest rate of absorption being in the duodenum.[18-20] That patients who underwent gastrectomy would develop thiamine deficiency is somewhat puzzling, because a large extent of the intestine presumably able to absorb thiamine was left intact. Recent reports of Wernicke's encephalopathy suggest that thiamine deficiency can occur in some, but not all, patients who undergo gastrectomy for cancer.[21-24] Some of these patients have shown electrophysiologic evidence of neuropathy, as well as Wernicke's encephalopathy.[21,24,25] Markkanen reported that erythrocyte transketolase activity decreased in 31% of patients who had operations involving the upper gastrointestinal tract, including partial gastrectomy.[25] These observations suggest that the relative abilities of different intestinal sites to absorb thiamine vary among individuals. Furthermore, only a few of the many patients who undergo gastrectomy develop neuropathy, so individual factors, possibly genetic in nature, may have an influence.

Most postgastrectomy patients in our series did not manifest neuropathic symptoms during the early period after operation, even though many of them had acute onset of symptoms. Thiamine is turned over relatively rapidly in the body, and is not stored in large amounts.

Patients who undergo gastrectomy could have a subclinical deficiency of thiamine, even with appropriate dietary intake. When patients experience increases in thiamine requirements due to fever, anorexia, heavy labor, or pregnancy, symptoms of thiamine deficiency may be precipitated. Increases in subclinical thiamine deficiency associated with aging also could account for the delayed appearance of neuropathic symptoms after gastrectomy in some patients.[26,27] Three patients with cancer received chemotherapy with either deoxifluridine or 5-fluorouracil. Fluoropyrimidines are reported to increase the cellular metabolism of thiamine.[28] This medication is considered to have contributed to the development of thiamine deficiency.

In addition to gastrectomy, chronic alcoholism is closely related to thiamine deficiency.[11] According to our previous study of consecutive patients with alcoholic neuropathy, 28 of 64 patients (44%) manifested thiamine deficiency.[29] In addition to dietary imbalance associated with chronic alcoholism, alcohol diminishes thiamine absorption in the intestine[30] and reduce hepatic storage of thiamine.[31] Decreased phoshporylation of thiamine to the active coenzyme thiamine pyrophosphate ascribed to alcohol may also contribute to the development of thiamine deficiency.[32-34] These observations support the view that some of the pathogenesis of alcoholic neuropathy are attributable to deficiency of thiamine absorption or metabolism.

**Clinical features**

We previously described the clinical features of 32 patients with thiamine-deficiency neuropathy.[29] All of the patients were nondrinkers. According to this report, 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; this was weakness in the lower extremities in 50% of patients and numbness in the distal lower limbs in 50%. Progression rate also varied; acute progression within 1 month was seen in 18 patients (56%), while slow progression over more than 1 year was seen in 19%. Impairment was usually motor-dominant, affecting 84% of patients. Some patients whose motor weakness progressed over days were initially thought to have Guillain-Barr_ syndrome. Motor symptoms were more predominant in the lower than upper extremities; even so, 81% showed weakness in the upper limbs. Sensory disturbance was present in the lower limbs in all

patients, and was also present in the upper limbs and the trunk in 78% and 28%, respectively. Varying degrees of numbness with or without painful sensations were noted in all patients, and painful sensations were reported by 22% of patients. Involvement of all sensory modalities was a common feature: superficial sensation was affected most in 9%; deep sensation was involved most in 28%; and, both modalities were affected equally in 63%. Biceps, patellar, and Achilles tendon reflexes were reduced or absent in most patients. Activities of daily living were impaired mainly because of the rapid progression of muscle weakness. Only 16% could walk unaided at the time of initial examination.

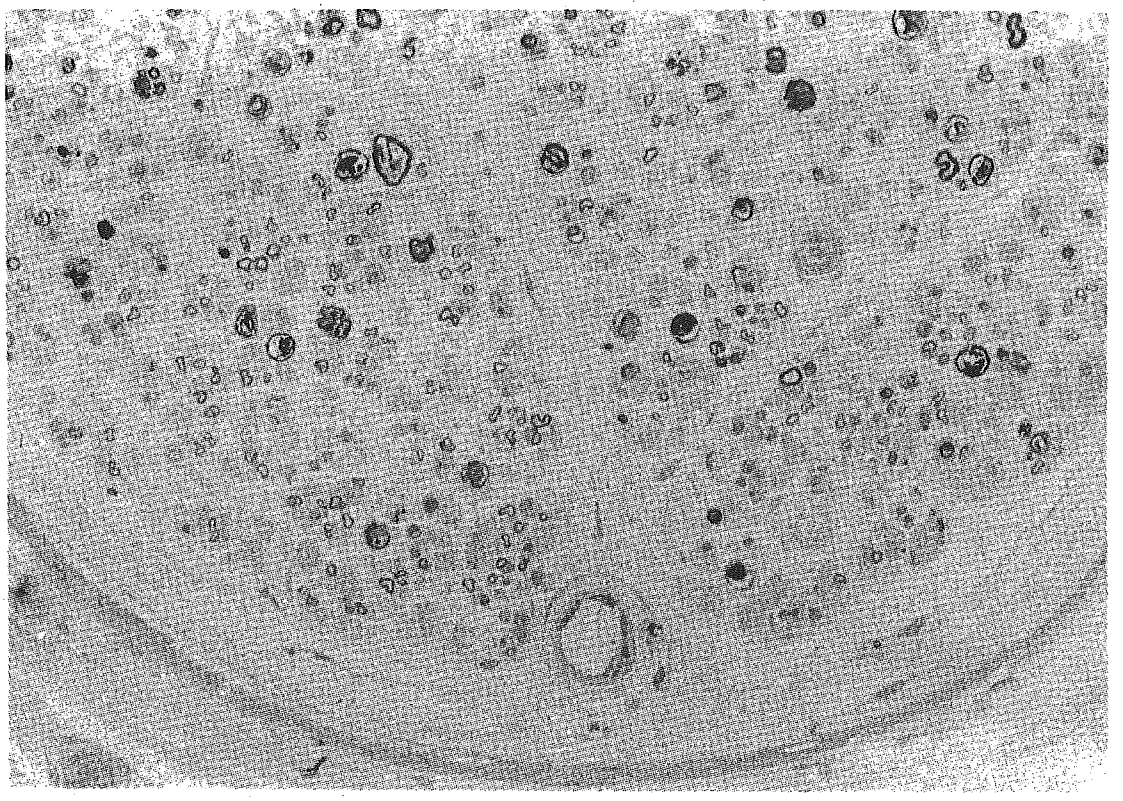
On the other hand, thiamine-deficiency neuropathy associated with chronic alcoholism show slightly different clinical features in the point that it is sensory-dominant, slowly progressive, and predominantly impairs superficial sensation with pain or painful burning sensation in comparison with nonalcoholic thiamine-deficiency neuropathy.[29,35] These differences are thought to be attributable to the toxic effects of ethanol. Recent studies indicate a direct neurotoxic effect of ethanol or its metabolites, involving ethanol-induced glutamate neruotoxicity,[36,37] 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 a 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.[42]

Clinical features of polyneuropathy and associated symptoms such as Wernicke's encephalopathy and congestive heart failure varied among individual patients. The cause of the variations of clinical features has not been determined. Genetic factors may relate to variations and susceptibility to thiamine deficiency. For example, thiamine-responsive megaloblastic anemia associated with diabetes mellitus and deafness results from a mutation of the gene encoding the thiamine transporter protein; and this genetic defect preferentially involves hematopoietic, pancreatic islet, and auditory apparatus cells.[43-45] Other factors that could influence clinical features are deficiencies of nicotinic acid,[46] vitamin B2,[47] vitamin B6,[48] vitamin B12,[49,50] and folate.[51] However, characteristic symptoms associated with these individual vitamin deficiencies were not present. These clinical pictures include anorexia, diarrhea, erythematous and

hyperkeratotic dermatitis, and mental changes in pellagra (nicotinic acid deficiency); cheilosis, glossitis, keratoconjunctivitis, and dermatitis involving nasolabial folds, scrotum and labia in vitamin B2 deficiency; and myelopathy in vitamin B12 and folate deficiency. Thus, these vitamin deficiencies could modify thiamine-deficiency effects to some extent, but could not be the major factors for variations in our series, because these characteristic symptoms were not present.

**Electrophysiologic and histopathologic features**

According to previously reported data concerning nonalcoholic thiamine-deficiency neuropathy,[29] nerve conduction studies mainly showed evidence of axonal degeneration more predominantly in the lower



Transverse section of sural nerve in a patient with thiamine-deficiency neuropathy. Note myelin ovoids, significant reduction of the density of myelinated fibers. Large myelinated fibers are reduced more than small myelinated fibers. Endoneurial edema with enlargement of the subperineurial space is present.

extremities with some slowing of conduction velocities. Sural nerve biopsy specimens also indicated axonal neuropathy (Figure). Myelinated fiber density was significantly reduced. On average, the density of large myelinated fibers was 22% that of normal controls, while the density of small myelinated fibers was 33% that of normal controls. Axonal sprouting was scarce in all cases. Predominant loss of large myelinated fibers was a characteristic feature. Reduction of unmyelinated fibers was also seen especially in cases with severe myelinated fiber loss.

Findings of nerve conduction studies on thiamine-deficiency neuropathy with chronic alcoholism were similar to those on nonalcoholic thiamine-deficiency neuropathy.[29] Sural nerve biopsy specimen findings were variable, occupying a range between nonalcoholic thiamine-deficiency neuropathy and alcoholic neuropathy with normal thiamine status; the latter showed characteristically small fiber-predominant loss and scarce subperineurial edema and myelin irregularity.

**Treatment and prognosis**

Patients were treated with thiamine. Initially, a 100-mg daily intravenous dose of fursultiamine, a disulfide derivative of thiamine, was given. A 75-mg daily oral dose of fursultiamine was administered subsequently.[13] Cardiomegaly, edema of the legs, and arrhythmias improved dramatically within a few days after initiation of thiamine administration. Paresis of the bladder and intestine improved within a few weeks. Improvement of muscle strength was evident at one week. Recovery of sensation was less dramatic than motor recovery. Wernicke's encephalopathy improved substantially, but Korsakoff psychosis persisted in many patients.

Overall, complete recovery was very rare, and some residual deficit persisted in most patients, although functional status was favorable after thiamine administration. Substantial functional recovery, particulary in motor and autonomic involvement, was achieved by thiamine supplementation at 3 to 6 months, but sensory symptoms and Korsakoff psychosis were particularly likely to show residual deficits. Patients with rapid progression were more likely to respond well to thiamine supplementation than those with slow progression. Treatment should be initiated as early as possible. We believe that thiamine should assayed and administered early in patients with sensorimotor neuropathy and a history of gastrointestinal surgery, heavy alcohol intake, or dietary imbalance. Multivitamin supplementation is also recommended

because vitamins other than thiamine can be deficient as well, and modify the clinical features. Prophylactic supplementation of thiamine following gastrectomy also is recommended.

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CASE REPORT

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# Widespread active inflammatory lesions in a case of HTLV-I-associated myelopathy lasting 29 years

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**Abstract** An autopsy case of human T-lymphotropic virus type I (HTLV-I)-associated myelopathy (HAM) of 29 years' duration is reported. The patient had no history of surgery or blood transfusion and likely contracted HTLV-I sexually while traveling in an endemic area. At age 45, the patient began to experience gait disturbance; he later developed spastic tetraparesis. Autopsy revealed marked gross spinal cord atrophy, particularly in the middle to lower thoracic levels. Myelin and axonal degeneration were identified predominantly in the middle to lower thoracic spinal cord, extending into the medulla oblongata and lumbar cord. Inflammatory infiltrates of mononuclear cells were diffuse in the white and gray matter of the spinal cord and medulla oblongata, particularly in perivascular areas. These infiltrates were also observed in perivascular areas of the pons, midbrain, cerebellum, and cerebrum. More than half of the infiltrating cells were positive for the pan-T cell marker UCHL-1, but some were positive for the B cell marker SL-26. There were far more CD8-positive cells than CD4-positive cells in the spinal parenchyma and perivascular areas. Neurons in the anterior horn, Clarke's column, and intermediolateral column were relatively well preserved. Active chronic inflammation was indicated. Despite the 29-year history of HAM, the presence of an active inflammatory reaction is surprising. We discuss possible modulation of the histopathological manifestations of HAM by corticosteroid therapy.

**Keywords** HTLV-I-associated myelopathy · Active inflammatory lesion · Myelopathy · Spastic tetraparesis · Corticosteroid therapy

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## Introduction

Human T-lymphotropic virus type I (HTLV-I) retrovirus causes adult T cell leukemia and lymphoma and a chronic progressive myelopathy known as HTLV-I-associated myelopathy (HAM) [3, 8, 13]. HAM was first reported and established as a clinical entity in 1986 by Osame et al. [14]. It is now known that the pathogenesis of HAM involves both viral infection and host immune response [8]. Clinically, HAM is characterized by slow progression of spastic paraparesis, involving mainly the lower extremities, pyramidal signs, and mild sensory and sphincter disturbances [7, 11, 13, 14]. Akizuki et al. [1] reported the first autopsied case of HAM in 1987, and more than 30 autopsied cases have been reported since. Pathology studies of autopsied cases indicate several characteristic pathological changes associated with HAM: marked infiltration of lymphocytes and monocytes, presence of foamy macrophages, and demyelination and axonal loss in the spinal cord white and gray matter, particularly in the anterolateral column of the middle to lower thoracic segments [1, 5, 6, 8, 12]. Here, we report an autopsied case of HAM of 29 years' duration with widespread active chronic inflammatory

cell infiltration that amends the phenotypic spectrum of HAM.

## Clinical summary

A Japanese man who was born and still lived in Aichi prefecture, Japan, a non-endemic area for HTLV-I infection, began to experience gait disturbance at the age of 45 years. He had no history of surgery or blood transfusion at that time or any family history of HTLV-I infection. Between the ages of 25 and 43 years, he traveled frequently to Southeast Asia (Taiwan, South Korea, and Thailand) and Kyushu, Japan, endemic areas for HTLV-I infection, and he had many opportunities for sexual transmission of the virus during his travels. The gait disturbance increased slowly but steadily, and the patient developed dysuria. At age 57, he was admitted to Aichi Medical University Hospital. Upon admission, neurological examination disclosed spastic gait, weakness and atrophy of the legs, and hyperreflexia in all extremities with bilateral Babinski's sign and ankle clonus. Cranial nerve function and superficial and deep sensation were normal. Cerebrospinal fluid (CSF) contained 2 mononuclear cells/$mm^3$, 23 mg/100 ml total protein, and 64 mg/100 ml sugar; pressure was normal. Serum and CSF were positive for anti-HTLV-I antibodies. A serological test for syphilis was negative. No abnormal lymphocytes were found in the blood or CSF. There was no other possible cause of immunodepression, such as HIV infection. The patient was diagnosed with HAM on the basis of the clinical symptoms and laboratory test results. Corticosteroid therapy was administered at this stage, and for a short time the symptoms and signs were slightly improved. However, the spastic paraparesis continued to worsen, and the patient became bed-ridden at age 70. Corticosteroid therapy was discontinued at this stage.

The patient visited Nagoya University Graduate School of Medicine for further evaluation at age 71. Examination revealed vertical gaze palsy, highly spastic tetraparesis with articular contracture of all four extremities, highly accentuated reflexes in all four extremities with bilateral Babinski's sign, and neurogenic bladder. Superficial sensation was normal, but the sense of vibration was mildly decreased in both legs. CSF contained 1 mononuclear cell/$mm^3$, 43 mg/100 ml total protein, and 63 mg/100 ml sugar. Serum and CSF were positive for HTLV-I antibodies at titers of 8,192× and 128×, respectively. Magnetic resonance imaging of the brain and spinal cord revealed mild frontotemporal atrophy, but no spinal cord lesions were identified. The articular contracture was diagnosed as HTLV-I-associated arthropathy on the basis of X-ray findings. Parkinsonism, including rigidity in all extremities and tremor in the upper extremities, was observed and treated with L-DOPA, which had an observable effect. The HAM diagnosis was confirmed, and Parkinson's disease was also diagnosed.

The patient was transferred to Higashi Nagoya National Hospital at age 72. He underwent gastrostomy at age 73 and tracheotomy at age 74. He suffered from frequent bronchopneumonia and died at age 74, 29 years after the onset of HAM and 4 years after the onset of Parkinson's disease.

The patient did not receive immunosuppressive treatment at any time during the 29 years of his illness or corticosteroid treatment during the 5 years prior to death.

## Autopsy: neuropathological examination and findings

A thorough autopsy was performed 9 h after the patient's death. Central nervous system tissues were fixed in 20% neutral formalin for 4 weeks and embedded in paraffin, and 8-μm-thick sections were prepared. The sections were mounted, deparaffinized, hydrated, and stained. For routine neuropathological study, sections were subjected to hematoxylin-eosin, Klüver-Barrera, and Bodian staining. Immunohistochemical analysis was carried out with antibodies to pan-T cells (UCHL-1, mouse monoclonal diluted 1:100; Dako, Glostrup, Denmark), pan-B cells (SL-26, mouse monoclonal diluted 1:100; Dako), helper/inducer T cells (CD4, mouse monoclonal diluted 1:100; Nichirei, Tokyo, Japan), suppressor/cytotoxic T cells (CD8, mouse monoclonal diluted 1:100; Dako), macrophages (CD68, mouse monoclonal diluted 1:100; Dako), microglia (HLA-DR, mouse monoclonal diluted 1:200; Dako), and α-synuclein (mouse monoclonal diluted 1:100; Chemicon, Temecula, CA). Antibody binding was detected by the labeled streptavidin-biotin method (Dako LSAB kit; DAKO). Peroxidase-conjugated streptavidin was visualized with 3,3′-diaminobenzidine (DAB; Wako, Osaka, Japan) as the final chromogen. All immunostained sections were counterstained lightly with Mayer's hematoxylin.

### Macroscopic findings

The brain weighed 1,480 g and showed moderate symmetric frontotemporal atrophy but no cerebellar or brainstem atrophy. Horizontal sections of brainstem showed depigmentation in the substantia nigra and locus ceruleus. The spinal cord showed marked atrophy and grayish discoloration of the anterolateral column, particularly in the thoracic region (Fig. 1A–C). Anterior and posterior nerve roots were well preserved, and the vessels of the brain and spinal cord showed no gross abnormalities.

### Microscopic findings

Fibrous thickening of the pia mater with mononuclear cell infiltration was observed throughout the spinal cord. Inflammatory infiltrates consisting of many mononuclear cells were observed in perivascular areas and in the

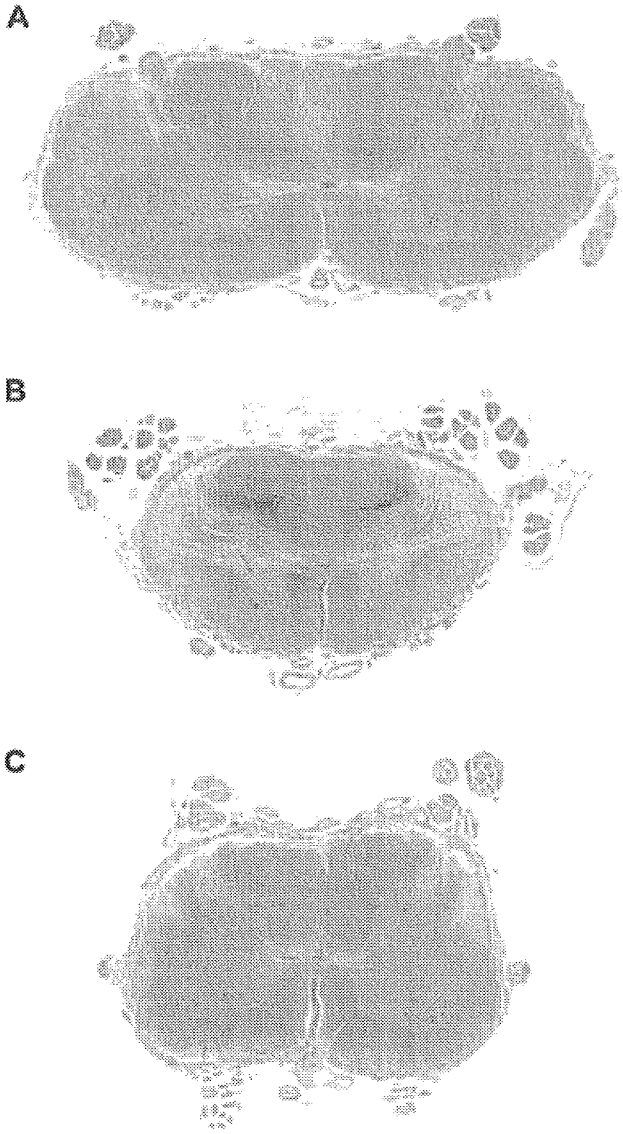


Fig. 1 Macroscopically, the spinal cord shows obvious bilateral atrophy of lateral and anterior columns with myelin pallor. A cervical cord, B lower thoracic cord, C lumbar cord. Klüver-Barrera stain

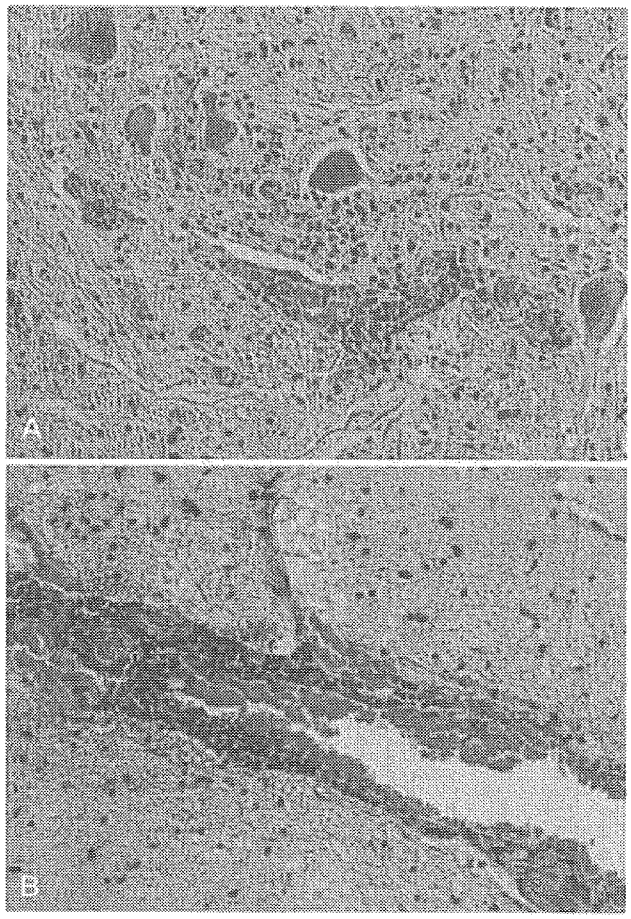


Fig. 2 Perivascular and parenchymal mononuclear cell infiltration indicates an active chronic lesion. A Lumbar cord, B temporal lobe. Hematoxylin and eosin stain, original magnification ×20

parenchyma of the spinal cord and medulla oblongata (Fig. 2A). Milder lesions composed of cuffs of perivascular cells were scattered in the pons, midbrain, cerebellum, and cerebrum, without adjacent tissue reaction or parenchymal lesions (Fig. 2B). The distribution of inflammatory lesions was horizontally symmetric at all spinal column levels, and the anterolateral column was the most severely affected.

Degeneration of the lateral corticospinal and spinocerebellar or spinothalamic tracts was evident. Demyelination and axonal degeneration appeared along the entire spinal cord, particularly in the middle to lower thoracic regions, and in the medulla oblongata. Demyelination was more prevalent than axonal degeneration. Axonal degeneration was more commonly found in small myelinated fibers than in large myelinated fibers. The posterior column was relatively free of degeneration and inflammatory infiltrates. Capillary proliferation was prominent in the spinal cord, particularly in the cervical and lumbar regions. Small-vessel hyalinization was visible in both the white and gray matter, particularly in the cervical and lumbar regions of the spinal cord, and was accompanied by gliosis in the surrounding tissues. In the vessels of the spinal cord, the endothelium showed no appreciable changes, and no obstructive changes were found. Neurons in the anterior horn, intermediolateral column, and Clarke's column were relatively well preserved. The number of large motor neurons in the anterior horn appeared normal. These findings indicated the presence of active chronic inflammatory cell infiltration. There was no evidence of malignancy.

### Immunohistochemical findings

More than half of the infiltrated cells stained positively for the pan-T cell marker UCHL-1 (Fig. 3A). UCHL-1-positive cells were identified predominantly around perivascular areas and in the parenchyma of the spinal cord and medulla oblongata. In the pons, midbrain, cerebellum, and cerebrum, UCHL-1-positive cells were identified around perivascular areas and meninges. Cells that stained positively for the pan-B cell marker SL-26 were sparse in perivascular areas and in the parenchyma of the spinal cord and medulla oblongata. CD4-positive cells were rare; a few were identified exclusively in meningeal lesions and perivascular areas of the spinal cord, brainstem, cerebellum, and cerebrum. Few CD4-positive cells were identified in the spinal cord parenchyma. CD8-positive cells were present in perivascular areas of the spinal cord, brainstem, cerebellum, and cerebrum and scattered in the parenchyma of the spinal cord and medulla oblongata (Fig. 3B). Although a few CD68-positive cells were identified, predominantly in perivascular areas and in the parenchyma of the spinal cord and medulla oblongata, no HLA-DR-positive cells were identified in the parenchyma or perivascular areas of these regions.

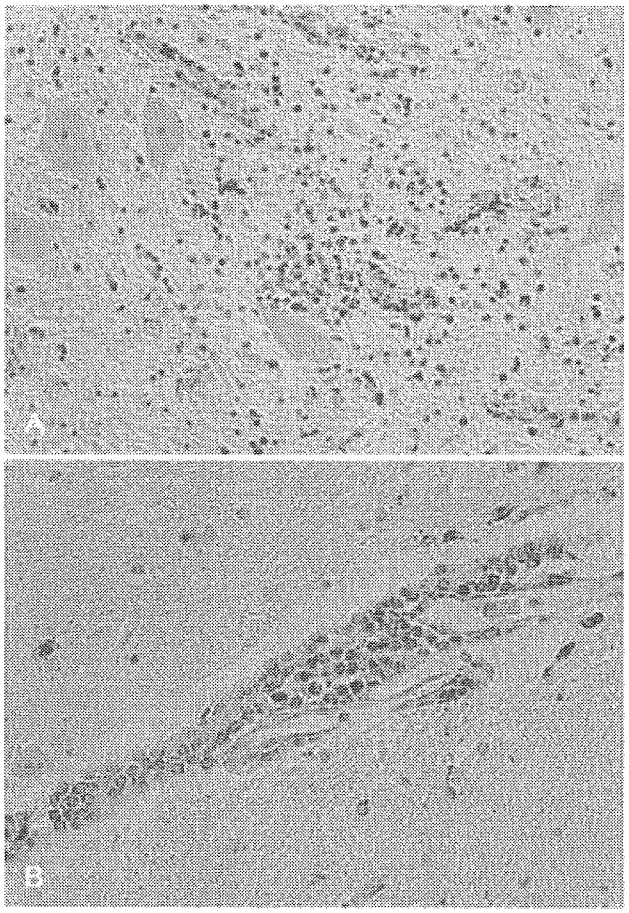


**Fig. 3** Perivascular and parenchymal inflammatory infiltration in the spinal cord. **A** Lumbar cord, UCHL-1 stain; **B** medulla oblongata, CD8 stain. Original magnification **A** ×20, **B** ×40

### Parkinson's disease lesions

Although neuronal loss was mild, many scattered free melanin granules were present in the substantia nigra and locus ceruleus. Lewy bodies were frequent in the substantia nigra, locus ceruleus, and sympathetic ganglia. A few cortical Lewy bodies were also identified in the cerebral cortex. These Lewy bodies immunolabeled with α-synuclein antibody. Interestingly, many residual neurons in the intermediolateral column of the thoracic region showed α-synuclein immunolabeling. No other significant age-related pathologies were identified.

## Discussion

HTLV-I is transmitted primarily through breast milk, sexual intercourse, blood transfusion, or sharing of contaminated needles by drug users [8]. The incubation period varies, ranging in most cases from a few years to several decades [8]. In the present case, we believe that HTLV-I was transmitted sexually several years before the onset of symptoms. The incubation period depends to some extent on the route of infection: blood transfusion is not only a much more efficient means of transmitting infection than breast-feeding or sexual intercourse, but it also tends to be associated with a shorter incubation period before the development of disease [8]. HAM patients with a history of blood transfusion respond well to corticosteroid therapy, although the exact pharmacological mechanism is not known [12, 15].

The pathological findings of previously reported autopsy cases of HAM are similar and include spinal cord lesions consisting of marked perivascular and parenchymal infiltration of lymphocytes and foamy macrophages, demyelination, axonal loss, and gliosis [1, 6, 7, 8, 9]. The characteristic lesion distribution suggests a chronic inflammatory process that starts in the middle to lower thoracic spinal cord and extends gradually both rostrally and caudally [6, 7]. Izumo et al. [9] offer a detailed neuropathological description of HAM as follows: (1) T cell-dominant mononuclear cell infiltration; (2) diffuse and symmetric degeneration of the anterolateral columns and inner portion of the posterior columns, involving both myelin and axons; (3) presence of cytotoxic T cells and apoptosis of helper/inducer T cells; (4) in vivo localization of HTLV-I provirus in perivascular infiltrated T cells; and (5) accentuation of inflammatory lesions at sites of slow blood flow.

The present case showed active chronic inflammatory infiltration that is surprising despite the 29-year presence of HAM. Prior descriptions of HAM with clinical histories of more than 10 years include monotonic degen-