Folic Acid-Responsive Neurological Diseases in Japan

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Summary Folic acid (folate) levels were measured in the serum of patients with various neurological diseases in Japan. Thirty-six patients showed decreased serum folate levels among 343 consecutive neurological patients (10.5%). Folate administration (15 mg/d) to folate-deficient patients improved neurological symptoms in 24 of 36 cases (67%). Serum folate levels were significantly lower in female than in male folate-deficient patients. Folate-deficient patients showed predominantly axonal neuropathy, which responded to folate supplementation more markedly. Male patients more frequently exhibited neuropathy, especially demyelinating and motor-dominant neuropathy, than females. Anemia was correlated with male sex and low serum folate levels. Male patients were more responsive than females to folate treatment. More male patients had taken excess alcohol or received gastrectomies than females. Neurological symptoms were more frequently improved by folate supplementation in patients with neuropathy than exclusive encephalopathy. Serum folate levels were lower in patients with encephalopathy, especially those with dementia, while folate therapy was more effective in neurological patients without dementia. Dysgeusia and anemia improved in all patients after folate administration. Neurological patients with malabsorption or treated with continuous drip infusion were resistant to folate therapy. Since folate-responsive neuroencephalopathies are not rare among patients with neurological diseases in Japan, the serum folate level would serve as a valuable indicator for folate supplementation therapy.

Key Words folic acid, neuropathy, anticonvulsant, anemia

Folic acid (folate) is required to transfer one carbon units in the de novo synthesis of nucleotides and amino acids including methionine. Experimental results with folate-deficient mice suggest a neurochemical change in the serotonin and dopamine system (1). Neurological symptoms associated with folate-deficiency have been reported in an increasing number of patients, occasionally suggesting a causal relationship between a decrease in serum folate level and central or peripheral nervous manifestations in Europe and the United States (2), but not in Japan. Evaluation of the relationship between folate deficiency and neurological symptoms is difficult, since most patients suffer from nutritional disorders or excessive alcohol intake, resulting in deficiency of nutrients other than folate (3). In addition, dysfunctions in the central nervous system (CNS) including psychiatric symptoms can induce anorexia or malnutrition, worsening further the vitamin deficiency in a vicious circle (4).

The administration of thiamin and cobalamin has recently become the standard treatment recipe for Japanese patients with neurological disorders, especially those with a history of excessive alcohol intake, gastrointestinal (GI) symptoms or surgery. In fact, most of the patients examined in the present study had been given thiamin and cobalamin before they were referred to our clinic.

Moreover, folate deficiency is reported to be much less frequent in Japan than in Europe or the United States (5). Since neurological symptoms are ameliorated by folate supplements in most cases, we investigated the frequency of folate-responsive neurological patients in our clinic and the characteristics of folate-responsive patients, compared with folate-resistant neurological patients. This study is the first to elucidate factors which determine the effectiveness of folate therapy and to disclose the frequency of folate-deficient neurological diseases in Japan.

PATIENTS AND METHODS

We examined the serum folic acid levels in 343 Japanese neurological patients (168 males and 175 females; mean age and SD, 57.0±19.6 y) who visited the outpatient clinic at the Third Department of Internal Medicine (Neurology), Hiroshima University Hospital or Seaside Hospital, Hiroshima. Neurological patients were clinically diagnosed using neuroradiological, electrophysiological and other laboratory tests as cerebrovascular diseases (148 cases, including vascular dementia: 42 cases), Alzheimer’s disease (38 cases, including 4 vegetative patients), Parkinson’s disease (26 cases), frontal dementia (5 cases), including 2 cases of Pick’s disease and 1 case each of amyotrophic lateral sclerosis (ALS) with dementia, non-Alzheimer non-Pick
dementia with Fahr’s syndrome (6), and frontal dementia with canities, other neurodegenerative diseases (23 cases), multiple sclerosis (19 cases), alcohol neuroencephalopathy (41 cases), meningencephalitis (7 cases), depression (4 cases), peripheral neuropathy without history of excessive alcohol intake (67 cases), dysgeusia (7 cases), cervical spondylosis (2 cases), cerebro palsy (2 cases), familial spastic paraparesis (2 cases), and 1 case each of CO poisoning and hypothyroidism. Several patients had more than 2 diseases. Patients with alcoholic neuroencephalopathy were classed as drinkers who had drunk >300 L alcohol in their lives.

We performed electrophysiological studies, mental tests and neuroradiological examinations in all cases and then administered folate (15 mg/d) to 36 cases. The effect of the folate supplement was assessed after 60 d and cases were evaluated as improved when any one clinical sign or symptom was ameliorated. Folate administration did not cause any side effects in any cases.

Serum folate concentration was measured by chemiluminescence (7). The normal range for the serum folate level was assigned as 4.0–12.0 ng/mL. We considered patients with serum folate levels lower than the normal limit (<4 ng/mL) as folate-deficient.

Statistical analyses were performed using the \( \chi^2 \) test and ANOVA t-test. The statistical software used for this analysis was JMP. \( \chi^2 \) values were included in the paper when a significant difference was found for categorical data.

**RESULTS**

**Folate deficiency in patients with neurological diseases**

The serum folate level decreased in 36 of 343 Japanese neurological patients examined and the frequency was calculated to be 10.5%. The age range of these cases with low serum folate levels was 55.5 ± 19.3 y. No significant difference was observed between cases with normal folate levels and those with folate deficiency. The serum folate level was not significantly related to the age of folate-deficient patients (\( p > 0.5 \)). The ratio of males to females in the folate-deficient group did not differ significantly from that in the normal folate group (\( p > 0.05 \)).

The serum folate level was, however, significantly (\( p < 0.05 \)) higher in males (2.92 ± 0.88 ng/mL) than females (2.21 ± 0.90) in the folate-deficient group (Fig. 1). We did not observe any significant relationships between the serum folate level and serum cholesterol or protein levels.

**Neuropathy accompanied by folate deficiency**

Neuropathy manifested clinically and electrophysiologically in 27 cases, of which encephalopathies were combined in 13 cases. We compared serum folate levels in 27 folate-deficient patients with neuropathy (53.0 ± 16.7 y) with those lacking neuropathy (63.2 ± 26.1 y). The difference in age was not significant (\( p > 0.1 \)). Serum folate levels were 2.74 ± 1.00 ng/mL and 2.58 ± 0.72 in patients with and without neuropathy, respectively, and the difference was not significant (\( p > 0.5 \)). Male patients exhibited neuropathy more frequently than females (\( \chi^2 = 12.1, p < 0.001 \)). Neurological symptoms were more frequently improved by folate supplement in patients with neuropathy than without it (\( \chi^2 = 5.77, p < 0.02 \)).

Nerve conduction studies revealed that 15 cases exhibited a decrease in amplitude without a delay in latency, while 5 cases showed a delay in latency, suggesting axonal (axonopathy) and demyelinating neuropathy, respectively. These two neuropathies were combined in 7 cases. Axonopathy was predominant among folate-deficient patients. Serum folate levels (and ages) were 3.42 ± 0.13 ng/mL in patients with demyelination (54.6 ± 19.3 y), 2.49 ± 1.13 in those with axonopathy (48.6 ± 14.4), and 2.79 ± 0.92 in combined neuropathy patients (61.1 ± 18.9) (Fig. 2). No statistical difference was found between the serum folate levels of patients with axonopathy and demyelination (\( p > 0.1 \)).

Male patients more frequently exhibited demyelinating neuropathy than females (\( \chi^2 = 14.0, p < 0.005 \)) (Fig. 3A). Neurological symptoms seemed to be more frequently improved by folate supplements in patients with axonopathy than without neuropathy (\( p = 0.058 \)) (Fig. 4).

Neuropathy was motor- and sensory-dominant, and almost equally involved in 7, 11 and 9 cases, respectively (Fig. 3B). Lower extremities were usually involved more extensively and severely than upper extremities. Cranial neuropathy was observed in 5 cases, including 7 cases with dysgeusia.

Serum folate levels and age were 2.96 ± 0.1 ng/mL and 51.1 ± 16.6 y in sensory-, 2.87 ± 1.04, 59.0 ± 18.0 in motor-dominant, and 2.37 ± 0.99, 50.6 ± 16.7 in combined neuropathy patients, respectively, with no statistically significant difference in age (\( p > 0.1 \)) or folate level (\( p > 0.5 \)).
Male patients more frequently exhibited motor-dominant neuropathy than females ($\chi^2 = 14.8$, $p < 0.002$) (Fig. 3B). Neurological symptoms seemed to be more frequently improved by folate supplements in patients without neuropathy than patients with sensory- or motor-dominant neuropathy ($p = 0.079$). Multivariate logistic regression analysis revealed that neuropathy was not significantly correlated with any factor, independent of other factors, in folate-deficient patients. 

**Encephalopathy accompanied by folate deficiency**

Encephalopathies were observed in 22 cases among 36 folate-deficient neurological patients. Encephalopathy manifested as intellectual impairments such as dementia in 17 cases neuroradiologically, including 17 cases of brain atrophy. 5 cases of high intensity areas on T2 weighted images, and 3 cases of reduced cerebral blood flow revealed by SPECT, or electrophysiologically in 5 cases with delay in P300 latency, and 3 cases with slowing of the basic rhythm in electroencephalography. We found a decreased level of folate in 4 cases, clinically diagnosed as frontal dementia, and 1 case each of Pick's disease, ALS-dementia, dementia with Fahr's syndrome and frontal dementia with canities.

Serum folate levels were $2.44 \pm 0.99$ and $3.10 \pm 0.68$ ng/mL in patients with and without encephalopathy, respectively, and the difference was significant ($p < 0.05$), while the age of two groups was not significantly
Fig. 5. Serum folate levels and age in demented patients.

(A) Serum folate levels in demented patients. Demented patients showed significantly ($p<0.02$) lower folate levels.

(B) Difference in age between folate-deficient patients with and without dementia. Demented patients were significantly ($p<0.02$) older. Dots, vertical bars and broken horizontal bars show means, standard errors and deviations, respectively.

\[\text{Different (57.3±20.7 y and 52.7±18.1 in the encephalopathy and non-encephalopathy groups; } p=0.50)\text{. Demented patients showed markedly low serum levels (2.30±0.94 ng/mL), compared with those without dementia (3.06±0.79; } p<0.02; \text{ Fig. 5A). Patients with dementia were significantly (}p<0.05\text{) older (62.3±19.3 y) than those without dementia (49.5±18.2; Fig. 5B).}

Anemia in folate-deficient neurological patients

Anemia was found in 13 cases (36% of folate-deficient neurological patients; 9 females and 4 males), including macrocytic anemia in 7 cases. Serum folate levels were significantly ($p<0.005$) lower in 13 anemic neurological patients (1.95±0.63 ng/mL) than 23 non-anemic neurological patients (3.01±0.84) (Fig. 6). Anemia was observed more frequently in females than males ($\chi^2=14.68$, $p<0.0001$). The incidence of anemia was not significantly different between folate-responsive and resistant neurological patients ($p>0.5$). Multivariate logistic regression analysis revealed that anemia was correlated with female sex ($\chi^2=4.04$, $p<0.05$) and a low serum folate level ($\chi^2=5.22$, $p<0.05$), independent of other factors in neurological patients.

Effect of folate on neurological symptoms

A folate supplement was given as described above. Folate administration improved neurological symptoms in 24 of 36 cases. Anemia and dysgeusia improved after the administration of folate in all 13 and 7 patients, respectively. Age was not significantly different between folate-responsive (52.8±18.2 y) and resistant patients (61.0±19.3; $p>0.05$). There were 18 and 6 male and female patients in the responsive group, and 7 and 5 in the resistant group. Male patients were more responsive than females to folate treatment ($\chi^2=6.24$, $p<0.05$). Serum folate levels were not significantly different between folate-resistant (2.57±0.94 ng/mL) and responsive patients (2.77±0.91; $p>0.5$). No significant difference was observed in the effectiveness of folate therapy between patients with and without encephalopathy ($p>0.05$), whereas folate-deficient patients without dementia were more frequently ameliorated by folate administration than those without dementia ($\chi^2=6.99$, $p<0.01$).

Multivariate logistic regression analysis revealed that folate therapy was more effective in neurological patients without dementia ($\chi^2=3.97$, $p<0.05$), independent of other factors. However, 8 patients with dementia responded to folate therapy and their mental scores im-
proved above the lower limit.  

Other systemic abnormalities and folate-responsive neurological diseases

We examined systemic abnormalities in 36 folate-responsive neurological patients. Systemic abnormalities included other vitamin deficiencies, anemia, excessive alcohol intake, previous gastrectomy, gastric malabsorption, tube feeding, continuous drip infusion and anticonvulsant administration.

All folate-deficient patients with a history of excessive alcohol intake exhibited neuropathy, although 7 of 10 alcoholic patients had encephalopathy. Similarly, all folate-deficient patients with a history of gastrectomy showed neuropathy, while 2 of 5 gastrectomized patients presented encephalopathy.

Anticonvulsants such as phenytoin, valproate, zonisamide or carbamazepine had been administered in 4 cases. Neurological symptoms in all 4 cases were improved only by folate supplements. Deficiencies in other vitamins were found in 8 cases; thiamin in 6 cases, riboflavin in 1 case, cobalamin in 1 case, and vitamin E deficiency in 2 cases. Folate administration alone improved neurological symptoms in 5 of 8 cases, while further improvements were attained by the administration of other vitamins.

Folate-deficient neurological patients poorly responded to the folate supplements when they were treated with tube feeding ($\chi^2=9.84, p<0.002$) or continuous drip infusion ($\chi^2=5.69, p<0.02$), or had malabsorption symptoms ($\chi^2=8.04, p<0.005$). Folate responsiveness was not significantly different between those with and without a history of gastrectomy ($p>0.5$).

Folate-deficient neurological patients poorly responded to folate supplements ($\chi^2=3.49, p=0.062$) and the history of alcohol intake did not influence the effect of folate supplements ($p>0.5$). Multivariate logistic regression analysis showed that folate therapy was not effective in neurological patients with malabsorption ($\chi^2=5.75, p<0.02$) or continuous drip infusion ($\chi^2=3.88, p<0.05$) independent of other factors.

**DISCUSSION**

Folate has been known to participate biochemically in the transfer of one carbon units, and to serve as a hydrogen donor for the hydroxylation of aromatic amino acids including phenylalanine, tyrosine and tryptophan (1, 8, 9). Folate deficiency is thought to cause dementia (3, 10), subacute combined degeneration (10, 11), neuropathy (12, 13), multiple sclerosis (14, 15), and cancer in the GI tract (16). Folate deficiency is a common vitamin deficiency occurring in approximately 10% of the U.S. population (17). However, the frequency and importance of folate deficiency has not been fully elucidated in neurological diseases, especially in Japan.

Vitamins B$_1$ or B$_12$ are often administered to neurological patients, but folate is not recognized as an important factor associated with neurological diseases such as neuropathy or dementia. The present study demonstrated the following points:

1) Many patients with neurological symptoms were found to be folate-deficient.

2) Neurological symptoms were frequently improved after folate supplements, particularly in male and nondemented cases without malabsorption or continuous drip infusion.

3) Several novel characteristics were revealed in folate-deficient neuropathy and encephalopathy. Thus, folate needs to be examined in serum and given to patients with malnutrition.

The major causes of folate deficiency found in this study were disorders in the GI tract, excessive alcohol intake or anticonvulsants as described previously (12, 18, 19). In addition, we found 8 neurological patients without previously reported causes (20–22). These 8 cases had been treated with various drugs such as antibiotics or psychomimetics. Folate deficiency could be caused by the side effects as-yet-unidentified drugs, since many chemicals are known to interfere with folate metabolism (19). Drugs responsible for folate deficiency should be identified.

Many neurological symptoms have been reported to be associated with folate deficiency, but the frequency of the association has not been investigated in detail. The most common neurological disorder was neuropathy, followed by dementia. Neuropathy was observed in the lower extremities more severely than the upper extremities. Sensory axonopathy was dominant in the folate-deficient neuropathy demonstrated electrophysiologically, consistent with previous reports (12, 22), while multivariate analysis did not detect any differences among subtypes of folate-deficient neuropathy. Axonopathy responded more readily to folate therapy, suggesting that axonopathy is a prototype of folate-deficient neuropathy which can be modified by other factors concomitant with diseases, leading to demyelination.

We found 7 cases with gustatory impairment (dysgeusia) and folate administration improved this after 60 d. Commonly dysgeusia induced a loss of appetite in folate-deficient patients and worsened malnutrition and folate deficiency. Therefore, further studies on folate-responsive dysgeusia with more patients are needed to clarify whether it is due to neuropathy or a GI tract disorder.

The present study revealed a correlation between sex and folate-deficient neurological diseases. The serum folate level was higher in male than female folate-deficient patients. Male patients more frequently exhibited demyelination or motor-dominant neuropathy and anemia, which appeared to be more responsive to folate therapy. The male predominance could be explained either by history of alcohol ($\chi^2=8.89, p<0.005$) or of gastrectomy ($\chi^2=4.00, p<0.05$) or by a higher serum folate threshold of neurological manifestation than females. The latter possibility could be confirmed by the lower incidence of demyelination and anemia, and lower serum folate level in females.

Encephalopathy involved mostly cognitive dysfunction, of which the features were different from those found in Alzheimer’s disease. The folate-deficient cognitive dysfunction was characterized by a change in
mood, a decrease in motivation, behavioral disorders, slight disturbance of consciousness, and mild memory disturbance. Cognitive dysfunction could be classified as dementia according to ICD-10. Noticeably, 4 folate-deficient patients were diagnosed as frontal dementia i.e. Pick’s disease. ALS-dementia, dementia with Fahr’s syndrome (6) and frontal dementia with canities (23). The food intake of these 4 cases decreased in total volume and was unbalanced, consistent with the notion that the frontal lobe is related to behavior and appetite (24). The nutritional abnormality due to dysgeusia appears to accelerate folate deficiency, implying that folate administration could help to stop the progress of frontal dementia.

Encephalopathy associated with folate deficiency may result from the vicious circle mentioned above, and patients with CNS dysfunction would show a more pronounced decrease in folate level and more readily resist replacement therapy. Moreover, some additional factors may have been involved in the pathogenesis of encephalopathy as in dementia. However, it should be stressed that folate therapy ameliorated many encephalopathy patients, including 8 cases with dementia.

Encephalopathy appeared more frequently in patients with lower serum folate levels (2.44±0.19 ng/mL) than those with neuropathy alone (3.10±0.24, p<0.05). Encephalopathy was often accompanied by neuropathy in folate-deficient patients (13 of 22 cases). Folate therapy was more successful for cases without dementia. Folate-resistant patients seemed to have a longer duration and a lower folate level, suggesting irreversible changes such as atrophy in the CNS. These results indicate that neuropathy may take place at a higher serum folate level, and further proceed to encephalopathy.

Folate administration improved neurological symptoms in 24 of 36 cases after 2 months. In other studies, folate was given for longer periods such as 9 to 39 months (12) or 50 to 240 d (25). We examined the effect after 2 months, but nonresponders are expected to be ameliorated by longer treatment.

We demonstrated that neurological patients with malabsorption or those treated with continuous drip infusion were resistant to folate therapy. Those patients may have had some other systemic impairments in addition to folate deficiency, so that supplement therapy failed to improve their symptoms.

The present study emphasized the importance of examination of serum folate concentrations and, if the concentration is low, supplementing with folate. Several groups had folate levels measured in the cerebrospinal fluid (CSF) (15). We determined serum folate levels, since CSF folate levels correlate well with serum folate levels (15), while the measurement in serum is more conventional and harmless in practical medicine or for common diseases like neuropathy or dementia. Examination of folate levels and treatment with folate are potentially useful in daily practice in Japan.

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REFERENCES


