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Case Report

A Patient in Whom Wernicke's Encephalopathy and Alcoholic Pellagra Encephalopathy Developed on Separate Occasions

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ABSTRACT

We report on a patient in whom Wernicke's encephalopathy (WE) and alcoholic pellagra encephalopathy (PE) developed on separate occasions. A 43-year-old man was referred to our hospital because of a progressive gait disorder. He presented with dermatitis, dementia, and gastrointestinal symptoms. Laboratory studies supported a diagnosis of PE : the serum level of nicotinic acid was low, but the thiamine level was normal. Treatment with nicotinic acid markedly improved symptoms and allowed discharge after several months. One year after discharge, the patient was readmitted because of recurrence of the gait disorder. He now presented with disorientation, Wernicke-Korsakoff syndrome, and ataxia. Laboratory studies supported a diagnosis of WE : the serum thiamine level was low, but the nicotinic acid level was normal. Administration of thiamine markedly decreased the neurologic symptoms. To our knowledge, this is the first reported case of WE and alcoholic PE developing at separate times.

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Key words : encephalopathy, alcoholic brain damage, Wernicke-Korsakoff syndrome, pellagra, ataxia

INTRODUCTION

The brain disorders of alcoholics have various causes. Ethanol neurotoxity, Wernicke's encephalopathy (WE), hepatocerebral degeneration, central pontine myelinolysis, Maechiafav-Bignami syndrome, and pellagra may all seriously disrupt brain function[1,2].

First described by Karl Wernicke in 1881[3], WE is manifested by ophthalmoplegia, ataxia, and a state of global confusion caused by thiamine deficiency. Although WE is a common neurologic disorder, it is often undiagnosed during life because many alcoholics with the condition fail to show typical symptoms[4-6].

In the first known description of pellagra in 1735, the condition was called mal de la rosa, a Spanish term referring to the typical reddish skin of the extremities[7]. The term pellagra, which refers to the roughness of the skin, was first used in 1777[8]. From that time, pellagra remained endemic for nearly two centuries in the southern Europe[9], usually a syndrome including dementia, dermatitis, and diarrhea due to a

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deficiency of niacin[10]. The first case of pellagra in the United States was reported in 1902, and soon thereafter pellagra became epidemic there[11]. In contrast, the term alcoholic pellagra (AP), or pseudopellagra, was first used in 1869[12]. Although brain lesions caused by the vitamin deficiency are rare, significant numbers of cases of pellagra encephalopathy (PE) or Wernicke's encephalitis (WE) still develop, particularly in alcoholics[13,14].

Because malnourished alcoholics often have deficiencies of both nicotinic acid and thiamine, WE and alcoholic PE can be difficult to distinguish. Patients with AP or WE may also fail to exhibit the classical triad of symptoms for AP or WE. We present a patient in whom WE and PE developed on separate occasions. We were particularly interested in examining serum vitamin levels and clinical symptoms that were strongly correlated with each encephalopathy.

CASE REPORT

A 43-year-old man was admitted to Aoto Hospital, The Jikei University School of Medicine, in early July of year 1 (the calendar year is omitted at the patient's request) because of progressive gait disturbance and weight loss. The patient was an alcoholic who had drunk at least 1 bottle of whisky daily for more than 10 years with no concern for nutrition. He had no history of pulmonary tuberculosis, diabetes, hypertension, liver damage, or any other major disorder.

Findings of physical examination on admission were: height, 168 cm; weight, 51.0 kg; temperature, 36.0°C; blood pressure, 128/78 mmHg; pulse, 86 per minute; and respiratory rate, 18 per minute. The eyes showed no signs of anemia or jaundice. The lung sounds were not coarse, and the cardiac rhythm was regular on auscultation. The patient denied diarrhea and claimed to have no appetite. The skin, especially that of the legs, was extremely dry with hyperkeratosis and hyperpigmentation.

On neurologic examination the patient was alert but apathetic and disinterested. Eye movements were normal. Tendon reflexes were hyperactive. Nerve-conduction studies confirmed the presence of peripheral neuropathy. Other findings of the neurologic and general physical examinations were normal. A biopsy of the leg skin showed psoriasiform epidermal hyperplasia, spongiosis, and parakeratosis. The neurologic findings and the results of biopsy were compatible with diagnoses of PE and pellagra dermatitis. The symptoms improved markedly with oral nicotinic acid therapy, and the patient could ambulate

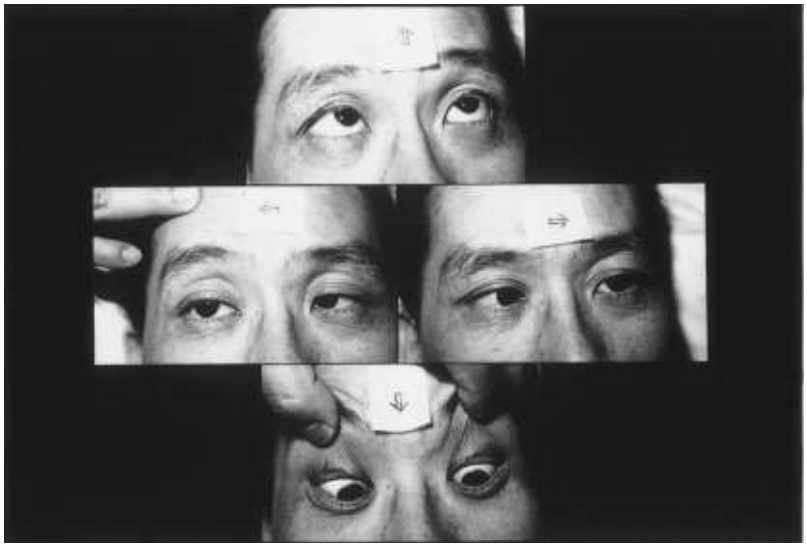


Fig. 1. The abnormal eye-movement in WE. Extraocular movement was disordered on both lateral views, exhibiting coarse nystagmus on lateral gaze and lateral rectus palsy.

and care for himself after two months. He was in our hospital for six months because of his gait disturbance and was discharged in December of year 1.

Soon after discharge, the patient stopped taking the prescribed nicotinic acid supplement and started drinking 1 bottle of sake daily. He was readmitted to our hospital in February of year 3 because of a progressive gait disturbance. He was malnourished (51 kg) on examination. His body temperature was 36.0°C and his blood pressure was 128/78 mmHg. The eyes showed no signs of anemia or jaundice, breath sounds were not coarse, and the cardiac rhythm was regular. The skin showed no significant changes, and the patient complained of neither diarrhea nor anorexia. On neurologic examination the patient was disoriented to time, place, and person and

Table 1. Serum concentrations of vitamin in the PE and WE

Vitamins	(Normal range)	(A) PE	(B) WE
B1	(20–50 ng/ml)	34.0	14.0
B2	(65–125 ng/ml)	68.4	65.0
B6	(6.5–45 ng/ml)	6.7	6.8
B12	(230–800 ng/ml)	280.0	480.0
Follic acid	(2.4–9.8 pg/ml)	2.4	2.6
Nicotinic Acid	(5.0–7.9 μg/ml)	4.1	6.7

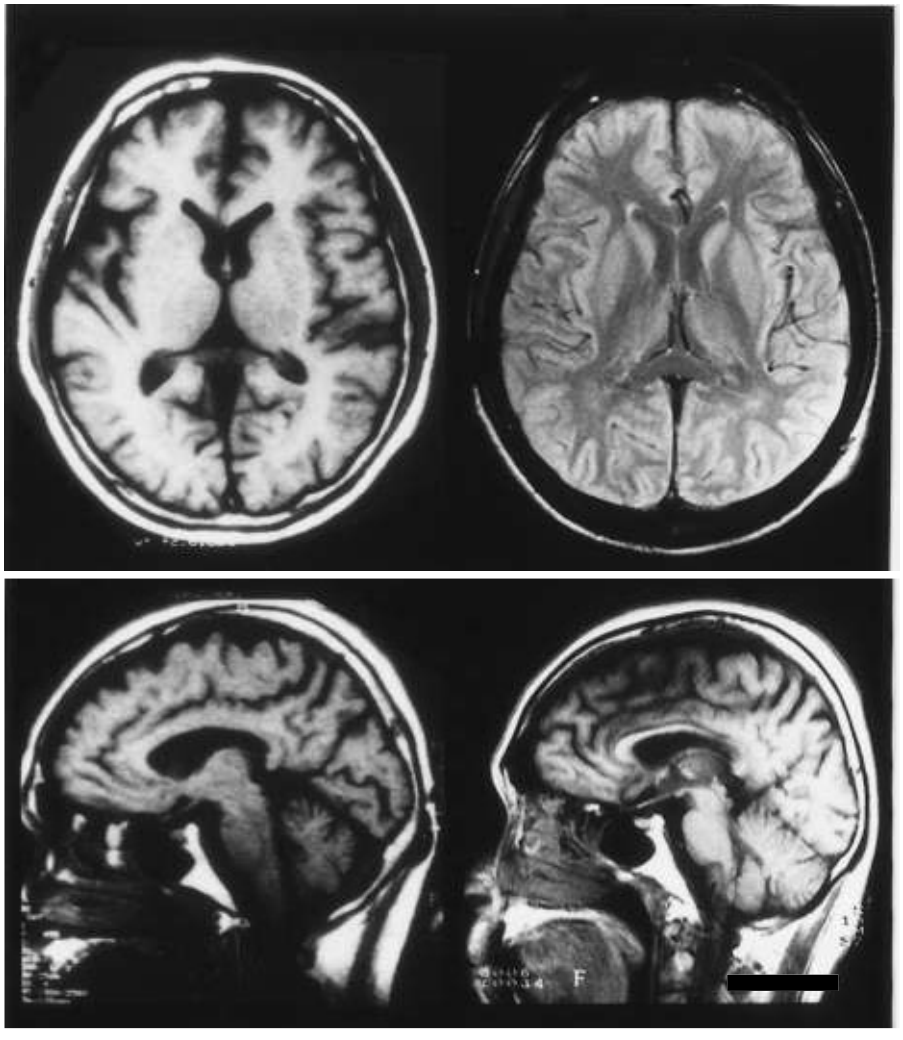


Fig. 2. MRI findings in PE and WE. The MR during the admission for PE revealed only slight atrophy in the frontal lobe (Fig. 2A), whereas MR during the admission for WE revealed an area without hyperintensity surrounding the third ventricle and the aqueduct (Fig. 2B).

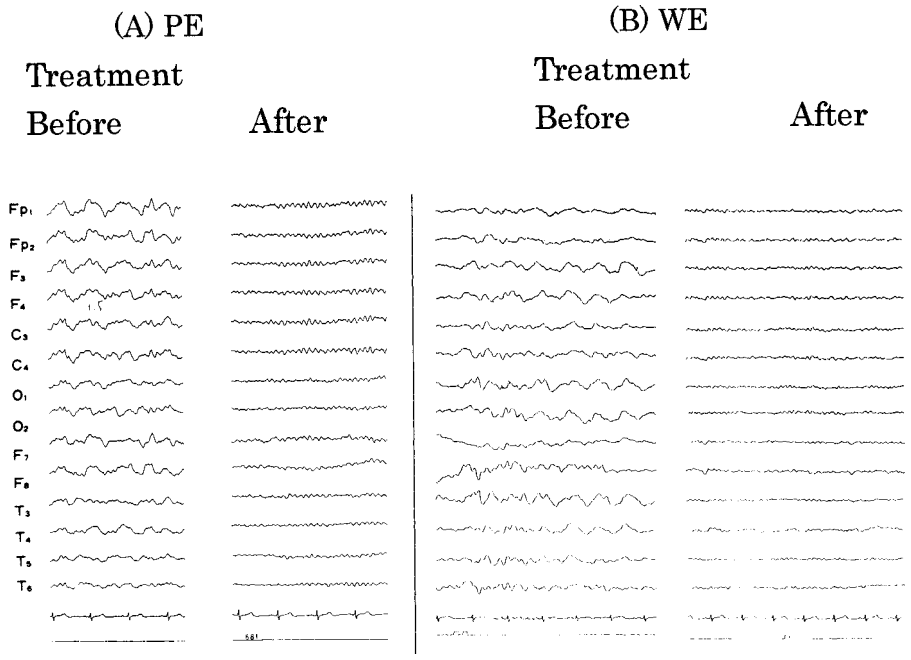
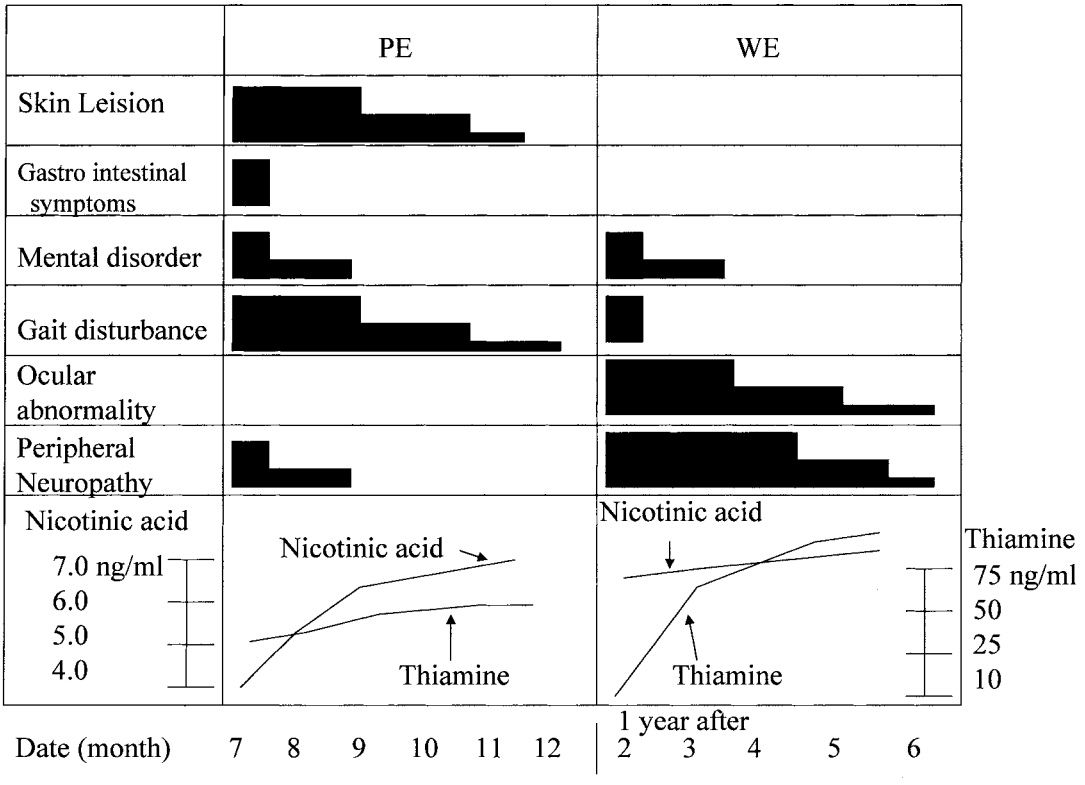


Fig. 3. EEG findings in PE (Fig. 3A) and WE (Fig. 3B) before and after treatment with nicotinic acid (PE) and thiamine (WE). Diffuse delta waves seen before treatment in both PE (Fig. 3A, left panel) and WE (Fig. 3B, right panel) suggested a metabolic abnormality. EEG finding after treatment clearly showed improvements in both PE (Fig. 3A, left panel) and WE (Fig. 3B, right panel).

Table 2. Clinical course of a combined case of PE and WE.



showed severe short-term memory deficits and dyscalculia. Although the pupils were bilaterally equal and reactive to light, extraocular movement was disordered on both lateral views, exhibiting coarse nystagmus on lateral gaze and lateral rectus palsy (Fig. 1). The deep tendon reflexes were uniformly absent, and the gait disturbance appeared to be mainly due to a symmetrical sensory impairment and ataxia of the lower extremities. Several days after admission, the patient exhibited global confusion, hallucinations, and delirium tremens. Although doll's eyes and caloric responses were absent, the patient exhibited bilateral Babinski signs. Wernicke-Korsakoff syndrome was diagnosed on the basis of these findings.

Comparison of the laboratory and radiologic findings of the 2 encephalopathies

To confirm the clinical diagnosis, we conducted more detailed blood tests in addition to the routine blood test, liquor test, computed tomography of the brain, electroencephalography (EEG), and magnetic resonance (MR).

The serum concentration of thiamine was 14.0 ng/ml during the first admission (less than normal range, Table 1A) and 34.0 ng/ml during the second admission (within normal range, Table 1B). In contrast, the serum nicotinic acid concentration was 4.1 ng/ml during the first admission (less than normal range) and 6.7 ng/ml during the admission time (within normal range). There were no significant changes in serum levels of other vitamins between the first and second admissions. Thus, serum levels of vitamins supported the clinical diagnoses of PE for the first admission and of WE for the second admission.

Because computed tomographic scans obtained during the first admission, when PE was diagnosed, and the second admission, when WE was diagnosed, showed no significant changes (data not shown), MR was performed during both admissions. An MR scan obtained during the first admission showed only slight brain atrophy in the frontal lobe (Fig. 2A), whereas MR performed during the second admission revealed an area without hyperintensity surrounding the third ventricle and the aqueduct (Fig. 2B).

EEG findings were obtained when he developd PE (Fig. 3A) and WE (Fig. 3B) foe each before and after treatment with nicotinic acid (for PE) or thiamine

Table 3. Clinical and pathological findings of 9 cases of the combind alcoholic encephalopathies

Case	1	2	3	4	5	6	7	8	9	
Author and	Serdau	Serdau	Serdau	Serdau	Serdau	Park	Teare	Wallengren	Current	
Reference	(14)	(14)	(14)	(14)	(14)	(17)	(18)	(19)	Case	
Time	1988	1988	1988	1988	1988	1991	1991	2002	2003	
Age. Sex	54F	53F	?	?	?	51M	44F	40F	47M	
Clinical diagnosisis	mutism	AE	AE	AE	AE	WD	WD+APE	WD	APE	WD
Clinical features										
Delirium	−	+	+	+	+	+	+	−	−	+
Ataxia	+	+	+	+	+	+	+	+	−	+
Ophthalmoplegia	+	+	−	−	−	+	−	+	+	+
Dementia	−	−	−	−	−	−	+	−	+	−
Dermatitis	−	−	−	−	−	+	−	+	+	−
Diarrhea	−	−	−	−	−	+	−	−	+	−
Treatment										
Vitamin B	−	+	+	+	+	+	+	+	−	+
Nicotinic acid	−	−	−	−	−	+	+	+	+	−
Pathological diagnosis	APE+WD+ MBD	APE+WD	APE+WD	APE+WD	APE+WD	APE+WD	Alive	Alive	Alive	

AE: Alcoholic encephalopathy APE: Alcoholic pellagra encephalopathy
WD: Wernicke/Korsakoff disease MBD: Marchiafava/Bignami disease

(for WE). The diffuse delta waves seen before treatment during the first admission (Fig. 3A, left panel) and second admission WE (Fig. 3B, right panel) suggested a metabolic abnormality. Although EEG was of limited use for discriminating between PE and WE, EEG findings after the treatments clearly showed improvements during both the first (Fig. 3A, left panel) and second admissions (Fig. 3B, right panel).

Comparison of the clinical courses of the 2 encephalopathies

During the first admission the patient had dermatitis, gastrointestinal symptoms, and dementia (Table 2), which are compatible with the classic triad of pellagra. In marked contrast, he had neither skin changes nor gastrointestinal symptoms during the second admission, when WE was diagnosed. Consciousness was unaltered during the first admission for PE but was impaired for several days during the second admission for WE because of global confusion, which is a typical symptom of Wernicke–Korsakoff syndrome. Interestingly, gait disturbance was observed during both admissions but appeared to be mainly due to muscle atrophy from malnutrition during the first admission for PE and due to a symmetrical sensory impairment and ataxia of the lower extremities during the second admission for WE. Ocular abnormalities were not present during the first admission, but disordered extraocular movement was observed during the second admission for WE (Fig. 1). The diagnosis of WE was established with the triad of ataxia, Wernicke–Korsakoff syndrome, and abnormality of extraocular movement. Additionally, deep tendon reflexes were hyperactive during the first admission for PE but those were absent during the second admission for WE (not shown in Table). Although peripheral neuropathy was present during both admissions, it resulted from thiamine deficiency during the admission for WE[5,6], and polyneuritis was accompanied with PE. These findings of hyperactive deep tendon reflexes and peripheral neuropathy are consistent with PE[14].

The patient's gastrointestinal symptoms and mental disorder had improved after 2 months of treatment with 300 mg daily oral nicotinic acid (Table 2 bottom). These improvements correlated with the normalization of the blood nicotinic acid concentration. The patient was discharged in December of year 1 when the gait was normalized and the skin lesions are healed.

In contrast, the patient was given 50 mg of intravenous thiamine daily for 1 month during the second admission for WE; mental status and the gait had improved markedly after 2 months (Table 2). However, both the ocular abnormality and the peripheral neuropathy remained until just before discharge in June of year 3 after 4 months of hospitalization. The patient was well at last contact in April 2003.

DISCUSSION

Nine cases of combined PE and WE have been reported (Table 3): 5 cases reported by Serdau et al.[14] in 1988 and 4 subsequent cases, including the present case.

The classic symptoms of WE are global confusion, ocular abnormality, and ataxia; however, only 16% of cases exhibit this classic triad, and 19% of cases exhibit none of the classic signs[15]. Of the 9 combined cases of WE and PE reported, 3 cases (33%) showed the classic triad of WE and 6 cases showed 1 or 2 of the classic symptoms, including delirium (4 of 6 cases), ataxia (6 of 6 cases), and opthalmoplegia (2 of 6 cases). Therefore, the probability of the classic triad of WE being present might be higher in combined cases of alcoholic PE and WE than in solitary cases of nonalcoholic WE. Moreover, ataxia would be an important diagnostic sign for WE as all combined cases showed the ataxia. This finding might be explained by malnutrition in alcoholism exacerbating WE and producing the typical symptoms[10].

The classic clinical triad of pellagra is dementia, dermatitis, and diarrhea; however, all three symptoms are present in less than 50% of cases, and dermatitis is present only in 30% of cases[13]. In the 9 reported cases of combined WE and PE (Table 3), dementia, dermatitis, and diarrhea (gastrointestinal symptoms) were present in only 3, 3, and 2 cases, respectively.

Moreover, only our present case exhibited the complete clinical triad for PE. Of the 8 other cases, only 2 were diagnosed clinically as combined WE and PE; the other cases were diagnosed as WE (2 cases), alcoholic encephalopathy (2 cases), and mutism (1 case).

Therefore, the clinical triad for PE is unreliable for the diagnosis of combined PE and WE. This conclusion is supported by the 5 cases reported by Serdau et al. (cases 1 to 5), none of which showed the classic PE triad at admission and were only diagnosed as combined PE pathologically[14]. Interestingly, our case showed the respective criteria for PE and WE as each developed separately. Among the previously reported cases of combined WE and PE, none involved separate development of the two alcoholic encephalopathies. Serum concentrations of vitamin B and nicotinic acid often decrease together in alcoholism because such a decrease is frequently present[10] in alcoholism. Interestingly, serum concentrations of nicotinic acid and vitamin B in our patient closely coincided with the development of WE and PE.

Our patient drank at least 1 bottle of whisky per day for more than 10 years with no concern for nutrition; PE then developed. Soon after discharge, he stopped taking the prescribed nicotinic acid supplement and started drinking 1 bottle of sake daily. After another year, he was readmitted to our hospital.

The explanation for the change in the patient's clinical appearance is that he received intensive treatment with nicotinic acid during his first admission which was sufficient even 1 year later to prevent pellagra from recurring. However, the change in the type of alcohol consumed from whisky to sake might also explain the change in clinical appearance. Indeed, the prevalence of pellagra in the United States has historically been higher in persons whose dietary staple was corn[9], because corn contains less niacin but large amounts of leucine, which may prevent the production of nicotinamide-adenine dinucleotide phoaphate and reduce the activation of nicotinic acid[16]. In contrast, red wine is a poor source of niacin[16], and the frequency of alcoholic pellagra in France might be explained by the prevalence of wine drinkers, because Serdau found that 21 of 22 patients with pellagra were heavy wine drinkers[14]. Thus, the type of alcohol may affect the prevalence of alcoholic pellagra.

In conclusion, we have described what we believe to be the first reported case of 2 alcoholic encephalopathies developing at separate times in a single patient. Our review of the 9 reported cases of combined PE and WE suggests that the classic triad of pellagra is not reliable for diagnosis but that ataxia is usually present in such combined cases. The diagnosis of combined PE and WE should be considered when alcoholic patients show encephalopathy of unknown cause, despite the absence of typical symptoms for WE and, especially, for PE.

References

1. Lieber CS. Biochemical and molecular basis of alcohol-induces injury to liver and other tissues. N Engl J Med 1988; 319: 1639-50.
2. Charness ME. Brain leisions in alcoholics. Alcohol Clin Exp Res 1993; 17 (1): 2-11.
3. Wernicke C. Lehrbuch der Schirnkrankheiten fur erzte und Studierende. Berlin: Theodor-Fischer-Verlag, Vol. 2, 1881: 220-42.
4. Torvik A, Lindboe CF, Rodge S. Brain leisions in alcoholics. A neuropathological study with clinical correlation. J Neurol Sci 1982; 56: 233-48.
5. Harper C. The incidence of Wernicke's encephalopathy in australia: a neuropathological study of 131 cases. J Neurol Neurosurg Psychiatry 1983; 46: 593-8.
6. Harper C. Wernicke's encephalopathy: a more common disease than realized. J Neurol Neurosurg Psychiatry 1979; 42: 226-32.
7. Major RH. Classic descriptions of disease. 3rd ed. Springfield, III, Charles C. Thomas, 1945: 607-15.
8. Major RH. Don Gasper Casal, Fancois thiery and Pellagra. Bull Hist Med 1944; 16: 351-61.
9. Roe DA. The social history of pellagra. Ithaca, NY: Cornell University Press; 1973.
10. Victor M. Persistent altered mentation due to ethanol. Neurol Clin 1993; 11: 639-61.
11. Bollet AJ. Politics and pellagra: the epidemic of pellagra in the US in the early twentieth century. Yale J Biol Med. 1992; 65: 211-21.
12. Leudet E. Recherches pour servir a I'histoire de la pellagra sporadique et de la pseudopellagre des alcoolises. Comptes Rendus des Seances et Memoires de la Societe de Bioologie, Paris. 1869; 19: 3-29.
13. Ishii N, Nishihara Y. Pellagra among chronic alcoholics; clinical and pathological study of 20 necropsy cases. J

Neurol Neurosurg Psychiatry 1981 ; 44 : 209–15.
14. Serdau M, Hauw–HC, Laplane D, Buge A, Castaigne P, Goulon M, et al. The clinical spectrum of alcoholic pellagra encephalopathy : a retrospective study of 22 pathological cases. Brain 1988 ; 111 : 829–42.
15. Harper CG, Giles M, Finlay–Jones R. Clinical signs in the Wernicke–Korsakoff complex : a retrospective analysis of 131 cases diagnosed at necropsy. J Neurol Neurosurg Psychiatry 1986 ; 49 : 341–5.
16. Connor EB. The etiology of pellagra and its significance for modern medicine. Am J Med 1967 ; 42 : 859–67.
17. Park SH, Na DL, Lee JH, Kim BJ, Myung HJ. Alcoholic pellagra encephalopathy combined with Wernicke disease. J Korean Med Sci 1991 ; 6 : 87–93.
18. Teare JP, Hyams G, Pollock S. Acute encephalopathy due to coexistent nicotinic acid and thiamine deficiency. Br J Clin Pract 1993 ; 47 : 343–4.
19. Wallengren J, Thelin I. Pellagra-like skin leisions associated with Wernicke's encephalopathy in a heavy wine drinker. Acta Derm Venereol 2002 ; 82 : 152–4.