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Acute Wernicke's encephalopathy. Comparison among the clinical features, magnetic resonance images and neuropathology findings

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ABSTRACT
An acute case of Wernicke's encephalopathy (AWE) is here reported in a 24 year old woman who vomited all ingested food. Onset of AWE was insidious with muscular weakness and a progressive motor disturbance evolving to total paralysis until the patient was unable to stand up or even keep her head up. Associated language disturbance and confusional state developed, followed by oculomotor paresis and nystagmus in all directions. A magnetic resonance study on day 56th showed hyperintensities in periventricular regions, including ventromedial thalamic area and mammillary bodies, mesencephalic tegmenta at quadrigeminal and periaqueductal regions. Though the pontine tegmentum also showed periventricular hyperintensity, the latter tapered down to the upper third of the medulla oblongata near the vestibular nuclei. Patient died on day 60th. The brain displayed severe hemorrhage associated to capillary endothelial swelling, total necrosis of the neuropil and myelin loss in all the affected areas. The lesions in this case are characteristic of the acute phase of Wernicke's encephalopathy due to thiamine deficiency. The lesional intensity seems to be the most relevant among the extense series of cases of AWE described in the scientific literature. Moreover, it is the only case in which the clinical features, the magnetic resonance and the neuropathological findings permit a strict and precise comparison.
Key words: Ingested food, Wernicke's encephalopathy, magnetic resonance.

Encefalopatía aguda de Wernicke. Comparación entre las características clínicas, las imágenes de resonancia magnética y hallazgos neuropatológicos

RESUMEN
El caso corresponde a una mujer de 24 años con intolerancia a la ingesta de alimentos y vómitos continuos durante 60 días, periodo en que insidiosamente desarrolló las manifestaciones clínicas de encefalopatía de Wernicke en etapa aguda. El inicio de la AWE fue insidioso, con debilidad muscular que progresó lentamente hasta total parálisis motora con incapacidad para la marcha y mantener erecta la cabeza. Se asoció después con trastornos del lenguaje (dislalia) y de conciencia (confusión mental). Así como parálisis oculomotriz y nistagmus en todas direcciones. La paciente ya en coma falleció en el día 60, ocho días después de su ingreso al hospital. El estudio de resonancia magnética en el día 56 mostró hiperintensidad en regiones periventriculares, núcleos ventromediales del tálamo, tubérculos mamilares, tegmento mesencefálico en la lámina quadrigémina y región periacueductal, tegmento pontino y tegmento bulbar. El cerebro mostró hemorragia intensa asociada a tumefacción del endotelio capilar, necrosis y desmielinización del tejido en todas las áreas de lesión antes descritas en la resonancia magnética. Las lesiones en este caso corresponden y son características de la fase aguda de la encefalopatía de Wernicke por deficiencia de tiamina. Estas intensas lesiones constituyen caso único entre la extensa serie de casos ya descritos en la literatura pertinente; el caso permite la comparación estricta y precisa entre las manifestaciones clínicas, los hallazgos en la resonancia magnética y los hallazgos neuropatológicos.
Palabras clave: *intolerancia a la ingesta de alimentos, encefalopatía de Wernicke, resonancia magnética.*

INTRODUCTION

Wernicke's encephalopathy was first described by Carl Wernicke, a German neuropsychiatrist in 1881.[1] Of the three cases he described, two were related to chronic alcholism and one to malnutrition, the latter a young woman whose suicidal attempt left her with esophageal stenosis and could not ingest food. The brain lesions were similar in the three cases: mainly the periventricular regions around the third and fourth ventricles and the aqueduct, mammillary bodies, the massa intermedia and ventromedial nuclei of the thalamus, the quedrigeminal lamina, the oculomotor and vestibular nuclei.[2,3]

Wernicke's encephalopathy is a clinical neurological entity always appearing as an acute medical emergency, potentially fatal but readily reversible if treated early with thiamine. Due to the findings in large series of cases of AWE in chronic alcoholics, for many years it was believed that Wernicke disease was due to the toxic affects of alcohol. It was not until the report by Alexander, et al.,[4] that the relation to thiamine deficiency was established. Vitamin $B_{1,}$ or thiamine is an essential cofactor for energy

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metabolism, a coenzyme in intermediate carbohydrate metabolism.[5]

Thiamine is converted to thiamine pyrophosphate (TPP) or thiamine diphosphate by the enzyme thiamne pyrophosphatase –TPP is a prostetic group in many enzymes such as trnasketolase (pentose phospahate pathway), pyruvate dehydrogenase complex (pyruvate decarboxylation) and alpha-ketoglutarate dehydrogenase complex (citric acid cycle). The relation of AWE to a nutritional disease was suspected at recognizing Wernicke disease as a complication of gastric carcinoma and other disturbances affecting the alimentary tract (as in one of Carl Wernicke's cases) and of hyperemesis gravidarum. The report of Alexander, et al.[4] drew attention to the similarity of the pathologic changes in pigeons deprived of vitamin B and the observed lesions in Wernicke disease. It was then concluded that the lesions in many thiamine-deficient mammalian species also bore such a resemblance. It is now well established that deficiency of thiamine is the specific nutritional factor responsible for most of the symptomatology of Wernicke disease. In fact, ophthalmoplegia, nystagmus and ataxia as well as many of the initial mental symptoms such as apathy, drowsiness, listlessness, inattentiveness, lack of concentration and to sustain a conversation, are reversed and clear rapidly with thiamine administration.[3]

We consider the case here reported as unique due to the intensity of the lesions. Also, it is a case in which the clinical features, the magnetic resonance images and the neuropathology findings permit a strict and precise comparison.

CASE CLINICAL DATA

A 24 yr. old right-handed woman, born and living in Mexico City Not relevant family history. Denies alcohol. The patient had been well forty days before entering the hospital; symptoms started insidiously with nausea and vomiting, always associated to ingestion of food. Though the patient also noticed general malaise and feeling weak, she did not stop her usual house chores. Twenty days following onset, she sought medical advice. The physician prescribed treatment with parenteric solutions (not specified), vitamins and antiemetics. Nine days later her clinical condition worsened, the muscular weakness increased affecting mainly the lower limbs, the patient could not walk unless aided by some other person; By day fifty two, both the left and right upper limbs also became paretic. Involuntary tremor developed in both upper limbs. Four days before being admitted into the hospital the patient was unable to maintain the head in erect position, "my head sways to all sides". At the time of admission the patient was vomiting, somnolent and dyslalic. Physical exam: Blood pressure 140/90 mm Hg. Pulse: 88 beats/min, respiratory rate 20 breaths/min, temperature 36 °C (96°F). heigh: 1.55 m. b/w approx. 70 kg. At initial neurological evaluation: the patient was alert, oriented; cognition normal. Cranial nerves: Optic nerve: pupils were round and equal, 3 mm each, photomotor reflex normal, eyes in central position, ocular movements, abduction and adduction abolished; vertical bilateral nystagmus when attempting upper gaze. Funduscopic examination showed blurred disks on the nasal side but no papilledema, venous pulse normal, there was a slight papillary hemorrhage on the left eye. Bilateral neurosensory hypoacusis, mainly in the right ear. The rest of the cranial nerves were normal. Knee jerk and other deep-tendon reflexes were graded I+, symmetric throughout; the plantar responses were flexor. The patient could hardly move her arms and legs, the quadriparesis was both proximal 3/5 and distal 4/5, slightly predominant over the right side. Exteroceptive sensibility was normal; the proprioceptive sensibility slightly decreased on the right. Negative Kernig and Brudzinsky signs.

Hospital daily follow up

- **First day.** CT scanning not reported. Lumbar puncture. CSF opening pressure 220 mm/H_2O; closing pressure: 130; cells lymphocytes 1/mm^3, protein 43 mg/dL; glucose 121 mg/dL. TP, TTP normal. Blood: glucose 175, creatinine 0.7, urea nitrogen 26, sodium 144, potassium 3.4 chloride 117, hemoglobin 14.3.
- **Third day.** Consciousness deteriorates, patient became stuporous GA: pH 7.46, PCO_2 37.9, PO_2 59.4, HCO_3 27.6, sat O_2 92.4, sodium 148, potassium 3.9, chloride 131, Glucose 133
  Fourth day: shortness of breath, bradycardia 50 beats/min, BP 110/80 mm Hg. Patient is referred to ICU; CT scanning. Feverish (temp. not measured). GA: pH 7.44, PCO_2 40.7, HCO_3 27.9, Sat O_2 99.9, Sodium 145, potassium 3.7, chloride 133, glucose 151, urine culture: *Escherichia coli* < 100,000 UFC/mL, HIV negative, protein 5.5-3.4, G 2.1, TGO 144, TGP 507, alkaline phosphatase 54, bilirubin (mg/dL) total 0.8, direct 0.3, iodine 0.5, hemoglobin (g/dL) 9.6, hematocrit (%) 31, mean corpuscular volume (μm^3) 31, leukocytes (per mm^3) 6900, TP TT platelets were normal, fibrinogene 658, VDRL negative.
- **Fifth day.** Patient in coma. Both eyes in central position, absent eye movements with oculocephalic maneuvers, the pupils areflectic, 3 mm in diameter, bilateral papilledema. Due to respiratory paralysis endotracheal intubation was done and connected to continuous

positive-pressure ventilation. The patient was flaccid and areflexic. Na 155, K 4.1, chloride 145, glucose 236

- **Sixth day.** Magnetic resonance imaging (MRI, vide infra for description of findings), somatic sensory evoked potentials, brain stem evoked potentials (not reported), hormone profile. TSH, T3 T4 were normal, Luteinizing hormone 380 mU/mL(3-25), Follicle-stimulatng hormone 1.8 mU/mL (3-17), Prolactin 129.5 ng/mL (0- 25) Growth hormone and Cortisol were normal, Lactic deshydr0ogenase 312 (109-193) TGO 48, TGP 274, CSF: OP 90, FP 49, cell count 0, protein 102, glucose 110.
- **Eight day.** CSF: cell count 3 lymph., protein 129, glucose 55. Exitus lethalis.

Magnetic resonance imaging

It proved useful in depicting the typical mesencephalic/diencephalic lesions. Coronal sections: showed abnormal hyperintensities in mammillary bodies, ventromedial thalamic nuclei, and periependymal regions of the third ventricle. Brain stem axial sections: with hyperintensities on the dorsal mesencephalic area at the quedrigeminal plate, around the Sylvian aqueduct and the pontine tegmentum. The hyperintensity appears reduced at the periventricular region of the fourth ventricle close to the area of the vestibular nuclei (Figures 1, 2 and 3).

Neuropathological findings

- **Macroscopic examination.** Autopsy findings limited to the brain. The brain showed moderate diffuse edema, brain weight was 1,275 g. The sulci and gyri show their usual configuration. The lateral ventricles are of normal dimensions. The third and fourth ventricles and the Sylvian aqueduct appear reduced and the periventricular and periaqueductal regions show severe hemorrhage. In the mesencephalon the hemorrhage extends dorsally to include the superior and inferior colliculi. The hemorrhage around the wall of the third ventricle extends down to the mammillary bodies and up the ventromedial thalamic regions (Figures 4, 5 and 6). The hemorrhage around the fourth ventricle extends to the adjacent parenchyma in the upper third of the pons, tapering downwards to become a mild hemorrhage in the upper third of the medulla oblongata, where only the region of the vestibular nuclei show a few petechiae.
- **Microscopic examination.** Paraffin sections were stained with the Klüver-Barrera method for myelin and nerve cells, hematoxylin/eosin, and Masson trichromic techniques. There is marked spongy disintegration of

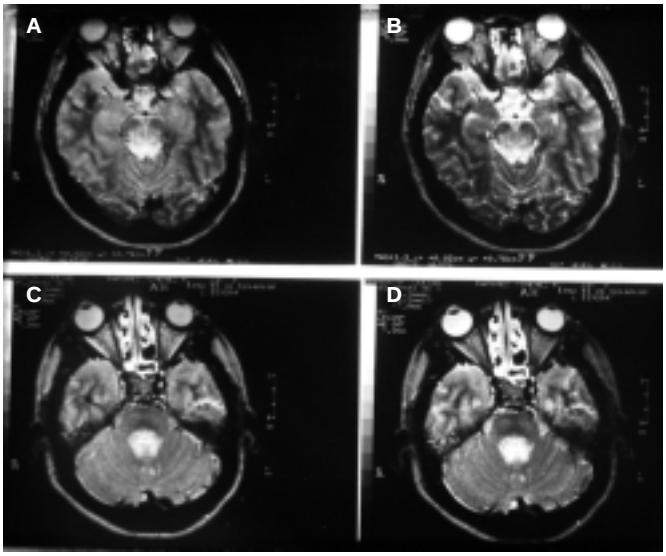

Figure 1. Acute Wernicke's encephalopathy (AWE). Magnetic resonance. Axial T1 Gadolinium enhanced brainstem images: hyperintensities in mesencephalic and pontine tegmental regions (see text for description).

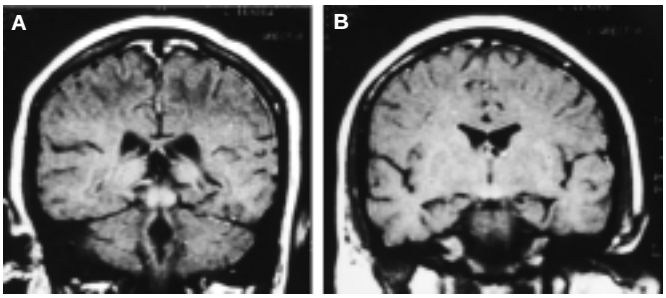

Figure 2. AWE. **A.** MRI coronal T1 gadolinium enhanced image: hyperintensities in the mesencephalic tectum, and **B.** in the mammillary bodies.

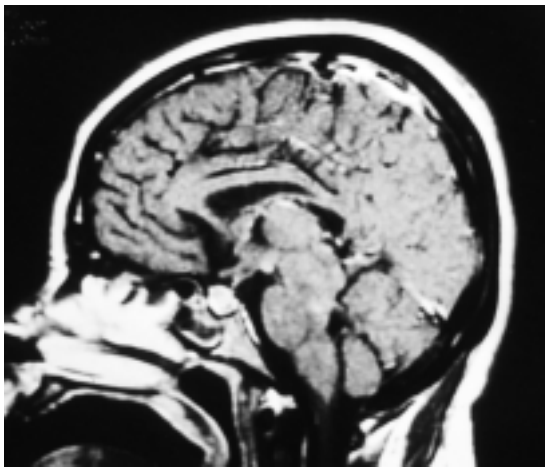

Figure 3. AWE. MRI sagittal T1 gadolinium enhanced image: hyperintensities in diencephalon and brainstem (se text for description).

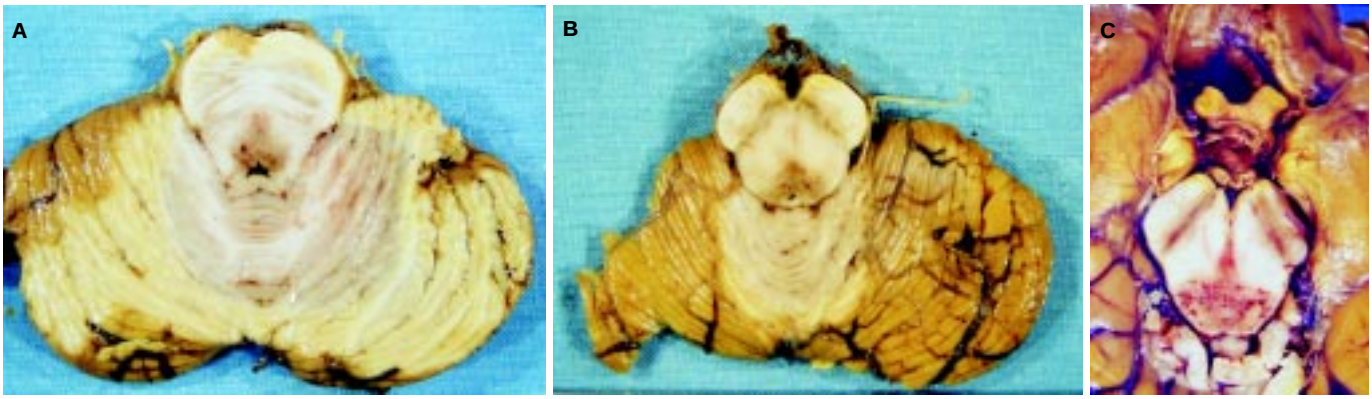

Figure 4. AWE. Brainstem axial sections: **A.** pontine tegmentum hemorrhage. **B y C.** Tegmental and periaqueductal hemorrhages in lower and upper mesencephalon.

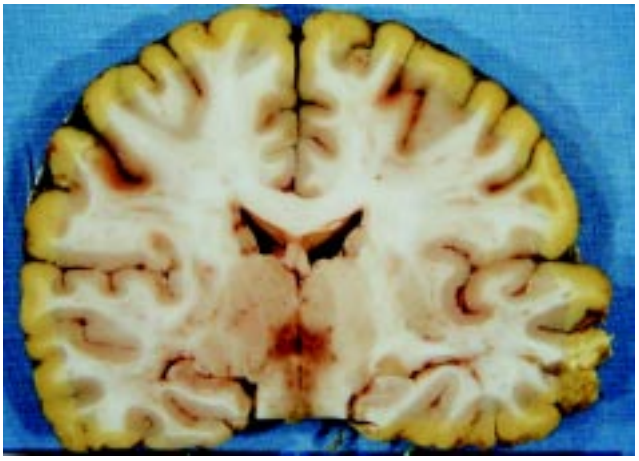

Figura 5. Hemispheric coronal section. Hemorrhage in periventricular region, ventromedial thalamic nuclei and upper mesencephalic tegmentum.

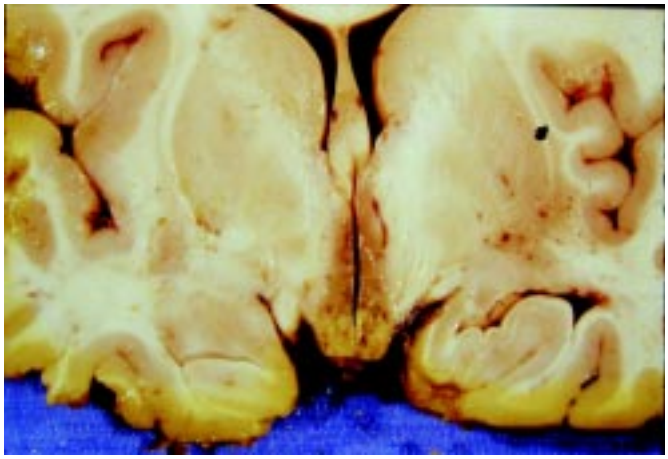

Figure 6. AWE. Hemispheric coronal section. Hemorrhage in periventricular region and mammillary bodies.

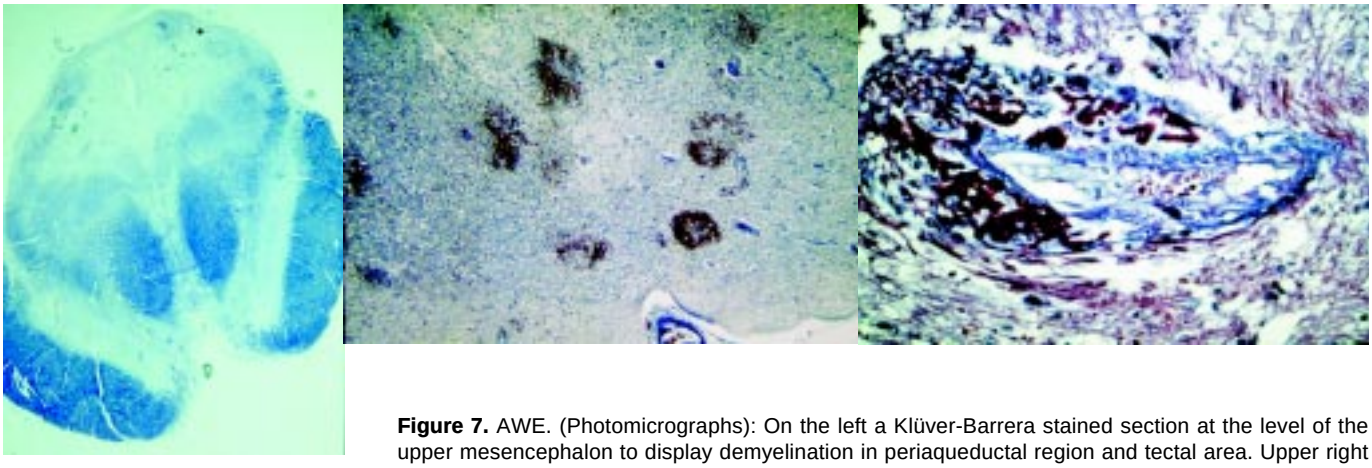

Figure 7. AWE. (Photomicrographs): On the left a Klüver-Barrera stained section at the level of the upper mesencephalon to display demyelination in periaqueductal region and tectal area. Upper right a hematoxylin/eosin stained section at level of the upper *Medulla oblongata* to show petechiae in the vestibular nuclei region. Lower right a trichromic Masson stained section to show pericapillary erythrocyte extravasation and endothelial swelling.

the neuropil with severe endothelial swelling and subependymal extravasation of red blood cells. The endothelial swelling appears as a prominent change around the hemorrhagic lesions. The nervous tissue in the hemorrhage is totally necrotic including both nerve cells and myelinated structures; no macrophages or reactive astrocytes are identified. There is evidence of slight demyelination and edema in the periphery of the affected areas (Figure 7).

Neuropathological Diagnosis. Acute Wernicke´s encephalopathy.

DISCUSSION

The fatal outcome in the case here reported constitutes a florid example of the seriousness of thiamine deficiency; a case in which magnetic resonance imaging displayed the characteristic findings. One could be led to think that possibly in this case, previous to Wernicke's encephalopathy (WE) to develop its characteristic clinical symptomatology, it could have been prevented, and even at the moment when the early neurological signs began appearing, if she had been treated in due time, the patient would have not ever evolved to a full Wernicke's encephalopathy and be still alive.

In spite of the precise clinical and neuropathological description of Wernicke´s encephalopathy over a century ago, and of the several cohort series that have amply confirmed the clinical manifestations, its relation to thiamine deficiency, and the fact that it is treatable and preventable, Wernicke's encephalopathy remains an underdiagnosed entity.[5] Prevalence of WE at autopsy in both chronic alcoholic and non-alcoholic population far exceeds the rate of recognition during life.[5] All practicing physicians, and all neuropsychiatrists must always be aware and familiarized with the epidemiology and clinical features of AWE to avoid the costly health care that result from the irreversible neurological sequelae of this disorder.

Wernicke encephalopathy is a potentially fatal clinical entity if treatment is delayed once the clinical symptomatology appears, The most common neurological sequelae are memory deficit, amnesia, and chronic cognitive impairment, seen mainly in alcoholics, sequelae that constitute the clinical findings underlying the so-called Wernicke-Korsakoff syndrome.[3]

Our case showed the classical AWE clinical triad ocular abnormalities, ataxia, and a global confusional state. The characteristic images in the magnetic resonance, and the brain lesions of the acute stage of WE most severe neuropathological findings.[1-3, 5]

Magnetic resonance constitutes, at present, the most useful technique to reach a prompt diagnosis of the acute Wernicke's encephalopathy at clinical presentation. In our case the clinical features, the characteristic and remarkable MR images and the marked and severe postmortem macroscopic and microscopic findings of the acute Wernicke's encephalopathy, make this a unique case, with no match in the scientific literature on this subject. In fact, only a few cases have been already reported in which there was a precise comparison of the magnetic resonance images with the neuropathology findings.[6 7] The majority of reports are concerned with the description to surviving cases having been timely diagnosed by MR imaging, and given the proper thiamine treatment.[8-11] Of the 26 cases, 14 female and 12 males, reported by Zuccoli and associates,[11] only 50 per cent had a history of alcohol abuse. Clinically only 38 per cent of those cases showed the classical triad of the disease at clinical presentation, 80 percent with changes in consciousness, ocular symptoms in 77 percent and ataxia in 54 percent. The MR findings were essential for the precise diagnosis, 85% showed symmetric lesions in both the medial thalamic nuclei and the periventricular region of the third ventricle, 58% in the mammillary bodies, 65% in the periaqueductal area, 38% in the tectum and only 8% in the dorsal medulla. The authors also make a remark that the MR mammillary body contrast enhancement was statistically correlated to the alcohol abuse group, a fact also mentioned in the study by Fei and associates.[12] The latter, a retrospective study, included 12 nonalcoholic patients with Wernicke encephalopathy; the MR imaging features and their clinical characteristics were compared before and after the thiamine administration. Seven of the patients had consciousness problems, lethargic or in mild coma; in all seven cases there were symmetrical paraventricular lesions. Three out of the 12 patients had no consciousness changes or only slight drowsiness, their MR imaging findings showed lesions in the periaqueductal area only. Gadolinium enhancement of the mammillary bodies was observed only in two of three patients. The two patients that were in deep coma had in addition to the typical MR imaging features symmetric cortical involvement, both had poor prognosis, one died and the other remained in a persistent vegetative state during a follow-up of two years; eight patients showed clinical recovery and accordant resolution of abnormal hyperintense signals in both T2-weighted and FLAIR after thiamine supplementation. Interestingly in a more recent study Zuccoli and associates[13] did a retrospective analysis and comparison of both the clinical symptomatology and the MR findings in 56 cases of WE (29 females, 27 males), all improved after thiamine administration. Forty-three percent of the patients had a history of alcohol abuse; 57% were non alcoholics. On MR imaging 80% showed

evidence of symmetric lesions in the medial thalami and in the perivenricular region of the third ventricle: 59%, in the periaqueductal area; 45%, in the mammillary bodies; 36% in the tectal plate; and 7%, in the periventricular gray matter ventral to the fourth ventricle. The authors conclude that the hyperintensity lesions in the medial thalamus and mammillary bodies were mainly in the alcoholic group of patients. The cohort of 56 cases reported by Zuccoli, et al.[13] must be considered relevant and accept the validity of their conclusion, as compared to the small number of cases in other series. The MR findings in our case, a non alcoholic woman, showed intense contrast enhancement of the lesions in the mammillary bodies, lesions also confirmed in the post mortem findings; moreover, the non alcoholic female case reported by Wernicke[1] also showed lesions in the mammillary bodies. In Sang-Jin's case[14] of a brain abscess who developed a WE associated to insidious excessive vomiting, there were hyperintense lesions in cerebellar dentate nuclei, tegmentum of the lower pons, red nuclei and in the mesencephalic tectum, lesions were evident in FLAIR and T2-weighted images. In a recent report by Mascalchi and associates[15] two cases of WE are described in which the technique of thalamic single – voxel-proton MR spectroscopy T2 weighted images demonstrated N-acetylaspartate/creatinine ratios to be low without detectable lactate; the choline creatinine ratio was not decreased as shown by T2. If in the future a more numerous cohort may show similar results, the spectroscopy technique may become a valuable diagnostic aid in cases of Wernicke encephalopathy.

The ocular signs are the hall mark of Wernicke's encephalopathy.[5] Nystagmus, both horizontal and vertical, is present in 85% of patients, and bilateral paralysis of the lateral rectus muscle is seen in 54%. Conjugate gaze palsies, usually horizontal, develop in approximately 45% of the cases.[3] Pupillary abnormalities, such as areflexia and anisocoria, ptosis and retinal hemorrhages are less frequent in neurological examination; however, in our case there were areflectic pupils and papiledema from the fifth day, ocular abnormalities most likely related to the severe vascular mesodiencephalic lesions. Equilibrium disorder appears in the early stages of WE, associated to the bilateral vestibular paresis. In those cases with gait ataxia, if present it is usually due to vermian cerebellar lesions that frequently develop in chronic alcoholics.[10] Mental symptomatology is usually characterized by apathy, inattention or inability to concentrate in the early stages but rapidly progressing to impaired conciousness, stupor, and coma. It is important to recognize the rapidly progressive nature of AWE since mortality rate is high, 10 to 20 percent, opportune treatment with thiamine will revert all the neurological abnormalities. It is important to remember that in severe cases of AWE there is also a tendency to develop peripheral neuropathy with the secondary neurological consequences affecting stance and in most cases gait as well; peripheral neuropathy appears in about 80 per cent of the cases of AWE. In our case peripheral neuropathy developed early in the process leading to WE; the neuropathy was severe enough by day 52, as to make the patient unable to walk and keep her head up. In general the CSF does not show any specific changes that may help in the diagnosis, only a modest elevation of the protein content has been reported. In our case the protein content (129 mg) was indeed elevated in the last CSF exam done just before the death of the patient; the protein increase was undoubtedly related to the severe tissue lesions already developed in her brain. Disordered cardiovascular function has also been observed in cases of AWE, including postural hypotension, syncope and tachycardia, probably related to impaired function of the autonomic nervous system.[3,5] In our case there were transitory shortness of breath and bradycardia on the fourth day, however, the blood pressure remained within normal limits. In a catamnestic study of 50 cases[16] (38 alcoholics) it was found that of the surviving patients (30) 19 had residual symptoms at neurological examination three years later: mnemonic disorders 12, disorientation 6, ataxia 8, nystagmus 4, paresis of ocular muscles 3, dysarthria 3, intention tremor 1, polyneuropathy 3. Memory disorder constitutes the main residual symptom in some successfully treated cases of AWE, the so-called Wernicke-Korssakoff syndrome. In a recent study Kim, et al.[17] considered of interest the level of the resting-state functional connectivity in the mammillothalamic tract, it was low in seven chronic alcoholic cases recovering from of WE as compared to healthy comparisons.

It is convenient at this moment to comment on another nutritional cause of AWE also leading to thiamine deficiency, which in spite of the fact of the many cases already reported in the medical literature seems to have not been given the proper attention it deserves, namely AWE due to *Hyperemesis gravidarum.* Most reported cases are those of pregnant women cursing the 12th to the 15th weeks of gestation, associated with severe hyperemesis and intolerance to food ingestion.[18-20] Similar mechanism, continuous vomiting the main risk factor, that leads to AWE has been described in cases in which bariatric surgery was performed,[21,22] usually within the first 2 weeks to 18 months following the procedure. The authors report 32 cases (27 were women); the classical symptomatologic triad of acute Wernicke encephalopathy developed in 21 cases.

COROLLARY

It is important to make emphasis to the fact that in any case of malnutrition and hyperemesis one must consider the possibility of preventing development of WE. Moreover, it is well established that intravenously given dextrose solution, as it usually occurs in those patients, consumes thiamine reserve hence interfering the proper function of the two major enzyme systems in which thiamine acts as a cofactor: the first related to glycolysis that leads to oxidative decarboxylation of pyruvic and alfa-ketoglutaric acid, and second the transketolation steps of the phosphoglyconate pathway (hexose monophospahte shunt) the main alternate route of carbohydrate metabolism. Therefore thiamine supplementation should always be added to any given dose of i.v. dextrose solution.

In any case of clinically suspected WE the treatment is to immediate give a large dose of thiamine (150-300 mg a day parenteral) for at least several days. No need to wait for blood thiamine levels or neuroimaging study results. Indeed Wernicke's disease is always preventable, and if early treatement is given, there will be no residual or minimal neurological deficits. It always be kept in mind that in untreated cases the outcome may be disastrous as the patient will die or neurological deficits will remain, usually amnesia as in the Wernicke-Korssakoff syndrome.[23, 24] It is the experience of the authors of this paper that both vestibular disorder and oculomotor ophthalmoplegia start to improve within a few hours subsequent to thiamine infusion.

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CARL WERNICKE, BIOGRAPHYCAL DATA[1,2]

Carl Wernicke was a German physician, neuropsychiatrist, neuroanatomist and neuropathologist. He was born in May 15, 1848 in Tarnowitz, Upper Silesia, originally Germany in Prussia, at present in Poland renamed Tarnowskie Gory. He died due to injuries suffered during a bicycle accident in Thüringen Wald, Gräfenroda, Germnay, June 15, 1905. He studied medicine and graduated at the University of Breslau in 1870; there he worked as assistant to Heinrich Neumann in the Alterheiligenhospital. Under the tutorial direction of Theodore Hermann Meynert he started his scientific career at the Neurologic Institute in Vienna. Wernicke's first contribution in neuroanatomy was the description of three primordial convolutions in the cerebral cortex (Das Urwindungssystem des menschlichen Gehirns). Of particular interest it must be mentioned his pioneer description of the symptomatology due to thrombosis of the posterior inferior cerebellar artery, based only in his own research of the arterial supply of the *Medulla oblongata*, an assumption confirmed later by Wallenberg In a small book published in 1874 he described the aphasias associated to impaired psychic processes by lesions in different areas

of the brain. The book included the first accurate description of the sensory aphasia due to a lesion in the posterior, superior region of the left temporal gyrus, region now holding the eponym of Wernicke's area and the language deficit as Wernicke's aphasia. Wernicke's contribution was that not all language deficits were the result of damage to the Broca's area. Wernicke is internationally recognized because of his study in aphasia.. He followed with graduate studies in Breslau, and Berlin in order to become habilitated for neuropsychiatry (1875-1876). From 1876 to 1878 he worked at the Berlin Charité in the clinic for psychiatry and nervous diseases under Karl Wesphal. From 1878 to 1884 he established a private practice in Berlin. In 1885 he obtained a position as a faculty member at University of Breslau where he remained until 1904. In his three volume book, *Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende*, published in 1881-1883, he included the first description of Wernicke's Encephalopathy, which he named "acute hemorrhagic superior polioencephalitis" (*Die akute haemorrhagische Polioencephalitis superioris*). In his book he defined the new entity in both clinical and anatomical terms, known later on to be caused by thiamine deficiency. In the *Lehrbuch* he intended to comprehensively describe the cerebral localization of all neurologic and psychiatric diseases. To Carl Wernicke all mental disorders were diseases of the brain, in fact, he devoted his career to find the morphologic bases for psychiatric disorders and did not believe in the classification proposed by Emil Kräpelin, whom he considered an ardent adversary. Because of the concepts in Wernicke's book *Grundiss der Psychiatrie in Klinischen Vorlesungen,* Karl Jaspers considered that Wernicke was a "brain mythologist". In 1904 Carl Wernicke was appointed Professor and Director of Neurology and Psychiatry at the University of Halle. Less than one year after he suffered severe injuries in a bicycle accident that caused his death.

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