COMA AND DEATH IN UNRECOGNIZED WERNICKE'S ENCEPHALOPATHY

AN AUTOPSY STUDY

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SUMMARY — Eleven out of 36 autopsied cases of Wernicke's encephalopathy had developed coma. None of these patients had the diagnosis during life. There were six men and five women with ages ranging from 36 to 50 years (mean 36.6). Seven of these patients were heavy drinkers, three exhibited signs of severe malnutrition, whereas one was being evaluated for a disseminated gastric cancer and one was in treatment of hyperemesis gravidarum. Two patients were brought to the hospital after found unconscious at home. Neuropathological examination disclosed gross changes in the mammillary bodies in eight cases and microscopic changes in all cases. In one case there was atrophy of the anterior superior part of the vermis. Petechial hemorrhages were observed particularly in the walls of the third ventricle. Microscopically there were in addition to hemorrhages, glial proliferation, endothelial hypertrophy and necrosis of nerve cells and myelin. Central pontine myelmolysis was observed in one case. Wernicke's encephalopathy is a clinically underdiagnosed condition. Coma may mask its classical clinical picture or even be the sole manifestation. Although coma points to a poor outlook it may be reversed by thiamine administration. Any patient with Coma of unknown etiology should be given parenteral thiamine.

KEY WORDS: Wernicke's encephalopathy, coma, clinical diagnosis, neuropathology.

Coma e morte na encefalopatia de Wernioke: estudo necroscópico

RESUMO — Numa série de 36 casos de encefalopatia de Wernicke autopsiados, 11 haviam desenvolvido coma. Em nenhum desses pacientes comatosos o diagnóstico foi estabelecido durante a vida. Seis desses pacientes eram homens e 5 mulheres, com idades entre 26 a 50 anos (média de 36,6). História de alcoolismo crônico foi positiva em 7 casos, sinais de desnutrição grave ocorreram em 3; uma paciente (apresentava câncer gástrico e uma, hiper emese gravídica. Dois pacientes foram admitidos ao hospital após terem sido encontrados em coma em suas residências. O exame neuropatológieo revelou alterações macroscópicas nos corpos mamilares em 8 casos — atrofia, descoloração e espongiose. Atrofia da porção anterior e superior do vermis do cerebelo foi observada em um caso. Era 5 casos havia hemorragias petequiais no diencéfalo, principalmente próximas às paredes do terceiro ventrículo. A microscopia revelou além das hemorragias, proliferação glial, hipertrofia do endotélio vascular e necrose de neurônios e mielina. Mielinólise pontina central ocorreu em um paciente. A encefalopatia de Wernicke é pouco diagnosticada clinicamente. O coma pode mascarar as outras manifestações clínicas da doença ou pode constituir sua única manifestação. Embora seja um sinal de mau prognóstico, o coma pode ser revertido pela administração de tiamina. É enfatizado que todo paciente em coma de causa não estabelecida deve receber altas doses de tiamina.

PALAVRAS-CHAVE: encefalopatia de Wernicke, coma, diagnóstico clínico, neuropatologia.

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Wernicke's encephalopathy is a potentially fatal neurologic disorder caused by thiamine deficiency. It occurs most commonly in severe alcoholics 19 although is has been also reported in non-alcoholic clinical conditions such as malnutrition, malabsorption syndromes, anorexia associated with malignant disease and chemotherapy[1 6], upper gastrointestinal obstruction i, prolonged fasting 3,6,1s, intravenous feedings, hemodialysis[14] and hyperemesis gravidarum 12,15,17,27. it may manifest by a classical clinical triad-oculomotor dysfunction, ataxia and mental confusion — which yields promptly the correct diagnosis. Coma is considered as a rare manifestation of the illness 24 but its presence in patients with a history of chronic alcohol abuse or with other risk factors for a nutritional disorder should favor the diagnosis of Wernicke's encephalopathy 9,22,25.

We describe a series of comatose patients in whom the diagnosis of Wernicke's encephalopathy was only obtained during autopsy studies and emphasize the need of thiamine administration in all patients with coma of unestablished etiology.

METHODS

We reviewed all cases with a post-mortem diagnosis of Wernicke's encephalopathy examined at the Department of Neuropathology of the Federal University of Minas Gerais Medical School between January 1978 to December 1990. In aill cases the macroscopic description of the brains was reviewed and the glass slides for optic microscopy were re-examined confirming the presence of the characteristic pathological changes of Wernicke's encephalopathy.

Clinical data were obtained from hospital charts and included information on the neurological examination at admission and during* evolution. Only patients with coma of unknown origin at admission or who developed coma in clinicaly unsuspected Wernicke's encephalopathy make up the present series.

RESULT'S

There were 36 (2.2%) cases of Wernicke's encephalopathy among 1655 brains examined at autopsy. In 11 of these cases the diagnosis was clinically unsuspected as patients presented coma during their stay or at admission to the hospital. Data on those 11 cases are summarized in Table 1. There were six women and five men with ages ranging from 26 to 50 years old (mean 36.6, SD 8.9). Previous history of chronic alcoholism was present in seven patients. Four patients had clinical signs of alcoholic liver disease whereas one had evidence of acute pancreatitis. Severe malnutrition was. diagnosed in three patients, one of them had developed respiratory failure. Pulmonary tuberculosis was clinically diagnosed in one case. One patient was in evaluation for an advanced gastric carcinoma and a 28-year-old housewife developed confusion and coma during treatment of hyperemesis gravidarum. Two patients with history of heavy alcoholism were brought to the hospital after found stuporous at home.

General autopsy reports were reviewed in 10 cases. Hepatic cirrhosis was found in two patients and acute hepatic degeneration described in other two cases. In three cases there was pancreatitis and in two patients autopsy revealed pulmonary tuberculosis. In one patient post-mortem examination confirmed gastric carcinoma with disseminated pulmonary metastases.

Gross neuropahological examination revealed cerebral cysticercosis in two patients. The mamroillary bodies were macroscopically affected in eight cases (72.7%) showing variable degrees of atrophy, from sligth reduction of size to almost complete shrinkage. Their surface had a brownish or grayish discoloration and a spongy appearance. Cerebellar atrophy involving the anterior superior part of the vermis was observed in one case. In five cases petechial hemorrhages were found around the ventricular system, particularly in the walls of the third ventricle.

The main pathological changes observed in our series are shown in Table 2. Characteristically the lesions had a symmetrical distribution in the tissue around the third ventricle and the floor of the fourth ventricle. Other diencephalic and brainstem structures were involved in a lesser intensity and frequency. The mammillary bodies were microscopically affected in all cases. There were spongiosis and a microglial and astrocytic proliferation in nine cases. The endothelial cells had become hypertrophic and the number of blood vessels was increased in the involved areas in six cases. Extravasation of red blood cells into the perivascular spaces and small hemorrhages were found in five cases. In eight cases the neurons had a normal appearance. Necrosis of nerve cells and myelin was also observed. Typical features of central pontine myelinolysis with breakdown of myelin in the midline of the basis pontis,

Table 1. Cases of coma in clinically unsuspected Wernicke's encephalopathy.

Case	Age	Sex	Clinical diagnoses	Alcoholism	Associated findings at autopsy
1	29	M	Coma of unknown origin	+	Pancreatitis
2	27	F	Malnutrition	—	Hepatic cirrhosis; cerebral cysticercosis
3	46	M	Hepatic failure	+	Hepatic cirrhosis; pulmonary and intestinal tuberculosis
4	37	M	Hepatic failure	+	Fatty liver degeneration
5	33	F	Malnutrition; respiratory failure	—	Not reported
6	50	F	Gastric carcinoma	—	Gastric carcinoma; lung metastases
7	46	M	Hepatic failure	+	Pulmonary tuberculosis
8	28	F	Hyperemesis gravidarum	—	Acute liver degeneration
9	35	F	Acute pancreatitis; malnutrition	+	Pancreatitis
10	26	M	Hepatic failure	+	Fatty liver degeneration
11	46	F	Coma of unknown origin	+	Pancreatitis; cerebral cysticercosis

Table 2. Neuropathological findings in Wernicke's encephalopathy.

Neuropathological findings	Number of cases	Percent
Mammillary bodies:	11	100
Atrophy	8	72.7
Spongiosis	9	81.8
Discoloration	8	72.7
Cerebellar atrophy	1	9.1
Periventricular hemorrhages	5	46.4
Glial proliferation	9	81.8
Endothelial hypertrophy	6	54.5
Necrosis of nerve cells/myelin	4	36.4
Central pontine myelinolysis	1	9.1

infiltration of numerous macrophages and sparing of nerve cells and axons were noted in one case in addition to changesi in the mammillary bodies and small hemorrhages in the periventricular area. The cerebellar cortex was affected in one case. There were loss of Purking cells and proliferation of the Bergmann astrocytes in the folia of the superior vermis.

COMMENTS

Since its original description in 1881 26 Wernicke's encephalopaty has been described worldwide in alcoholics and in non-alcoholic patients who develop thiamine deficiency for any reason. Thiamine or vitamin B^1 is an essential coenzyme in intermediate carbohydrate metabolism 20. When intake is lower than daily requirement — approximately lmg — it is mobilized from body reserves and only its metabolites are detected in the urine 29. Experimental studies show that when it is completely excluded from the diet, a state of total body depletion develops in 18 days 28.

Studies on the incidence of Wernicke's encephalopathy in autopsy series are scarce in the world literature. Cravioto and colleagues [2] in 1961 found typical pathological changes of the disease in 1.7% among 1600 consecutive autopsies at the Bellevue Hospital. Victor et al.[23] found a post-mortem incidence of 1.9%. In Perth, Australia, Harper [7,10] reported an incidence of 1.7% among 2891 autopsies and 2.8% among 4677 brains from patients over 20 years of age respectively. A lower figure of 0.8% has been found in Oslo, Norway[21]. Cur series of 36 cases represents 2.2% of consecutive autopsies in patients of all ages in a teaching hospital in Brazil. This figure is probably higher than that reported in a teaching hospital in Western Australia [10] and may stand as the highest incidence of the disease so far published. To the best of our knowledge no similar study to date has been conducted in this country.

The higher incidence of Wernicke's encephalopathy in Brazil may be a consequence of the poor nutritional condition of the papulation. As a matter of fact four of our 11 cases (36.4%) were definitely non-alcoholics, two of them exhibiting clinical signs of severe malnutrition. History of alcoholism was also absent in two other cases, a patient with gastric cancer and a patient with hyperemesis gravidarum. Therefore the high frequency of Wernicke's disease in non-alcoholic patients in Brazil is not in agreement with published series from more developed countries where chronic malnutrition is not widely disseminated and people probably have a greater reserve of thiamine. Just two (0.8%) of the 245 patients studied by Victor and collaborators [23] in the United States and 10% of patients in Harper's series [10] in Australia had no history of alcohol abuse. In this latter series malnutrition was reported in just one patient (0.8%) among 131 cases of Wernicke's encephalopathy, contrasting with the high figure (27.3%) in our series.

Most investigators agree that Wernicke's encephalopathy is clinically underdiagnosed [5,10,16,19,21] and there is a large discrepancy between the clinical and the pathological number of cases [10]. Only 20% of the cases confirmed by post-mortem examination were diagnosed clinically as Wernicke's encephalopathy [10]. The clinical signs of ophthalmoplegia, nystagmus, ataxia and mental changes are not invariably present in the same patient. In a retrospective study of the clinical signs of 97 autopsy-proven cases of Wernicke's-Korsakoff syndrome with good clinical documentation at their medical records Harper and collaborators[11] found the classical triad in only 16%; two of those signs were present in any combination in 28% of the cases and an isolated sign occurred in 37%, 34% of them being mental changes. In 19% of the patients no clinical sign was detected. Only 33 of the 97 cases were diagnosed during life. In our series of 36 autopsied cases none of the 11 patients (30.5%) who developed coma was diagnosed as Wernicke's encephalopathy during life. Our figure is therefore very close to that reported by Harper and colleagues[11].

The probable reason for the relatively few number of cases clinically diagnosed in comparison to the frequency found at necropsy studies is the existence of a subclinical encephalopathy in which the apparent clinical signs are absent [10,13]. A chronic form of the disease with a progressive character develops as repeated acute clinical or subclinical episodes occur causing cumulative structural damage to the brain.

Coma may mask the more characteristic clinical features of the disease or may occur as the sole manifestation of Wernicke's encephalopathy. It develops in consequence of diencephalic or periaqueductal lesions and has often been precipitated in susceptible individuals by naso-gastric or intravenous hyperalimentation without adequate thiamine supplementation.

The estimated mortality rate is 10% to 20%. This figure may be even higher if the clinically undiagnosed cases are included. Respiratory failure is a frequent cause of death in these patients as vital brainstem structures are involved [7,8]. Bronchopneumonia is also a frequent terminal complication.

Coma is a sign of poor outcome although its reversibility has been documented after thiamine administration[4]»is,25. Therefore it cannot be overemphasized that any patient with impaired conscious level, particularly in the presence of history or signs of alcohol abuse or any nutritional disorder, the diagnosis of Wernicke's encephalopathy should be seriously considered. Such patients should be given, before glucose, high dose parenteral thiamine. Such a simple treatment may prevent the manifestations of the disease and even save the patient's life.

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