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The incidence of Wernicke's encephalopathy in Australia—a neuropathological study of 131 cases

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SUMMARY In a nine year necropsy study in Western Australia, the incidence of Wernicke's encephalopathy was 2·8%. The incidence appears to be increasing. Although Wernicke's encephalopathy is a nutritional disorder, the majority of cases occur in the alcoholic population. Only 20% of the 131 cases studied had been diagnosed clinically as Wernicke's encephalopathy. This large discrepancy between numbers of cases diagnosed clinically and pathologically suggests that chronic Wernicke's encephalopathy, which comprised 83% of the cases, may be the end result of repeated subclinical episodes of Wernicke's encephalopathy. Thus, Wernicke's encephalopathy could be considered a "progressive" disorder and as patients respond well to thiamine replacement therapy, early diagnosis is important. Alternatively, prevention by vitamin enrichment of alcoholic beverages may have to be considered in an attempt to minimise the social and economic impact of Wernicke's encephalopathy on Western society.

Clinical and pathological studies throughout Australia indicate a high, and probably rising, incidence of a potentially preventable disease caused by thiamine (vitamin B1) deficiency—Wernicke's encephalopathy or the Wernicke-Korsakoff syndrome.[1–5] A similar trend is apparent in other Western civilisations[6,7] and probably exists even in Third World countries[8] though largely overlooked because of lack of formal epidemiological studies. Although Wernicke's encephalopathy is caused by a nutritional deficiency of thiamine, it is seen today almost exclusively in the alcoholic population.[1,9] From a clinical point of view, the traditional triad of confusion, ataxia and ophthalmoplegia will only be evident in a small percentage of cases and the diagnosis has been unsuspected prior to death in a significant proportion of cases.[10,11] In the acute stage of Wernicke's encephalopathy, there is a dramatic response to parenteral thiamine. Thus, this disease is potentially preventable and the group at risk an obvious one, although not readily accessible.

The Department of Neuropathology at the Royal Perth Hospital provides a state wide service for the 1 300 000 population. A relatively high proportion of the brains from those dying in the metropolitan area are examined and cases of Wernicke's encephalopathy have been studied in a prospective fashion since 1973. Altogether, 131 cases have been studied and in most cases, medical records were available for clinico-pathological correlation.

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Results

In a post mortem study of Wernicke's encephalopathy in Western Australia between 1973 and 1981, 131 cases were diagnosed pathologically from 4677 brains examined from patients over 20 years of age. This is an overall incidence of 2·8%. There is some variation in the incidence from year to year as shown in table 1. The Department of Neuropathology at the Royal Perth Hospital receives material from many sources, the most important for this study being the Perth City Coroners Department. Eighty-three cases of Wernicke's encephalopathy were diagnosed from 1783 coroners necropsies, an incidence of 4·7% compared to an incidence of 1·7% from necropsies performed in Royal Perth Hospital.

The age and sex distribution are shown in table 2. Seventy-five per cent of the cases were male and 25% female. The peak age incidence was in the fifth decade. Twelve per cent (16) of the cases were of aboriginal extraction. The aboriginal population

Table 1 *Wernicke's encephalopathy—Perth 1973–1981*

Year	Number of brains examined*	Number of cases of Wernicke's encephalopathy	Incidence
1973	505	6	1·2%
1974	538	12	2·2%
1975	601	18	3·0%
1976	560	15	2·7%
1977	486	10	2·1%
1978	438	15	3·4%
1979	532	9	1·8%
1980	499	29	5·8%
1981	518	17	3·3%
Total	4677	131	2·8%

*Includes only "at risk" group (over 20 years)

Table 2 *Sex and age distribution of 131 cases studied*

Males	98	(75%)
Females	33	(25%)
Ages (yr)		
30–39	9	
40–49	16	
50–59	54	(41%)
60–69	25	
70–90	27	

makes up only 2·4% of the total Western Australian population. In 90% of the 131 cases, alcoholism was the predisposing cause for the nutritional deficiency. One patient had malnutrition. Clinical information was not available on the other 12 cases, but most of these had other stigmata suggestive of alcoholism such as fatty livers or cirrhosis. Despite the fact that the majority of these cases had been examined in one of the teaching hospitals of Perth prior to their death, often on numerous occasions, only 20% (26 cases) had a clinical diagnosis of Wernicke's encephalopathy or the Wernicke-Korsakoff syndrome.

From a pathological point of view, the cases of Wernicke's encephalopathy can be readily classified as either acute, chronic or acute on chronic. The incidence of these various stages of Wernicke's encephalopathy are shown in table 3. Sixty-six per cent were chronic, 17% acute and 17% acute on chronic. Commonly associated clinical problems in these patients included epilepsy (11%), peripheral neuropathy (11%), alcoholic cardiomyopathy (4%) and 4% died with terminal hypothermia. Sixty per cent had liver disease which included cirrhosis (37%), fatty liver (21%) and acute alcoholic hepatitis (2%). Central pontine myelinolysis, although not diagnosed clinically, was found in two cases.

NEUROPATHOLOGY

The macroscopic neuropathological findings of the 131 cases are listed in table 4. The most consistent

Table 3 *Pathological classification of the 131 cases studied*

Acute	22(17%)
Acute on chronic	23(17%)
Chronic	86(66%)

macroscopic abnormality was shrinkage and brown colouration of the mamillary bodies (fig 1) which is characteristic of chronic Wernicke's encephalopathy and was seen in 75% of the cases. Ventricular dilatation, assessed subjectively, was noted in 34% of cases. Periventricular haemorrhages (fig 2) were present in 5% of the cases and were seen only in the acute or acute on chronic stages of the disease. Frank necrosis of tissue was occasionally seen in acute Wernicke's encephalopathy in periventricular regions (fig 3). The lesions were characteristically distributed around the ventricular system, particularly in the walls of the third ventricle and the floor of the fourth ventricle. The incidence of involvement of these areas is listed in table 5.

Histologically, the acute lesion was characterised by changes in and around blood vessel walls. There was extravasation of red blood cells (diapedesis) into the perivascular spaces and in some instances these extend outwards into the parenchyma to form "ball" microhaemorrhages (fig 4) or macroscopically evident haemorrhages (fig 2) as described above. The endothelial cells became hypertrophic. Tissue necrosis also occurred in a periventricular distribution, but was seen only in the most severe acute and acute on chronic cases.[12] In less severe cases, there was a spongiosis of the affected areas suggestive of oedema. An astrocytic reaction was recognised by

Table 4 *Neuropathological macroscopic findings (131 cases)*

	Incidence
Cerebral atrophy	21%*
Ventricular dilatation	34%
Mamillary body atrophy	75%
Periventricular haemorrhage	5%
Cerebellar vermal atrophy	34%

*Includes three cases of Alzheimer's disease.

Table 5 *Neuropathological microscopic findings*

Site	Incidence of abnormalities
Mamillary bodies	99%
Third ventricular wall	61%
Thalamus	61%
Midbrain	50%
Pons	50%
Medulla	33%

the third or fourth day. The neurons showed relatively little alteration, but myelin and axons are often destroyed. By day 10, the most dramatic histological feature was hypertrophy and hyperplasia of

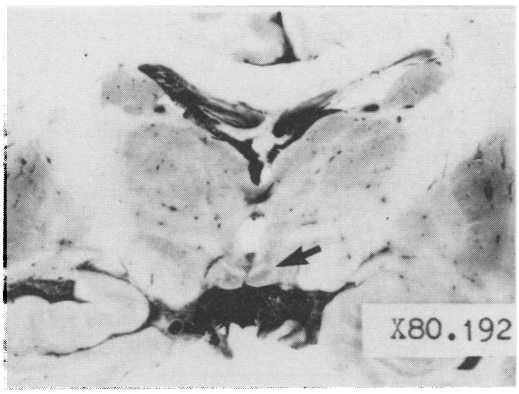

Fig 1 *Coronal section of the cerebral hemispheres showing dark, shrunken mamillary bodies (arrow). This is the most characteristic macroscopic finding in chronic Wernicke's encephalopathy.*

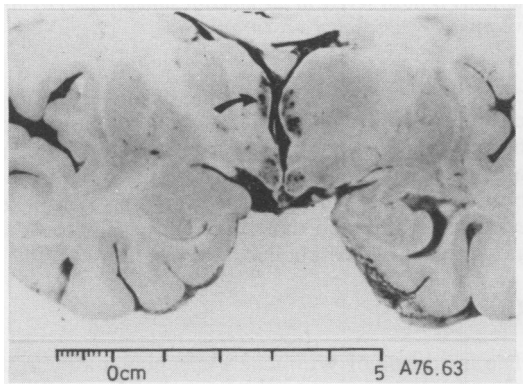

Fig 2 *Coronal section of the cerebral hemispheres showing small haemorrhages in the mamillary bodies and walls of the third ventricle (arrow). The diagnosis of acute Wernicke's encephalopathy was only made at necropsy.*

endothelial cells and budding and proliferation of capillaries (fig 5). Apart from occasional histiocytes, there was generally no inflammatory reaction. In chronic lesions, parenchymal elements were lost and reactive changes were largely restricted to astrocytes. There was usually a slight increase in numbers of blood vessels, but the endothelial cells appeared normal. This change was recognised most easily in the mamillary bodies (fig 6). These structures were abnormal in 99% of the cases and therefore serve as the single most reliable area to examine histologically when screening cases for Wernicke's encephalopathy.

Cerebral atrophy was noted in 21% of the cases and this most commonly involved the frontal lobes. In a separate study which included a large number of these cases, it was shown that male patients with

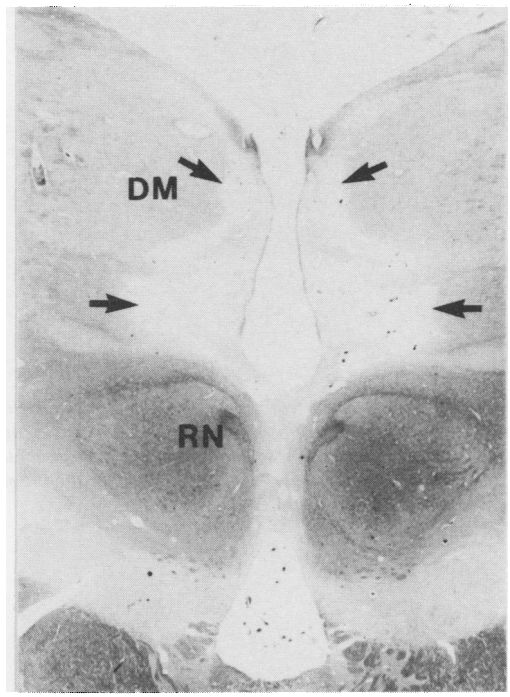

Fig 3 *A myelin stain of a coronal section of the diencephalon at the level of the red nuclei (RN) showing symmetrical necrosis (arrows) in the dorsomedial (DM) and centromedian nuclei of the thalamus and also involving the thalamic fasciculus. This is seen only in the most acute cases of Wernicke's encephalopathy.*

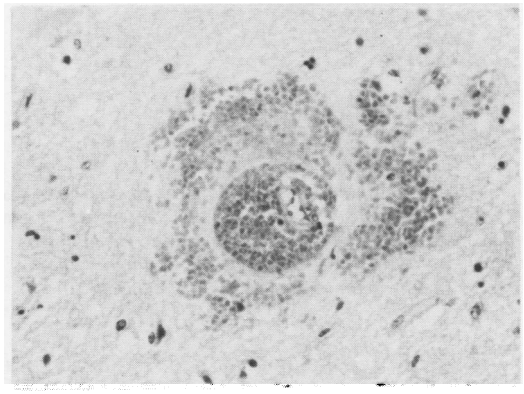

Fig 4 *Paraffin section from the floor of the fourth ventricle shows a small blood vessel surrounded by red blood cells in the perivascular space and parenchyma. This is a typical "ball" microhaemorrhage seen in the early stages of acute Wernicke's encephalopathy. (Haematoxylin & eosin × 400).*

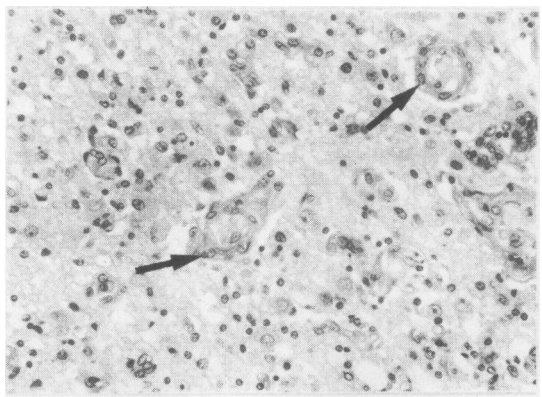

Fig 5 *Paraffin section from the mamillary body showing endothelial cell hypertrophy and hyperplasia (arrows) and capillary proliferation. These changes are typical of acute Wernicke's encephalopathy about 10 days after the onset of the disease. (Haematoxylin & eosin × 400).*

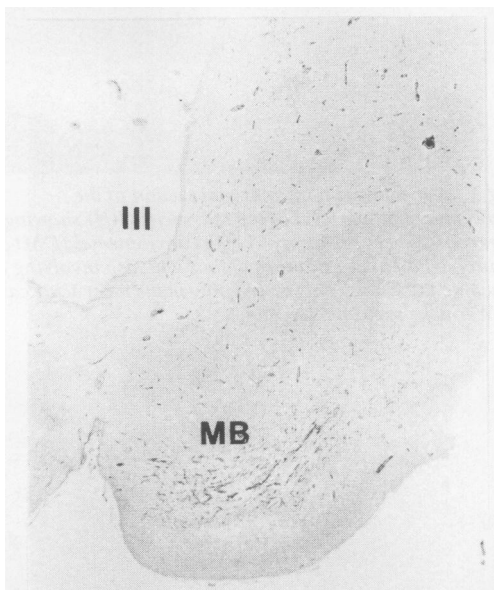

Fig 6 *Reticulin stain of the mamillary body (MB) of a case of chronic Wernicke's encephalopathy. There is shrinkage and central spongiosis and an apparent increase in the numbers of blood vessels in the centre of the mamillary body. (Reticulin stain × 40) III = third ventricle.*

Wernicke's encephalopathy had a mean brain weight (at necropsy) which was 67 grams lighter than the mean brain weight of a group of age matched controls.[13] Microscopically, there is a subtle patchy cortical neuronal loss.

Cerebellar atrophy involving the anterior superior part of the vermis (fig 7) was noted in 34% of the

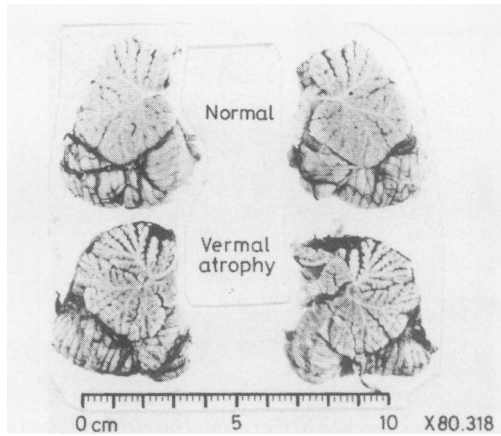

Fig 7 *Sagittal sections of cerebellar hemispheres from a normal patient and a patient with cerebellar vermal atrophy associated with chronic Wernicke's encephalopathy. The atrophy is most severe in the anterior superior part of the vermis where the foliae are shrunken.*

cases. However, on microscopic examination, 44% of the cases were considered to have significant loss of Purkinje cells and proliferation of the Bergmann astrocytes which are the characteristic findings of both cerebellar atrophy as part of Wernicke's encephalopathy and that which occurs in alcoholics alone (alcoholic cerebellar degeneration).

Discussion

The incidence of Wernicke's encephalopathy in the nine year necropsy study from 1973 to 1981 in Perth, Western Australia was 2·8% of all brains of patients older than 20 years. The incidence in the Cleveland Metropolitan General Hospital from 1963 to 1976 was 2·2% of 3548 consecutive necropsies performed in adults (18 years and older).[6] Cravioto *et al* in 1961[14] studied 1600 brains from patients coming to necropsy at the Bellevue Hospital over three years and the incidence of Wernicke's encephalopathy was 1·7%. Torvik *et al*,[9] in a recent necropsy study in Oslo, Norway found an incidence of 0·8%. Thus, the incidence of Wernicke's encephalopathy in Western Australia appears to be higher than elsewhere. This may, however, reflect the inclusion of brains from coroners' necropsies in which the incidence of Wernicke's encephalopathy was 4·7%. No similar study exists in the literature. The material from the Coroners' Department is obviously a very different population sample from that of a teaching hospital. However, it should be noted that 15% of patients were found to have alcohol-related reasons for their admission to hospital in a recent Australian study.[15] It is of interest to

note the fluctuation in incidence from year to year (table 1) and to speculate on the cause. The sudden drop in incidence in 1979 corresponded to the author's absence from Perth. This may have been coincidental, but as shown in a previous paper,[1] the brains of cases of Wernicke's encephalopathy often appear normal macroscopically and unless appropriate blocks are examined microscopically, approximately 30% of cases will be missed. There does appear to be a trend towards an increase in the incidence of Wernicke's encephalopathy over the nine year period. What possible explanation can be offered to explain this trend? The estimated average alcohol consumption in Australia has increased from 5784 grams/head per year in 1977 to 7424 grams/head per year in 1981.[2] The pattern of drinking habits has changed, with greater amounts of wine being consumed. At the same time, the cost of living has increased disproportionately to salaries and social security allowances so that the average alcoholic will have less money to spend in 1981 compared to 1973. The implication is that the alcoholic will forgo the "lesser necessities of life" such as food rather than change his drinking habits.

At the Royal Perth Hospital approximately 0·04% of all admissions are diagnosed as Wernicke's encephalopathy. In the last three years, there was an average of 14 new cases diagnosed clinically each year. This figure is comparable with the Massachusetts General Hospital where the figure was about 0·05%.[6] In a recent study from Sydney, New South Wales, Truswell and Apeagyei[2] showed that the annual incidence of Wernicke-Korsakoff disease had increased five fold in the last 15 years whereas the population had only increased 1·3 times. Considering that only 7% of people over the age of 20 years dying in Western Australia have necropsy studies of their brains and an average of 14 cases of Wernicke's encephalopathy are diagnosed pathologically each year, there appears to be a relatively large discrepancy between numbers of cases of Wernicke's encephalopathy diagnosed clinically and pathologically. This was also confirmed by clinicopathological analysis in that although the majority of the 131 cases had been seen in the teaching hospitals of Perth, only 20% were diagnosed clinically as Wernicke's encephalopathy. Why are so few cases of this syndrome diagnosed clinically? It is probable that the chronic form of the disease, which comprised 83% of the cases, can develop after repeated episodes of a subclinical encephalopathy in which the usual signs of mental confusion, ataxia, ophthalmoplegia, nystagmus and memory loss might be absent. Lishman[10] in his lecture on "Cerebral Disorders in Alcoholism" agreed with and expanded upon this hypothesis. Thus, it would seem that an accurate assessment of the incidence of Wernicke's encephalopathy in the population can only be achieved through pathological studies. However, it seems likely that detailed neurological assessment, including psychometric testing, will bring to light more clinical cases of Wernicke's encephalopathy.

Chronic Wernicke's encephalopathy could be considered as a "progressive disorder", each acute clinical or subclinical episode of Wernicke's encephalopathy causing cumulative damage, and it is therefore important to identify early cases, treat and prevent further progression. It is a matter of human nature that many of these patients, often well known in the outpatient and emergency units, are given a rather cursory examination and subtle signs of Wernicke's encephalopathy could be missed. Red blood cell thiamine assays, which reflect tissue levels of thiamine, are now available in the Royal Perth Hospital.[16] These may prove useful in the early diagnosis of thiamine deficiency states and the management of such patients.

The sex incidence (male:female = 3:1) probably reflects the drinking pattern of Australians and there has been no change over the nine year period.[1] Disturbing features are the number of young men and women dying with this disease and the high incidence of Wernicke's encephalopathy in the aboriginal community.

Although this disease is largely restricted to the alcoholic population, there are other specific situations which can predispose to acute Wernicke's encephalopathy and can cause sudden death.[12] These include prolonged intravenous feeding without adequate vitamin supplements,[11 17] fasting for obesity,[18] and hunger strikes. In these instances, the clinical course may be that of confusion and obtundation progressing fairly rapidly to coma.[11] The classical clinical signs of Wernicke's encephalopathy may not be apparent or may be masked by the coma.

The neuropathological findings of these 131 cases are similar to those of Victor, Adams and Collins[19] in their monograph on the Wernicke-Korsakoff syndrome. Routine neuropathology is unlikely to help our understanding of the distinctive periventricular distribution of the lesions. Likewise, an analysis of the neuropathological findings in the 11 cases which had been diagnosed clinically as Korsakoff's psychosis, has shown no significant differences in the distribution or severity of lesions from the 15 cases diagnosed clinically as Wernicke's encephalopathy.

One neuropathological aspect which deserves further attention is cerebral cortical atrophy which was present in 34% of cases (including three cases of Alzheimer's disease). Although this finding is based on a subjective assessment of the external appear-

ance and slices of the fixed brain, an analysis of fresh brain weights of a group of these cases (66) showed that the mean brain weight of males with Wernicke's encephalopathy was 67 grams less than that of an age matched normal control group.[13] This was a significant difference ($p < 0.001$). Interestingly, the mean brain weight of 61 male alcoholics who had no histological evidence of Wernicke's encephalopathy, was 75 grams less than the control group ($p < 0.001$). Torvik *et al*[9] also showed a mean brain weight difference of 31 grams in comparing 545 male alcoholics with 586 controls. They concluded that this confirmed the existence of a generalised alcoholic brain atrophy. From our study, both alcoholics with Wernicke's encephalopathy and those with no evidence of a nutritional deficiency had low mean brain weights. This suggests that alcohol, the factor common to both groups, is more important than nutritional deficiencies in causing a reduction in brain weight and cerebral cortical atrophy. Recent radiological studies[20,21] have also disclosed a high incidence of cerebral cortical "shrinkage", but some of these changes appear to be reversible.[21,22]

Having stressed the extraordinary frequency of this disease, it is obvious that it creates a significant social and economic burden to our community. Centerwall and Criqui[23] showed a significant cost-benefit in an analysis of the economic feasibility of preventing this disease by fortification of alcoholic beverages with thiamine. Certainly, these patients respond dramatically to thiamine supplements in the early or acute stages of the disease.[24] However, the optimal approach is prevention rather than cure.

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