# Autopsy prevalence of Wernicke's encephalopathy in alcohol-related disease

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*Objective.* To determine the autopsy prevalence of Wernicke's encephalopathy (WE) in patients dying from alcohol-related diseases.

*Design.* Prospective postmortem macroscopic and microscopic examination.

*Setting.* Adult autopsies at King Edward VIII Hospital.

*Methods.* Thirty-one consecutive autopsies were performed on patients who had died from alcohol-related diseases; these formed the study group. The control group comprised 10 patients with a negative history of alcohol and alcohol-related diseases. After examination of the brain, samples for histology were taken from the mamillary bodies and the wall of the third ventricle. Two subjects were excluded on account of additional unrelated brain pathology.

*Results.* Of the 29 patients studied, 17 (59%) were confirmed histologically to have WE. The histological lesions were classified as either acute (5), acute on chronic (9) or chronic (3) according to defined pathological criteria. Macroscopic abnormalities were not obvious in any of the patients in the study group. Chart analysis revealed that a disturbance of the mental state was the commonest neurological finding (9/17). Ocular palsy was not present in any of the subjects. Although 2 patients had been given thiamine prior to death, a clinical diagnosis of WE was not made in any of the cases studied.

*Conclusion.* This study proves that WE is a frequent finding in blacks with alcohol-related diseases. The high prevalence of WE found in adult autopsies (6.6%) without documented clinical evidence may have contributed to the mortality in these cases.

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Though preventable and eminently treatable, Wernicke's encephalopathy (WE) remains a potentially fatal disease that causes diagnostic confusion. Clinical[1] and pathological[2] studies indicate a rising incidence in Western countries. Autopsy studies have reported the highest prevalence in Western Australia[3] (2.8%). Today the deficiency state occurs almost exclusively in the alcoholic population.

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In Third-World countries this disease has been overlooked because of a lack of epidemiological data. Although we have noticed an increasing admission rate for WE over the past 5 years,[4] only isolated cases have been diagnosed at autopsy. This pilot study was undertaken to determine the post-mortem prevalence of WE at King Edward VIII Hospital, Durban. This is a large teaching hospital with 2 000 beds and serves the black community in the metropolitan area of the city.

## Materials and methods

Thirty-one cadavers with evidence of established alcohol-related diseases at autopsy were prospectively studied over an 8-month period from October 1988 to May 1989 at King Edward VIII Hospital. Two were excluded because of other concomitant brain pathology (meningitis, metastatic carcinoma) in the region of interest. The predominant autopsy findings in the remaining 29 subjects were alcoholic liver disease and pancreatitis (Table I).

**Table I. Autopsy diagnosis in the study group**

| | |
|---|---|
| Micronodular cirrhosis | 9 |
| Severe liver steatosis | 5 |
| Acute haemorrhagic pancreatitis | 4 |
| Chronic calcific pancreatitis | 3 |
| Alcoholic hepatitis | 3 |
| Chronic pancreatitis and micronodular cirrhosis | 2 |
| Acute pancreatitis and micronodular cirrhosis | 1 |
| Micronodular cirrhosis with hepatoma | 1 |
| Chronic pancreatitis and alcoholic hepatitis | 1 |
| | 29 |

The brains were examined macroscopically and weighed, and the external appearance of the mamillary bodies noted. In every case a block that incorporated the mamillary bodies and the wall of the third ventricle was embedded in paraffin wax and processed for histological examination. Each section was stained with haematoxylin and eosin, as well as phosphotungstic acid, luxol fast blue and Perl's prussian blue to look for gliosis, myelin fibre loss and iron deposition respectively. In addition, vascular proliferation was assessed using factor VIII antigen via immunoperoxidase staining.

The histological findings were classified as either acute, acute on chronic or chronic, according to defined histological criteria.[5] Acute WE was diagnosed when fresh perivascular 'ball' haemorrhages were present together with hypertrophic endothelial cells, spongiosis and budding and proliferation of capillaries (Figs 1 and 2). Chronic WE was diagnosed when iron-laden macrophages were present perivascularly together with absolute myelin fibre loss and gliosis (Fig. 3). When fresh perivascular haemorrhages as well as other features of acute WE were present in patients with chronic disease, it was classified as acute on chronic. Control samples were obtained from 10 patients who had died of diseases unrelated to alcohol abuse.

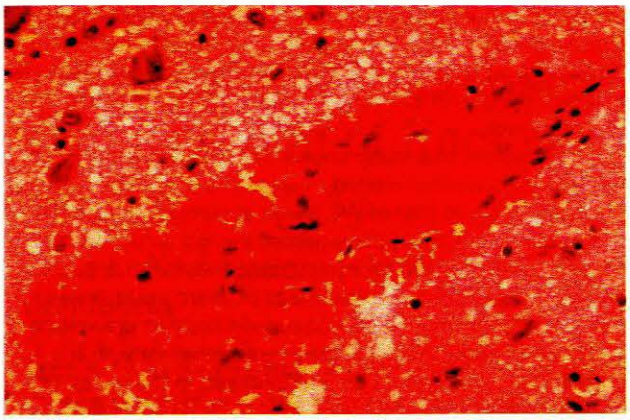

**Fig. 1. H and E stain showing fresh perivascular 'ball' haemorrhage.**

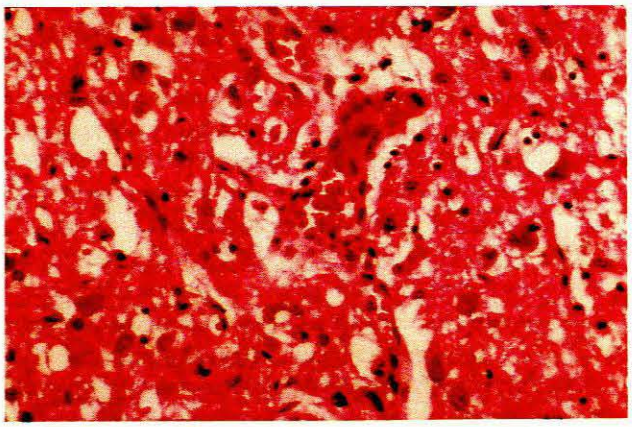

**Fig. 2. H and E stain demonstrating spongiosis and budding and proliferation of capillaries.**

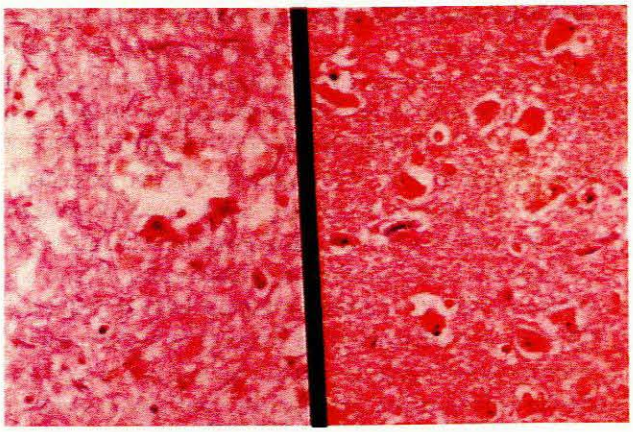

**Fig. 3. Luxol fast blue stain demonstrating absolute myelin fibre loss (normal histology in R frame).**

## Results

No macroscopic abnormalities were detected in any of the 29 patients studied. The mean brain weight in all 29 (1 293 g) was significantly lower ($P < 0.05$) than in the controls (1 321 g), in keeping with a degree of cerebral atrophy caused by chronic alcoholism.

The pathological changes are listed in Table II. In all cases the neurons were preserved and none of the controls showed any of the histological features described below. Seventeen patients (59%) exhibited histological features of WE (acute 5, chronic 3, acute on chronic 9). Their ages ranged from 31 to 60 years (mean = 47). Thirteen of the 17 patients were men. The brain weights in these 17 did not differ significantly from the remaining 12.

**Table II. Histological findings in WE (*N* = 17)**

| | Acute (5) | Chronic (3) | Acute on chronic (9) |
|---|---|---|---|
| Perivascular 'ball' haemorrhages | 5 | — | 9 |
| Hypertrophic endothelial cells | 3 | — | 2 |
| Spongiosis | 2 | — | 5 |
| Budding and proliferation of capillaries | 5 | — | 5 |
| Iron-laden macrophages | — | 3 | 9 |
| Absolute myelin fibre loss | — | 2 | 4 |
| Gliosis | — | 2 | 4 |

## Clinical findings

Although 2 patients had received thiamine intravenously prior to death, none of the 17 cases was diagnosed while the patient was still alive. Analysis of the clinical records revealed that 9 patients had an abnormal mental state, 1 patient had ataxia and another peripheral neuropathy. Apart from this, no other neurological deficit was noted in the case records. The clinical diagnoses in these 17 cases are listed in Table III. In the 10 patients who presented with alcoholic liver disease and/or pancreatitis, changes in the mental state were attributed to these illnesses rather than to WE.

**Table III. Clinical diagnosis in autopsy-diagnosed WE**

| | |
|---|---|
| Cirrhosis with portal hypertension and hepatic encephalopathy | 5 |
| Pancreatitis | 4 |
| Cardiac failure | 2 |
| Pulmonary tuberculosis | 3 |
| Alcoholic hepatitis | 1 |
| Pellagra | 1 |
| Hypoglycaemia | 1 |
| | 17 |

## Discussion

This study documents a high prevalence of WE (57%) in alcohol-related diseases. During the 8-month study period, 554 autopsies were performed at King Edward VIII Hospital. Of these, 257 were performed on patients older than 20 years, yielding a minimum 6.6% prevalence of WE in adult autopsies. Although these brains were not histologically examined for signs of WE, no macroscopic abnormalities of the mamillary bodies were documented. Previous autopsy studies show a prevalence of 2.8% in Western Australia,[2] 2.2% in Cleveland,[1] 1.7% at the Bellevue Hospital in New

York [6] and 0.8% in the Oslo Study.[7] The higher prevalence in our study is explained on the basis of case selection and the exclusion of coroner's autopsies.

Given the high incidence of alcohol-related trauma in the Durban area, it is highly probable that the inclusion of any coroner's autopsies from this magisterial district would have increased the prevalence of WE in this series significantly. This is in marked contrast to the approximately 2% prevalence in other published studies.[2,3,7] Unfortunately, as the cadavers subjected to medicolegal autopsies were not specifically examined to exclude the possibility of WE, the true incidence cannot be determined.

The mean brain weight in our study was 52 g less than that of age-matched controls, in keeping with the reduction in brain weight found in the Oslo Study[7] (31 g) and in Western Australia[2] (67 g), and indicative of generalised alcoholic brain atrophy. The histological examination was limited to the mamillary bodies since previous studies have shown that the mamillary bodies are affected in almost 100% of cases of WE.[3,8] It therefore seems unlikely that a significant number of cases could have been missed by us. The absence of macroscopic changes in the mamillary bodies is not surprising since Harper *et al.* found that these often appear normal.[2,9] In order to determine the true autopsy prevalence of WE, microscopic examination of the mamillary bodies would be required in all autopsies of adults dying of either natural or unnatural causes, irrespective of whether the clinical findings were suggestive of alcohol abuse.

In all 29 patients in this study there was a strong history of excessive alcohol intake. Liver histology revealed alcoholic hyaline in all cases and the alcoholic aetiology was also reflected in raised gamma-glutamyltransferase and mean red cell volumes from the case records.[10] Studies have shown that ingestion of alcohol does not result in WE if the dietary intake of thiamine is adequate.[9] Patients who abuse alcohol become thiamine-deficient[11] as a result of poor diet, interference with active gastro-intestinal transport of thiamine and liver disease,[10] a common consequence of alcohol abuse; in combination these lead to reduced body stores and impaired metabolism of thiamine.[12,13] All 6 patients in Harper's *et al.* prospective study[2] had cirrhosis of the liver; in addition 2 had pancreatitis with anorexia and vomiting.

Clinicopathological studies have stressed that the triad of altered mental state, ataxia and eye signs is seldom found. Harper *et al.* found that only 16% of patients had all three signs, 28% two signs, 37% one sign and 19% no signs.[14] In Torvik *et al.*'s[7] series, 1 out of 22 cases (acute and subacute) was diagnosed during life. Eye changes were recorded in only 4 cases. In our study only 2 patients had neurological deficit (ataxia and peripheral neuropathy); a further 2 had cardiac failure, but the clinical association with thiamine deficiency was not recognised! Nevertheless, the complete lack of ocular signs is worrying. A likely explanation is lack of clinical awareness in patients presenting with more overt signs of other alcohol-related organ disease. Furthermore, examination of eye movement in the comatose patient is often difficult, which makes it almost impossible to elicit ocular palsy. It has also been suggested that WE may evolve in the form of minor episodes comprising combinations of these more subtle features and that the clinical form of the disease develops after repeated episodes of subclinical encephalopathy. This may explain the complete lack of physical signs in those 12 patients in our study who had chronic changes of WE but no previous documentation of clinical illness.

In conclusion, this study shows that WE frequently accompanies alcohol-related disease in blacks. The high prevalence rate (6.6%) of WE found at autopsy in alcohol-related deaths, without documented clinical evidence, implies a greater need for clinical awareness of this entity in chronic alcoholics. Since the stress of intercurrent illness in patients with alcohol-related disease is likely to precipitate vitamin deficiency states, routine replenishment with B-complex vitamins should be administered to these patients on admission to hospital.

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