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An International Perspective on the Prevalence of the Wernicke-Korsakoff Syndrome

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In the Western world previous studies have shown that the majority of cases of the Wernicke-Korsakoff syndrome (WKS), which is caused by thiamine deficiency, occur in alcoholics. However, in France, a country with one of the highest per capita consumptions of alcohol, the prevalence of the WKS was found to be only 0.4% in a small retrospective autopsy study. This figure is compared with data sent to the authors by a number of neuropathologists from the U.S.A., Europe, Scandinavia and Australia. There was no obvious correlation between the prevalence rates of the WKS, which were highest in Australia (2.8% - previously published), and per capita consumption of alcohol. Other issues such as diet, National programs for supplementation of foods with thiamine, and drinking habits are considered. The pathological diagnosis of the WKS can often be made on macroscopic examination of the brain after fixation in formalin. The mammillary bodies are smaller than normal in most cases of chronic WKS. However in this study it was found that the most common causes of small mammillary bodies were Alzheimer's disease and atrophy due to transneuronal degeneration secondary to lesions in the hippocampus.

Key words: Thiamine deficiency, Wernicke-Korsakoff syndrome, prevalence, international perspective, pathology.

INTRODUCTION

Clinical and pathological studies suggest that there is a considerable variation in the prevalence of Wernicke's encephalopathy (WE) or as it is often called, the Wernicke-Korsakoff syndrome (WKS), throughout the world. Since, in Western countries, the disease is most commonly linked to alcoholism (Harper, 1983; Victor *et al.*, 1989) one might expect that the prevalence would relate to per capita consumption of alcohol (ethyl alcohol).

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There are good data on the consumption of alcohol throughout the Western world but relatively little recent data on the prevalence of the WKS. Thus we have not been in a position to permit such an analysis. The purpose of this study was to obtain such data and to examine other factors which might play a role in the development of the WKS. The disease is caused by a deficiency of thiamine and relatively simple public health measures such as thiamine supplementation of basic foods like flour and bread, which is the current practice in a number of countries (Yellowlees, 1986), may play an important role in modifying the prevalence of the WKS.

MATERIALS AND METHODS

During 1989-1990 one of the authors (CH) wrote to neuropathologists throughout the world inviting them to provide information from their autopsy files on their recent experience with the WKS. They were asked to indicate the number of recent cases, the number of brains examined during the same period of time and the type of hospital or referral centre from which the brains were derived. The data which were suitable for inclusion in the study is shown in Table 1. Several of the respondents had already published their data and this material has been included in Table 1 (Jellinger, 1976 ; Harper, 1983; Hauw *et al.*, 1988; Harper, *et al.*, 1989; Lindboe and Loberg, 1989) Most of the replies were from the USA, Europe and Australia. There were a number of responses from other countries including India, Pakistan and Thailand but accurate data on the prevalence of the WKS was not available.

Data was also collected specifically for this study from France because of the high per capita consumption of alcohol (Verhoek, 1992). Cases were collected from two different sources - the Forensic Institute in Paris and the Neuropathology Department of the Salpêtrière Hospital in Paris which deals with tertiary neurological referrals. Approximately equal numbers of male and female cases over the age of 18 years were selected at random from the 1989 to 1994 brain store of the Neuropathology Department at the Salpêtrière Hospital. The mammillary bodies were carefully examined macroscopically and a block of the mammillary bodies was taken from each of the brains. It has been shown that the mammillary bodies are abnormal (microscopically) in between 99% and 100% of cases of the WKS (Harper, 1983; Victor *et al.*, 1989). Cases from the Forensic Institute included all autopsies (over the age of 18 years) which had had tissue histology and brain fixation carried out from 1992 and 1993 inclusive. Tissue blocks were embedded in paraffin and processed in the usual manner. Sections were stained with hematoxylin and eosin and additional stains such as Perl's (to confirm that brown pigment in the mammillary bodies is iron) or reticulin (to highlight changes in vascular patterns) were only used if an abnormality was suspected after initial examination. All cases were examined by one of the authors (CH) and those considered abnormal, by all authors.

Table 1

Prevalence of Wernicke-Korsakoff Syndrome at Autopsy				
COUNTRY	CITY	CASE COLLECTION	PREVALENCE	ALCOHOL INTAKE (1989)**
Australia #	Perth	Forensic + Gen. Hosp	2.8%	8.4
Australia #	Sydney	Gen. Hosp	2.1%	8.4
Austria	Vienna	Uni Hosp	0.5%	10.3
Austria #	Upper Austria	Psych Hosp	1.1%	10.3
Austria	Vienna	Gen + Psych Hosp	1.3%	10.3
Belgium	Brussells	Uni Hosp	0.1%	9.5
Czechoslovakia	Prague	Uni Hosp	1.0%	8.7
France	Lyon	Gen Hosp	1.0%	12.8
France #	Paris	Neurol Hosp	1.3%	12.8
France	Paris	Neurol Hosp + Forensic	0.4%	12.8
Germany	Berlin	Uni Hosp	0.8%	11.1
Germany	Bielefeld	Uni Hosp	0.6%	10.4
Germany	Gottingen	Uni Hosp	0.3%	11.1
Germany	Heidelberg	Uni Hosp	0.8%	11.1
Norway #	Oslo	Gen Hosp	0.75%	4.2
UK	Glasgow	Neurol Hosp + Forenisic	0.5%	7.6
USA	Conneticut	Uni Hosp	1.0%	7.4
USA	Kansas	VA Hosp	0.1%	7.4
USA	Massachusetts	Gen Hosp	0.1%	7.4
USA	Miami	VA Hosp	0.6%	7.4
USA	Oklahoma	Gen Hosp	0.0%	7.4
USA	Phoenix	Neurol Hosp	0.3%	7.4

** National per capita consumption of ethanol in litres, (Verhoek 1992)
VA= Veterans Hospital
# See references by Harper 1983, Harper 1989, Jellinger 1976, Hauw et al 1988 and Lindboe and Loberg 1989.

RESULTS

French Study

Two hundred and fifty six brains were examined-one hundred and fifteen from the Salpêtrière Hospital and one hundred and forty one from the Forensic Institute . There were one hundred and sixty six males and ninety females. The mean ages of males and females were higher in the Salpêtrière Hospital cases (males-64 yrs; females-73 yrs.) than in the Forensic cases (males-44 yrs; females-47 yrs.).

Although there were a number of pathological abnormalities, only one case of Wernicke's encephalopathy was diagnosed. Thus, the prevalence of Wernicke's encephalopathy in this study was 0.4%. This case was from the Salpêtrière Hospital material. Review of the clinical notes revealed that the patient was a woman aged 63 years who had been a heavy drinker all her life. She had a complicated medical history and had suffered from a previous stroke with residual left hemiparesis and a head injury with subdural hematoma which was evacuated surgically four months before she died. At autopsy she was found to have a fatty liver. The brain was examined after fixation in formalin and weighed 1335 grams. It showed old traumatic lesions of the right frontal pole and an old

infarct in the watershed region between the anterior and middle cerebral artery territories on the right. Coronal sections of the cerebral hemispheres confirmed these findings and revealed mammillary bodies which were brown but of normal dimensions. Microscopy of the mammillary bodies showed increased numbers of small capillaries, gliosis and spongiosus of the neuropil and a relative preservation of neurons. There was no iron pigment seen. The microscopic changes were typical of chronic WE.

The mammillary bodies were abnormal in twelve other cases. The principal macroscopic abnormality, seen in 5 cases, was shrinkage of the mammillary bodies (Figure 1), similar to the change seen in the majority of cases of chronic WE. However microscopy revealed that three of these cases had Alzheimer's disease and the mammillary bodies were gliotic and contained numerous senile plaques (Figure 2). Of the other two cases one patient had had a thalamatomy and one patient had left sided hippocampal sclerosis (Figure 3). One patient with AIDS had progressive multifocal leucoencephalopathy with involvement of the mammillary body and six cases had small haemorrhages in the mammillary bodies and adjacent periventricular tissues in association with blunt head injuries.

International Study

Table 1 summarises the data on the prevalence of WE from the international respondents. Several of the neuropathologists had already published their data but these are included in the table and are marked with an asterix. The prevalence of WE varied from 0% in Oklahoma (USA) to 2.8% in Australia.

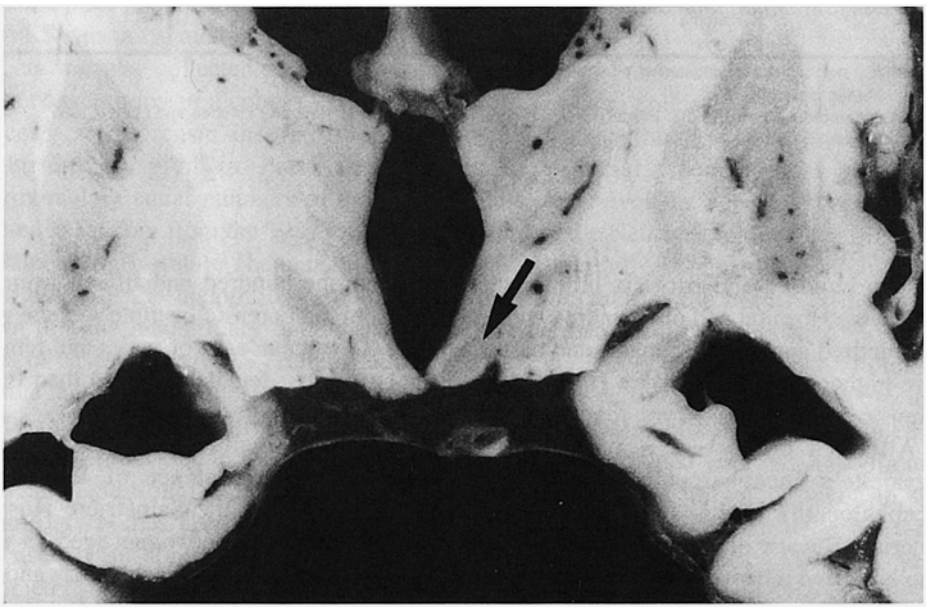

Figure 1. Coronal section of cerebral hemispheres at the level of the mammillary bodies (arrow) from a case of Alzheimer's disease showing shrinkage of mammillary bodies (compare with right mammillary body in Figure 3), **x4.**

Figure 2. Photomicrograph of mammillary body stained with hematoxylin and eosin showing spongiosus and senile plaques (arrows) in a case of Alzheimer's disease with shrinkage of mammillary bodies, **x180**.

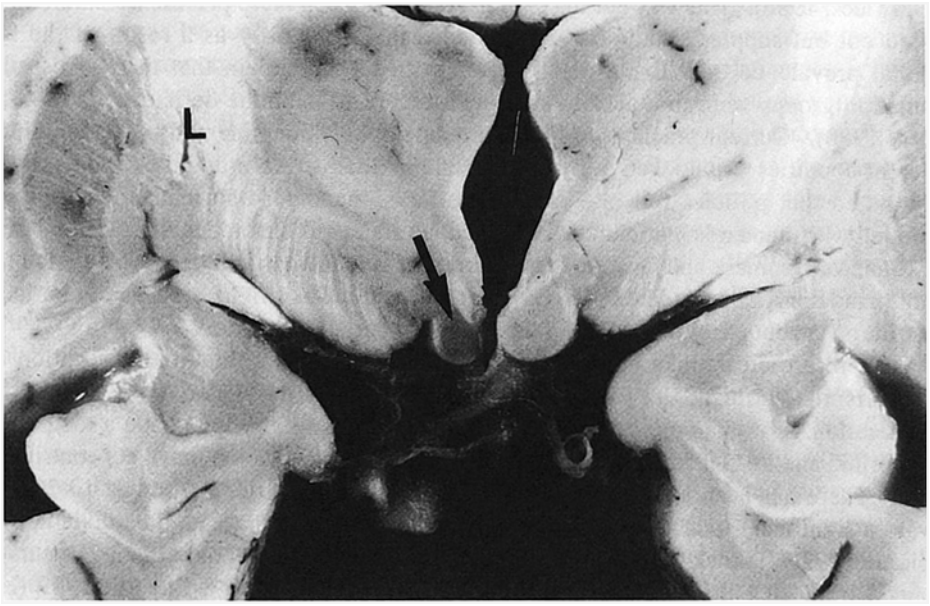

Figure 3. Coronal section of cerebral hemispheres at the level of the mammillary bodies, showing atrophy of the left mammillary body (arrow) secondary to a lesion of the left hippocampus (sclerosis of Ammon's horn). The right mammillary body is normal, **x4**.

DISCUSSION

Although only a small number of countries are represented in this study there are a number of conclusions which can be drawn. Considering the data from the Paris study together with the data in Table 1 there does not appear to be any relationship between the prevalence of WE and the national per capita figures for ethanol consumption (see table 1). Australia has the highest prevalence of WE and yet per capita consumption is less than in France, Germany, Czechoslovakia and Belgium (Verhoek, 1992). There is considerable variation of the prevalence of WE within individual countries (eg. Austria) and an important factor which must be taken into consideration in this regard is the type of hospital, institute or university from which the data were derived. Thus, in Austria, the prevalence was much higher in a general and psychiatric hospital than in a university hospital. This is understandable in that psychiatric hospitals and to a lesser extent general hospitals will see more patients with alcohol-related disorders than specialised university hospitals which are often tertiary referral centres. It has been noted previously that the prevalence is much higher in forensic material compared to hospital cases (Harper, 1983).

The reasons for the considerable variation in the prevalence of the WE both within a single country and between different countries is not immediately apparent but has been noted previously (Harper and Kril, 1990). Since WE is caused by a deficiency of thiamine one needs to consider dietary intake. This could be a key factor as many countries supplement basic foods such as flour and bread with thiamine (USA, UK and others) (Yellowlees, 1986). This was not the case in Australia when these prevalence studies were carried out but supplementation was introduced in 1991, partly as a result of the high national prevalence of WE but also because it had been shown that many Australian population groups were in a parlous state with regard to thiamine deficiency (Wood and Breen, 1980). Current practice on flour enrichment with thiamine and other vitamins in different countries was looked at by Axford and Williams (Axford and Williams, 1981). They noted that policies fell into four categories - mandatory enrichment; enrichment permitted with standards; enrichment permitted, no standards and no legal provision. In the UK, Canada, Denmark and Guyana the requirement is mandatory. In the USA, enrichment is not mandatory, but standards are laid down and the bulk of flour marketed is enriched. Most European countries, including France, prohibit enrichment.

As there are clear links between alcohol consumption and thiamine absorption and metabolism (Thomson *et al.*, 1987), drinking habits may also be an important consideration. For example, Australians, particularly younger people, have a tendency to binge drink, and this leads to higher peak blood alcohol levels which may be a contributing factor. There has been a general trend in most Western countries in the last 10-20 years toward a significant reduction in per capita alcohol consumption (Haut comité de la Santé publique 1992; Verhoek, 1992). In France, consumption in adults older than 15 years has dropped from 22.1 litres (pure ethanol per capita) in 1975 to 16.8 litres in 1989 (Haut Comité de la Santé publique, 1992). The Australian experience is similar with per capita consumption dropping from 9.4 litres in 1975 to 8.4 litres in 1989 (Verhoek, 1992). This downward trend has continued since 1989 in both countries. It should be remembered that

extrapolation of data from one city to the entire country is not realistic. The variability in drinking patterns in France emphasises this point. Data from the Ministry of Health in France show that mortality rates in men from alcoholism, alcoholic psychosis and cirrhosis are almost 100% higher in Bretagne and Nord-Pas-de-Calais than in most other regions (Haut comité de la Santé publique, 1992). The pattern of drinking in Third World countries however appears to be increasing and, given the relatively poor diet in some areas, it would be surprising if the prevalence of WE was not quite high (Edwards, 1979). In a recent autopsy study from South Africa, during an eight month period, twenty nine Black patients died from alcohol-related diseases - seventeen of these had WE (Naidoo *et al.*, 1991).

Although WE is most closely linked to alcoholism, there are a number of other conditions which predispose to the development of the disease. Malnutrition is obviously important as are starvation diets, gastric stapling, anorexia nervosa and long term parenteral feeding without adequate vitamin supplements (Dreneck *et al.*, 1966; Harper, 1980). A number of other isolated reports exist and recently there have been several cases of WE reported in patients with AIDS (Butterworth *et al.*, 1991).

The pathological features of chronic WE are said to be characteristic with little likelihood that a wrong diagnosis could be made. On macroscopic examination the mammillary bodies are usually shrunken and brown and sometimes spongiotic. However as shown in this study there are a number of other disorders which can cause a similar macroscopic appearance (see Figures 1 and 3). The most common is Alzheimer's disease but the correct diagnosis is easily made on microscopic examination when one can usually identify senile plaques even in the hematoxylin and eosin stained sections (see Figure 2). The diagnosis can be confirmed by the use of appropriate silver impregnation techniques. One of the most important microscopic features of chronic WE is a relative preservation of neurons in the periventricular lesions around the floor of the fourth ventricle and mammillary bodies (Victor *et al.*, 1989). This helps one to differentiate chronic WE from another important condition which can mimic the microscopic changes in the mammillary bodies - hippocampal sclerosis. Transneuronal degeneration with loss of some neurons in the mammillary body and shrinkage of many of the residual neurons is commonly seen in hippocampal sclerosis (Lindboe *et al.*, 1989; Schubert and Friede, 1979). Generally the change is unilateral. Posterior cerebral artery territory infarction can also induce changes in the mammillary body (unilaterally) which can mimic either acute or chronic WE, probably through lesions of the hippocampus.

Small hemorrhages are commonly seen in diencephalic structures in patients dying from head injuries. However, they are somewhat different to those seen in acute WE (in about 5% of cases) which are usually associated with vascular endothelial changes (hypertrophy and hyperplasia) (Harper, 1980). The vessels appear normal in the head injury cases. If there is any doubt about the diagnosis of WE based on the microscopic changes seen in the mammillary bodies, even after the use of special stains, other periventricular regions (eg. floor of fourth ventricle in medulla) should be studied in detail because most studies have shown that there are abnormalities in more than 50% of cases (Harper, 1983; Victor *et al.*, 1989).

Thus, although there is a good correlation between WE and alcoholism, the correlation with alcohol consumption of different populations is poor. The reasons for this are not immediately obvious but most likely relate to individual drinking patterns and diet. The latter, diet, is influenced by Government policies such as supplementation of foods with thiamine although as shown by the difference in prevalence of WE between France, the USA and the UK this may not be a critical issue for some countries.

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