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Size of Mamillary Bodies in Health and Disease: Useful Measurements in Neuroradiological Diagnosis of Wernicke's Encephalopathy

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Abstract

Background—As the resolution of noninvasive neuroimaging techniques improves, small structures such as the mamillary bodies can be visualized and measured. The mamillary bodies are pathologically small in a number of neurological disorders, the most common and important is chronic Wernicke's encephalopathy (WE), or the Wernicke-Korsakoff syndrome (WKS), as it is often called. This disorder is caused by vitamin B1 deficiency (thiamin) and is seen most commonly in people who drink excessive amounts of alcohol. The disorder is easily preventable by using oral or parenteral thiamin. The aim of this study was to establish a range for the volume of the mamillary bodies in normal and in various disease states, particularly WE.

Methods—Brains were taken from 2212 sequential autopsies performed at the New South Wales Institute of Forensic Medicine from 1996 through 1997. After fixation in 10% formalin, the brains were sectioned coronally and a block containing the mamillary bodies was dissected. The maximum vertical and transverse diameters of the mamillary bodies were measured using Mitutoyo vernier callipers and the volume calculated ($V = 4/3 (a^2b)$, where a and b are the vertical and transverse radii, respectively).

Results—There were 164 cases with significant pathological changes in the mamillary bodies. These included cases with WE (25), Alzheimer's disease (10), infarction (11), and trauma (55). All but two of the WE cases were chronic or acute on chronic. The mean volume of the mamillary bodies was reduced by 60% in cases with chronic WE and by 25% in cases with Alzheimer's disease. In normal cases, there was a significant age-related reduction in volume, and males had larger mamillary bodies than females. Cases with alcoholic cirrhosis of the liver had normal mamillary body volumes.

Conclusions—There is a gross shrinkage of the mamillary bodies in cases of chronic WE, but clinicians need to consider other diagnoses, such as Alzheimer's disease, which can also result in shrinkage. These quantitative data will be helpful in the neuroradiological diagnosis of some of these disorders, particularly WE.

Keywords

Mamillary Body; Volume; Wernicke's Encephalopathy; Alcohol; Neuroradiology

The Resolution of neuroimaging techniques is improving each year. Smaller and smaller neuroanatomical structures can be identified and studied, and the information can be used in clinical diagnoses. Magnetic resonance imaging (MRI) studies of the mamillary bodies were first reported by Charness and DelaPaz (1987). The mamillary bodies are pathologically small in a number of neurological disorders. Chronic Wernicke's encephalopathy (WE), a disease caused by thiamin deficiency and common in alcoholic populations (Harper, 1983; Victor et al., 1989), is characterized pathologically by periventricular lesions, the most common being atrophy of the mamillary bodies. These structures are located in the floor of the third ventricle and their normal volume is approximately 60 mm³ (each mamillary body). Charness and DelaPaz (1987) concluded from their study that measurements of the volume of the mamillary bodies provided a means of identifying cases of chronic WE during life. A recent autopsy study of the prevalence of WE in Australia identified a number of other pathological abnormalities in mamillary bodies; some of these also result in shrinkage or atrophy of these structures (Harper et al., 1997). Hence, accurate data on volumes of mamillary bodies in males and females of different ages and with different diseases would be helpful to clinicians and radiologists. The aim of this study was to establish such a profile to aid in clinical and radiological diagnosis.

Material and Methods

Brains were taken from 2212 sequential autopsies performed at the New South Wales Institute of Forensic Medicine from 1996 through 1997. After fixation in 10% formalin for 2 weeks, the brains were examined and sectioned at 10 mm intervals in the coronal plane. A block of tissue was taken which incorporated the mamillary bodies. This block was further sectioned in the coronal plane through the center of the mamillary bodies, and the vertical and transverse diameters of the mamillary bodies were measured using Mitutoyo vernier callipers. These blocks were then embedded in paraffin wax and processed for histological examination. Sections were stained with hematoxylineosin in the first instance but other stains were used in cases which showed pathological abnormalities. For example, Perl's stain for iron was used to characterize brown pigments which might have been caused by previous hemorrhage, and silver stains were used in cases that were suspected to be Alzheimer's disease. Blocks were taken from other areas of the brain giving consideration to the clinical diagnosis and the macroscopic findings. All cases were treated blind by the neuropathologist; macroscopic and microscopic reports were prepared on each of the cases.

To calculate the volume, an ellipsoid shape was assumed for the mamillary bodies, as adopted in other studies (Charness and DeLaPaz, 1987; Squire et al., 1990). The formula used to calculate the volume was $V = 4/3 (a^2b)$, where a and b are the radii in the transverse and vertical dimensions, respectively.

In each case, the following information was obtained from the Coroner's report: age, sex, circumstances surrounding the death, and alcohol history. The cause of death and other

relevant pathological findings were obtained from the forensic pathology reports. The cases were categorized into groups based on clinical information and the pathological diagnosis. Only cases that had no clinical history or pathological evidence of alcohol problems (eg., alcoholic cirrhosis of the liver) were used as the “normal” group when comparative analyses were made because studies have suggested that alcohol abuse can cause shrinkage of the mamillary bodies (Sullivan et al., 1999). The WE cases had the characteristic pathological lesions in the mamillary bodies and the periventricular region. No other neuropathological abnormalities were noted. These cases were subclassified into acute, acute on chronic, and chronic based on well described microscopic features (Victor et al., 1989). Clinical notes were sought from hospitals in the Sydney area for the 25 cases that were diagnosed as WE. Of these, 18 cases had well documented hospital admissions and are discussed below.

The data were entered onto a spreadsheet Statview (SAS Institute Inc, USA) for statistical analysis. One-way ANOVAs, followed by Fisher's protected *t*-tests, were performed to assess the differences between groups of cases with pathological abnormalities. Linear regression analysis was used to identify correlations between mamillary body volume and age for males and females. All the results are stated as means $\pm$ standard deviations.

Results

Of the 2212 cases brains examined, 2048 had normal mamillary bodies and 164 had pathological abnormalities. The volumes of the mamillary bodies in the “normal” groups and those with pathological abnormalities are listed in Table 1. Of the 164 abnormal cases, 62 have not been included in this table. The 62 included cases with mild gliosis of unknown cause, autolytic change, HIV encephalopathy, calcification, and hypoxic encephalopathy. The ratio of males to females in the study was approximately 2:1. The age range was 15 years to 102 years; the majority of cases were between 55 and 75 years old (Table 1).

As shown in Fig. 1, there is a slight but significant ($p < 0.001$) reduction in the volume of the mamillary bodies in relation to age in both males and females. There was a highly significant difference ($p < 0.0001$) between the volumes of the mamillary bodies in “normal” males and females (males $65.3 \pm 20.0 \text{ mm}^3$, females $59.8 \pm 19.2 \text{ mm}^3$).

In chronic WE, the mean volume of the mamillary bodies was reduced by 60% when compared with age and sex matched normals. The shrinkage was significant ($p = 0.05$) but less severe in cases of Alzheimer's disease where there was a 25% reduction in mean volume when compared with age and sex matched normals. In cases of infarction in the posterior cerebral artery territory and in cases of hippocampal sclerosis with secondary (trans-synaptic) degeneration, the affected mamillary body (ipsilateral) was significantly smaller (31% of the normal mean volume, $p = 0.001$).

To evaluate the effect of alcohol alone on the size of the mamillary bodies, cases with normal mamillary bodies were identified that had a history of definite alcohol problems (alcoholic cirrhosis of the liver) or suspected alcohol problems (based on clinical information, circumstances of death, and autopsy findings). Accurate evaluation of alcohol consumption was not possible for many of the cases but there were 92 cases with alcoholic

cirrhosis of the liver (4.5%) and 164 cases with a history that suggested alcohol problems (8%). There was no statistical difference in the volumes of the mamillary bodies between these three groups (cirrhosis $64.3 \pm 20.1 \text{ mm}^3$; history suggestive of alcohol problems $64.2 \pm 20.9 \text{ mm}^3$; without a history of alcohol problems $63.4 \pm 19.8 \text{ mm}^3$).

As shown in Table 2, the cases of WE were classified, using classical microscopic features, as chronic WE, acute WE, and acute on chronic WE (Harper, 1979; Victor et al., 1989). According to reviewed hospital medical records on 18 of the 25 WE cases, only 4 had been diagnosed as WE or Wernicke-Korsakoff syndrome during life. All 4 had been diagnosed as Korsakoff's psychosis and had the smallest mamillary bodies in the study (range: 12.6 mm^3 – 22.4 mm^3 ; mean, 18.8 mm^3).

In some cases of blunt head injury (with hemorrhage in the mamillary bodies) and in four of the acute or acute/chronic cases of WE (Table 2), there appeared to be swelling of the mamillary bodies but that was not statistically significant (p values 0.7 and 0.15, respectively).

Of the 2212 cases, there was information on 128 that suggested a history of substance abuse. Those cases were subject to a separate study by Garrick and colleagues who looked at accidental deaths caused by the use of illicit drugs in Sydney, Australia (Garrick et al., 1999). The mean mamillary volume for cases with reported substance abuse was $66.56 \pm 19.7 \text{ mm}^3$. Of the 128 cases, 122 had normal mamillary bodies, 3 showed traumatic hemorrhages, 2 were autolytic, and 1 showed hypoxic encephalopathy. The cases without a history of substance abuse but with normal pathology had a mean volume of $63.3 \pm 19.9 \text{ mm}^3$.

Discussion

The mamillary bodies can be measured accurately both during life using MRI and at autopsy. The pathological and radiological data are, in general, comparable but some studies are difficult to compare because of different methodologies (Sullivan et al., 1999). For example, mamillary body areas, rather than volumes, have been measured in several studies (Pittella and Giannetti, 1994; Raz et al., 1992a), and in some pathological studies, the measurements were made after tissues had been processed as paraffin wax blocks, which caused considerable shrinkage (Pittella and Giannetti, 1994) (Table 3).

As shown in this study, variation in mamillary body volumes in different groups of cases can be explained to some extent by the differences related to sex and age. Males have larger mamillary bodies than females, and there is a slight but significant reduction in mamillary body volume with increasing age. Age-related differences in mamillary body size have been demonstrated previously using MRI, but in that study the authors failed to show a difference between males and females (Raz et al., 1992a); however, there were only 82 cases compared with the 2048 normal cases reported here. The age-related shrinkage and sex differences are consistent with most other quantitative neuroanatomical data which show that brain volume and the volumes of subregions of the brain reduce with age and are smaller in women than in men (Double et al., 1996; Harper and Blumbergs, 1982). The latter seems to relate largely

to body height. In the case of age-related shrinkage, it has been shown that the reduction in brain volume is predominantly due to a loss of white matter (Double et al., 1996). The mamillary body has a number of white matter bundles within it (Ailing and Bostrom, 1980), which may explain the age-related shrinkage.

Previous authors have discussed the value of using mamillary body measurements from MRIs to confirm or refute clinical diagnoses (Charness and DeLaPaz, 1987; Squire et al., 1990). Squire and his colleagues (1990) used neuroimaging techniques to differentiate between patients with Korsakoff's syndrome and nonKorsakoff's amnesic patients. Charness and DeLaPaz (1987) used MRI to distinguish most WE patients from controls and elderly Alzheimer's patients. Our data showed that measurements of the mamillary bodies will help to identify most cases of chronic WE, but other diagnoses must be considered also, especially Alzheimer's disease. In cases of cerebral infarction (posterior cerebral artery territory) and hippocampal sclerosis, usually only one mamillary body will be affected and this, along with the clinical setting and other MRI changes, will help the clinician make the correct diagnosis.

Shrinkage of the mamillary bodies can occur very rapidly. D'Aprile et al. (1994) were able to demonstrate this by sequential MRI studies. They showed that the mamillary bodies were reduced in size in only 2 weeks after a 35-year-old woman presented with typical acute WE, was treated, and then rescanned. On the first scan, the T1-weighted image showed gadopentetate dimeglumine enhancement of the mamillary bodies and inferior quadrigeminal plate. This persisted in the follow-up scan 2 weeks later. The woman indicated short-term memory loss when examined 6 months later.

Some authors state that the diagnostic certainty of MRI is improved with the evaluation of two projections, e.g., sagittal and axial (Drayer, 1988). Atrophic alterations are better delineated on heavily weighted T1 or T2 MR images. In suspected WE patients however, there is difficulty in detecting signal changes in mamillary bodies in the axial plane, especially during the acute phase of WE (Donnal et al., 1990). This is due to a loss of signal changes in the mamillary bodies because of partial volume averaging with the suprasellar cistern (Donnal et al., 1990).

In the present study, cases with alcoholic cirrhosis of the liver and cases with a history suggestive of alcohol problems had mamillary body volumes within the normal range. This is contrary to the findings of an MRI study by Shear and her colleagues (1996) which indicated that patients with a history of heavy drinking had smaller mamillary bodies than controls. Belzunegui et al. (1995) noted an age-related decrease in neuronal numbers in the mamillary bodies, but this was not seen in the 24 males who consumed at least 120 g/alcohol per day. Their data also suggested that alcoholism accelerates the rate of neuronal loss in the mamillary bodies.

Sullivan and her colleagues (1999) have also shown that nonamnestic alcoholics have shrunken mamillary bodies. An important point to make in this regard is that there seems to be a large number of alcoholics who do not exhibit the classical clinical features of WE during life (Harper et al., 1986). At autopsy these cases are found to have the characteristic

neuropathology of WE. In fact, approximately 80% of pathologically diagnosed cases of WE are undiagnosed during life in spite of repeated admissions to major city hospitals (Harper et al., 1986, 1997). This could account for an apparent occurrence of shrunken mamillary bodies in alcoholics—they actually do have WE. To address the problem of failure to diagnose WE, use of a new operational criteria proposed by Caine and colleagues (1997) may be beneficial. They think too much reliance is placed on the classic triad for diagnosis of WE (ataxia, oculomotor dysfunction, and mental changes) and emphasize the need for a new criteria to classify alcohol-related neurological disorders. Their new operational criteria include any two of the following: dietary deficiency, eye signs, cerebellar signs, altered mental state, or mild memory impairment. In a retrospective analysis of pathologically diagnosed cases, an improved diagnostic rate was shown for Wernicke's encephalopathy, either alone or with amnesia (WKS) or hepatic encephalopathy.

Alzheimer's disease is the most common cause of dementia in our population and a number of authors have commented on thalamic and hypothalamic involvement including shrinkage of the mamillary bodies (McDuff and Sumi, 1985). These workers noted senile plaques and neurofibrillary tangles in the mamillary bodies of 74% of the Alzheimer's disease cases. Thus, although we only performed stains for Alzheimer's disease on cases that showed abnormalities on the hematoxylin and eosin stained sections of the mamillary bodies, we were unlikely to have missed large numbers of cases.

The mean volume of the mamillary bodies in the 10 cases of Alzheimer's disease was $45.5 \pm 22.4 \text{ mm}^3$ with a mean age of 85 years. The mean volume of an equivalent normal age cohort (28 cases) was $60.5 \pm 116.1 \text{ mm}^3$. This degree of brain shrinkage is consistent with other imaging studies that have shown a reduction in brain volume in Alzheimer's disease of 15% to 20% (Drayer, 1988). It is important to note that there may be a link between Alzheimer's disease and WE; Gold has suggested that pathological changes seen in Alzheimer's disease may be induced by thiamin deficiency (Gold et al., 1998). Although the pathological changes are entirely different in the two diseases, this hypothesis requires further study. None of the cases in the present study had evidence of both WE and Alzheimer's disease.

Conclusion

There is gross shrinkage of the mamillary bodies in cases of pathologically diagnosed chronic WE. Noninvasive diagnostic procedures such as MRI with comparative volume measurements of mamillary bodies may assist with the diagnosis of chronic WE, but clinicians need to consider other diagnoses such as Alzheimer's disease and hippocampal damage that can also cause shrinkage. As shown in previous similar pathological studies, there seems to be a significant number of chronic WE cases that are not diagnosed despite repeated clinical examinations in major hospitals. It is possible that there is no clinical correlate or deficit associated with the shrinkage of the mamillary bodies. This hypothesis has been proposed by Sullivan and her colleagues (1999) and states that there is a continuum of mamillary body shrinkage in alcoholics that may relate to the severity of cognitive dysfunction, particularly amnesia. However, as shown in the present study, alcohol abuse

does not appear to cause shrinkage of the mamillary bodies. Further studies that use MRI and clinical evaluation may enable us to establish which of these hypotheses is correct.

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Fig. 1.
Regression plot shows a significant reduction in the volume of the mamillary bodies.

Table 1

Mamillary Body Volumes in Different Pathological Disorders

Case type	No. of Cases	Mean volume (mm ³)	Mean age (years)	No. of males	No. of females	<i>p</i> value
Normal	2048	63.5 ± 17.6	59	1382	666	
Chronic WE	17	24.3 ± 11.1	65	17	0	< 0.0001
Alzheimer's disease	10	45.5 ± 22.4	85	3	7	0.005
Infarction	11	44.0 ± 17.1	75	7	4	0.002
Trauma (hemorrhages)	55	66.0 ± 22.4	58	39	16	0.400
Hippocampal sclerosis	12	45.5 ± 20	76	8	5	0.001

Table 2
Mamillary Body Volumes in Differing Stages of Wernicke's Encephalopathy Compared With the “Normal” Cases Without a History of Alcohol

	No. of cases	Mean volume (mm ³)	Mean age (years)
Normal	1954	63.4 ± 19.8	59
Chronic WE	17	24.3 ± 11.1	65
Acute on chronic WE	6	46.9 ± 32.9	58
Acute WE	2	70.9 ± 29.2	40

Table 3
Comparison of Mamillary Body Area and Volume From Previous Pathological and Radiological Studies

Author	Method	Study group	Volume (mm ³)	Area (mm ²)
Wilkinson and Davies, 1978	Histological sections (15 cases)	Young	49.2	
		Aged	23.9	
		Demented	24.5	
Pittella and Giannetti, 1994	Histological sections (40 cases)	Control		11.2 ± 3.2
		WE		10.0 ± 3.9
		Acute WE		12.9 ± 2.1
		Chronic WE		8.1 ± 2.5
Charness and DeLaPaz, 1987	MRI (53 cases)	Control	51.7 ± 2.5	
		Chronic WE	21.5 ± 5.8	
		Alzheimer's disease	40.1 ± 3.7	
Raz et al., 1992	MRI (82 cases)	Healthy		23.0 ± 10.0
		Patients		25.0 ± 8.0
		Combined		24.0 ± 8.0
This Study	Autopsy	Normal	63.4 ± 19.8	
		Chronic WE	24.3 ± 11.1	
	Formalin fixed (2212 cases)	Acute on chronic WE	46.9 ± 32.9	
		Acute WE	70.9 ± 29.2	
		Alzheimer's disease	45.5 ± 22.4	
		Hippocampal sclerosis	45.5 ± 20.0	