



***MENINGITIS IN SOUTH AFRICAN ADULTS***  
***- AN EVALUATION OF***  
***PROGNOSTIC INDICATORS,***  
***IMPACT OF HIV-INFECTION, AND***  
***DIAGNOSTIC DILEMMAS.***

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Dedicated to my Parents

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1. A Prospective Study of Glasgow Coma Scale (GCS), Age, CSF-Neutrophil Count, and CSF-Protein and Glucose Levels as Prognostic Indicators in 100 Adult Patients with Meningitis.



2. The Impact of HIV on Meningitis as Seen at A South African Academic Hospital (1994 to 1998).
3. Clinical, cerebrospinal fluid and pathological findings and outcomes in HIV-positive and HIV-negative patients with tuberculous meningitis.
4. Lymphnode biopsy as an aid in the diagnosis of intracranial tuberculosis.
5. Discrimination Between Viral and Nonviral Meningitis by Visually Analyzed and Quantitative Electroencephalography.
6. The value of adenosine deaminase iso-enzymes in the diagnosis of tuberculous meningitis.





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## SUMMARY

Meningitis remains a frightening disease with a high morbidity and mortality in spite of optimal treatment. In South Africa in particular, the incidence of HIV-infected patients with meningitis has risen considerably during the past decade.

The first part of this meningitis study evaluated prognostic indicators in meningitis. In 100 adult patients with meningitis it was found that the Glasgow Coma Scale (GCS) at admission was a good indicator of the ultimate prognosis of the patient, with a GCS value of  $> 12$  associated with a good outcome in 88 % of patients. A GCS value of  $< 8$  predicted an unfortunate outcome in 88 % of patients.

A high CSF protein level was also associated with an unfortunate outcome but the statistical significance was not as marked as with the GCS value. Age, CSF-neutrophil count, and glucose levels were also evaluated as possible prognostic indicators but were not found to be statistically significant.

The electroencephalograms of 12 patients with pneumococcal meningitis showed that a grade 4 dysfunction within 48 hours of admission indicated a poor outcome; CT brain scans of 26 patients with TB meningitis showed that an adverse outcome was seen particularly in patients with TB meningitis and infarcts while in 33 patients with bacterial meningitis no specific sign was found to indicate a bad prognosis - probably due to the small number of patients evaluated.

Prognostic factors in cryptococcal meningitis were lastly evaluated retrospectively in 44 patients; age, CSF white cell count and CD 4 counts were not found to be associated with outcome, while a GCS value of  $\leq 14$  at admission was found in almost three quarters of patients with an eventual adverse outcome.

The second part of the study evaluated the impact of HIV-infection on meningitis. Between 1994 and 1998, the HIV-epidemic caused a marked shift in the spectrum of meningitis towards chronic infections such as TB and cryptococcal meningitis, while the incidence of HIV-related cases with meningitis rose from 14 % in 1994 to 57 % in 1998.

A comparison of clinical, CSF and pathological findings and outcomes in 20 HIV-positive and 17 HIV-negative patients with tuberculous meningitis showed that HIV-infection does not significantly alter clinical and CSF findings in TB meningitis in South Africa, but ventricular dilatation and infarcts occur more frequently in HIV-positive patients.

Diagnostic aids in meningitis were assessed in the final part of this study. The polymerase chain reaction for TB was measured in the CSF of 10 patients with suspected tuberculous meningitis and disappointingly only positive in two patients in spite of positive CSF cultures for TB in an additional four patients.

Lymphnode biopsies were performed on seven patients with intracranial tuberculosis. Excision biopsy of an enlarged lymphnode showing caseating granulomas and/or acid-fast bacilli confirmed the diagnosis of TB within 48 hours of admission. Thus, lymphnode biopsies may be an effective and practical aid in diagnosing intracranial TB.

Adenosine deaminase (ADA) levels are often elevated in both tuberculous and bacterial meningitis. ADA iso-enzymes analysis in 26 patients however, showed that the ADA<sub>2</sub> iso-enzyme was the major contributor to increased ADA activity in the CSF of patients with tuberculous meningitis and not with bacterial meningitis.

The EEG was evaluated as diagnostic aid in 55 patients with meningitis to discriminate between viral and non-viral meningitis. Sensitivities of 70 % and 80 % of VEEG and QEEG's respectively were attained for the prediction of patients with non-viral meningitis, while the VEEG had a specificity of 100 % for the prediction of viral meningitis.

## INTRODUCTION

Some of the earliest medical literature contains references to central nervous system infections. Hippocrates already knew of the possible intracranial complications of otitis media (Hippocratic writings; Lloyd 1983) and descriptions of epidemics due to meningococcal meningitis from the early 19<sup>th</sup> century illustrate the fear that is felt by both physicians and laypersons when confronted with this disease. Thus, Dr Samuel Woodward of Torrington Connecticut, wrote in *The American Mercury*, Hartford, in 1807:

*The violent symptoms were great lassitude, with universal pains in the muscles, chills; heats, if any were in short duration; unusual prostration of strength; delirium, with severe pain in the head; vomiting, with indescribable anxiety of stomach; eyes red and watery and rolled up, and the head drawn back with spasm; pulse quick, weak, and irregular; petechiae and vibices all of the body and a cadaverous countenance and smell; death often closed the scenario within fifteen hours after the first attack ... the body, near the fatal period and soon after, became as spotted as an adder ....*

It was only in 1887 that the etiological agent involved in this "spotted fever" epidemic, then known as *Diplococcus intracellularis*, was discovered by Weichselbaum, (Benson *et al.*, 1988) and only after Quincke devised the lumbar puncture in 1891 (Quincke 1891) was it possible to diagnose meningitis during life.

Similarly, mankind has known tuberculous meningitis for many centuries, as illustrated by a hymn from *Rig Veda* (around 4000 B.C.).

*"From both thy nostrils, from both eyes  
from thy ears and from thy chin,  
forth from thy brain and tongue, I root  
consumption seated in thy head,  
forth from the neck and from the nape,  
from dorsal vertebrae and spine,  
from arms and shoulder-blades, I root  
consumption seated in thine arms."*

(R. V. X. □. 63, 1-6)

The initial description of tuberculous meningitis in the medical literature is frequently attributed to Robert Whytt following his description of febrile children with hydrocephalus in 1768 (Whytt 1768) but it was only in 1882, after the discovery of the tubercle bacillus by Robert Koch (Koch 1882), that the association between tuberculosis and meningitis was established unequivocally. This was further elucidated in the classic writings of Rich and McCordock in 1933 (Rich and McCordock 1933) when the pathogenesis of tuberculous meningitis was described in detail.

After initial mortality rates of nearly 100 % for meningitis in the 19<sup>th</sup> and early 20<sup>th</sup> century, a breakthrough in treatment of patients with meningitis came with the advent of anti-microbial therapy. In 1937, Schwentker published a report describing highly successful treatment of meningococcal meningitis with sulphanilamide (Schwentker 1937). It was in 1963 that the first sulfadiazine resistant strains of meningococci were described (Miller *et al.*, 1963). By 1969, resistance to sulfonamides was 72 % (Bennett and Young 1969) and penicillin became the drug of choice for meningococcal meningitis, reducing mortality rates dramatically. Similarly, after the advent of anti-tuberculous treatment from 1945 onwards, a significant



reduction in mortality associated with tuberculous meningitis was achieved (Smith and Vollum 1956; Lorber 1960; Meyers 1982). All these developments led to the belief that the threat of serious bacterial infectious diseases to mankind had been eliminated.

However, reality has shown that the mortality due to bacterial meningitis has not changed significantly during the last four decades (Roos *et al.*, 1991). In addition, the HIV-pandemic has been found to cause a spectacular increase of predominantly chronic forms of meningitis, e.g., tuberculous and cryptococcal meningitis, which are often difficult to treat in immunocompromised patients (Bergeman and Karstaed 1996). Thus, even in modern times, meningitis remains a frightening disease with a significant mortality and morbidity.

Factors influencing the outcome of patients with meningitis should be evaluated to understand why some patients have an unfavourable outcome in spite of optimal treatment. Patients, or their families, invariably ask about the prognosis of a specific condition and this information can be gained

from studies evaluating prognostic factors in meningitis. This is one of the primary aims of this study: to investigate prognostic factors in meningitis, including bacterial, tuberculous and cryptococcal meningitis.

During the first 10 years of the HIV-era, spread to South Africa was slow - probably due to political and geographical barriers. Unfortunately, this scenario has now changed dramatically and the late 1990's showed exponential increase in cases with HIV-infection and AIDS. Parallel to this, the number of cases with meningitis associated with HIV has soared, and the second part of this study specifically looks at the impact of HIV on meningitis in South Africa.

Finally, the diagnosis of a specific type of meningitis is often not straightforward in the acute stage, as cerebrospinal fluid findings of different types of meningitis may overlap or change during the course of the disease. It is with this in mind that this study also investigates some factors, including polymerase chain reaction, lymphnode biopsies, adenosine deaminase iso-enzymes and electroencephalography as possible diagnostic

aids in meningitis. Initially enthusiastic about developing a set of criteria to be helpful in the early and accurate diagnosis of the specific type of meningitis, the researchers could not use the data adequately as the statistical analysis was too complicated.

## Chapter 1

# PROGNOSTIC INDICATORS IN MENINGITIS

### Introduction

Since the advent of antibiotics most infective diseases appeared to have lost their threat to humans. However, meningitis remains one of the exceptions and in spite of adequate and aggressive antibiotic treatment - even with the newer agents available - the morbidity and mortality of patients with meningitis remain high. In S pneumoniae meningitis the mortality ranges from 17 % to 59 % in different studies (Quaade and Kirstensen 1962, Carpenter and Petersdorf 1962), with most studies reporting mortality rates of around 25 % - 30 % (Durand *et al.*, 1993, Hodges and Perkins 1975). Tuberculous meningitis often also carries a grave prognosis with a mortality of 15 % to 33 % (Kennedy and Fallon 1979, Manchander and Lal 1966). With the advent of the HIV-pandemic, the number of cases of cryptococcal meningitis has soared, and mortality rates of 35 % to more than 60 % have been reported for this disease (Stockstill and Kaufmann 1983, Chuck and Sande 1989, Moosa and Coovadia 1997).



In clinical neurology, it remains important to identify factors that influence the outcome of patients with meningitis and prognostic indicators are continuously being investigated.

**A PROSPECTIVE STUDY OF GLASGOW COMA SCALE  
(GCS), AGE, CSF-NEUTROPHIL COUNT, AND CSF-  
PROTEIN AND GLUCOSE LEVELS AS PROGNOSTIC  
INDICATORS IN 100 ADULT PATIENTS WITH  
MENINGITIS.**

**SUMMARY (for 1.1 - includes both 1.1.1 and 1.1.2)**

**Background**

The Glasgow coma scale (GCS) is an objective measurement of a patient's level of consciousness and has prognostic implications in traumatic head injuries. Morbidity and mortality of patients with meningitis have been related amongst others to level consciousness, hypoglycorrhachia, extremes of age, and high CSF protein values. In this prospective study of 100 patients the correlation between the GCS, age, CSF-neutrophil count and CSF-glucose and protein levels and the eventual outcome of the patients was assessed.

## Methods and patients

In 100 consecutive patients with meningitis (bacterial, viral, tuberculous, cryptococcal and other) the *GCS*, age, CSF-neutrophil count and CSF-protein and glucose levels were determined at admission. After treatment the outcome of the patient was assigned to one of four categories: healthy, minor and severe neurological deficits and death.

## Results

From a non-parametric one-way analysis of variance it was found that with respect to mean *GCS*-values significant differences were present among the favourable outcome categories compared to the adverse outcome categories ( $P < 0.0001$ ). The outcome categories did not differ significantly with respect to age, CSF-neutrophil count or CSF-glucose level, but did differ significantly with respect to the CSF protein level ( $P < 0,0025$ ). In addition, 88 % of patients with a *GCS* value of  $> 12$  had a good neurological outcome, while 88 % of those with a *GCS* value of  $\leq 8$  had a poor outcome.

## Conclusion

A good correlation between both the *GCS* and *CSF*-protein level at admission and the outcome of patients with meningitis was found, with the *GCS* value being a better prognostic indicator than high *CSF* protein levels.



### 1.1.1 The Glasgow Coma Scale as prognostic indicator

#### Introduction and survey of the literature

A few studies have looked at factors influencing the outcome of patients with meningitis in an effort to understand why patients do badly in spite of adequate treatment. Level of consciousness, hypoglycorrhagia, high cerebrospinal fluid (CSF) protein levels, extremes of age, early-onset seizures and absence of nuchal rigidity have amongst others, all been implicated as unfavourable prognostic factors in patients with bacterial meningitis (Quaade and Kirstensen 1962, Hodges and Perkins 1975, Weiss *et al.*, 1967). In tuberculous meningitis specifically, age, stage and duration of disease have been shown to have prognostic value, with both very young (< 5 years) and older (> 50 years) patients having a higher mortality (Kennedy and Fallon 1979, Berenguer *et al.*, 1992, Berger 1994).

The level of consciousness of a patient with meningitis has been related to the morbidity and mortality and deep coma has also been shown to have an

adverse prognosis. In a study of 493 episodes of bacterial meningitis, Durand *et al.*, (Durand *et al.*, 1993), found an overall mortality rate of 49 % in patients who were unresponsive or responsive to pain only, compared to 16 % of those who were alert or lethargic ( $p < 0,001$ ). Another study from Ohio (Hodges and Perkins 1975), reviewing 349 cases of bacterial meningitis, showed an overall case mortality rate of 27 % for bacterial meningitis, and patients with derangement of mental status (subdivided into three categories ranging from mild to severe) had a significantly higher case mortality rate than those without ( $p < 0,01$ ). Of patients with a "severe derangement of mental state" 45 % died. In studies of patients with tuberculous meningitis, older staging criteria by the British MRC of 1948 (MRC Report 1948), are frequently still used, namely: Stage I as the presence of non-specific symptoms and signs without alteration of consciousness; Stage II as disturbed consciousness without coma or delirium and minor focal neurological signs; Stage III as presence of stupor/coma, severe neurological deficits, seizures or abnormal movements. Almost 50 % of patients with Stage III disease have been reported to die (Smith 1964). Thus it is clear that most of the studies reporting on the level of consciousness as a prognostic indicator in meningitis utilize relatively vague terminology, e.g., "lethargy", "stupor" or "obtundation". An

objective measurement reflecting the level of consciousness has not been performed previously.

The Glasgow Coma Scale, originally described in 1974 by Teasdale and Jennett, (Teasdale and Jennett 1974) is a practical, objective measurement of a patient's level of consciousness (Table 1). The Glasgow Coma Scale is also useful in predicting the outcome of patients with head injuries where a score of less than 8 indicates a poor prognosis. In hypoxic patients, cerebrovascular disease or metabolic derangement it was shown that certain aspects of the Glasgow Coma Scale were associated with a poor outcome (Bates 1985). One recent report of the Research Committee of the BSSI (Research Committee BSSI 1995) showed in a retrospective analysis that absence of eye opening, no verbal response and no response to pain was associated with a high mortality in patients with meningitis - this triad of signs corresponds to a Glasgow Coma Scale value of 3/15.

Since the Glasgow Coma Scale is an objective way to determine a patient's level of consciousness, is easy and quick to perform and is well known by

medical staff, it is an ideal way to assess the patient's mental state in meningitis. In our study of 100 consecutive adults with meningitis, the Glasgow Coma Scale was therefore used to determine the patient's level of consciousness and the scores were then correlated with the ultimate outcome of the patients. In addition, the patient outcome categories were also compared to determine whether they differed significantly with respect to the age of the patients as well as the CSF-neutrophil count and the CSF-protein and glucose levels. The first 100 patients with meningitis, irrespective of etiology, were included in the study.

### Methods and patients

The Glasgow Coma Scale was determined in 100 consecutive adult patients with meningitis on admission. The following types of meningitis were included: 33 patients had bacterial meningitis (24 with S pneumoniae, four with N. meningitides; and one each of E.coli, Enterobacter spp., beta haemolytic streptococcus, group B Streptococcus, and Klebsiella pneumoniae), 24 patients with tuberculous meningitis, 15 patients with

cryptococcal meningitis, 10 with viral meningitis and 18 patients with meningitis of unknown aetiology.

In the patients with bacterial meningitis the diagnosis was made when cultures were positive for the specific pathogen; in tuberculous meningitis the diagnosis was made when the following criteria were met: When either CSF cultures for tuberculosis were positive, or Ziehl-Neelsen staining showed acid-fast bacilli, or post mortem confirmed caseating granulomas with meningeal exudates, the patient was classified as definite tuberculous meningitis. All other patients who had extraneural tuberculosis or improved on anti-tuberculous treatment with characteristic clinical and CSF findings (lymphocytic predominance, high protein, low glucose values) were classified as highly probable tuberculous meningitis. Those patients with only suggestive CSF findings but without proof of tuberculosis - often because the patient passed away before any tests could be done and post mortem examinations could not be performed for various reasons - were excluded from the study. Cryptococcal meningitis was diagnosed when Indian ink and/or cryptococcal antigens were positive and/or cultures showed Cryptococcus neoformans. The diagnosis of viral meningitis was made when

the CSF showed an aseptic meningitis with normal/mildly elevated protein level; normal/mildly depressed glucose level, and all the capsular antigen tests were negative, and the patient remained clinically stable or improved within 24 hours.

After the specific type of meningitis was treated adequately the outcome of the patient was assigned to one of four categories (usually at the time of discharge of the patient - the time period ranging from a few days to several weeks): No neurological deficit (NND), minor neurological deficit (MND), i.e. some neurological sequelae but could return to former level of functioning; severe neurological deficit (SND), i.e. severe deficit prohibiting former level of functioning, and death (D).



Table 1

GLASGOW COMA SCALE		
Eyes open	Spontaneously	4
	To verbal command	3
	To pain	2
	No response	1
Best motor response	Obeys	6
	Localizes	5
	Flexion-withdrawal	4
	Flexion-abnormal	3
	Extension	2
	No response	1
Best verbal response	Oriented	5
	Disoriented	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
		15

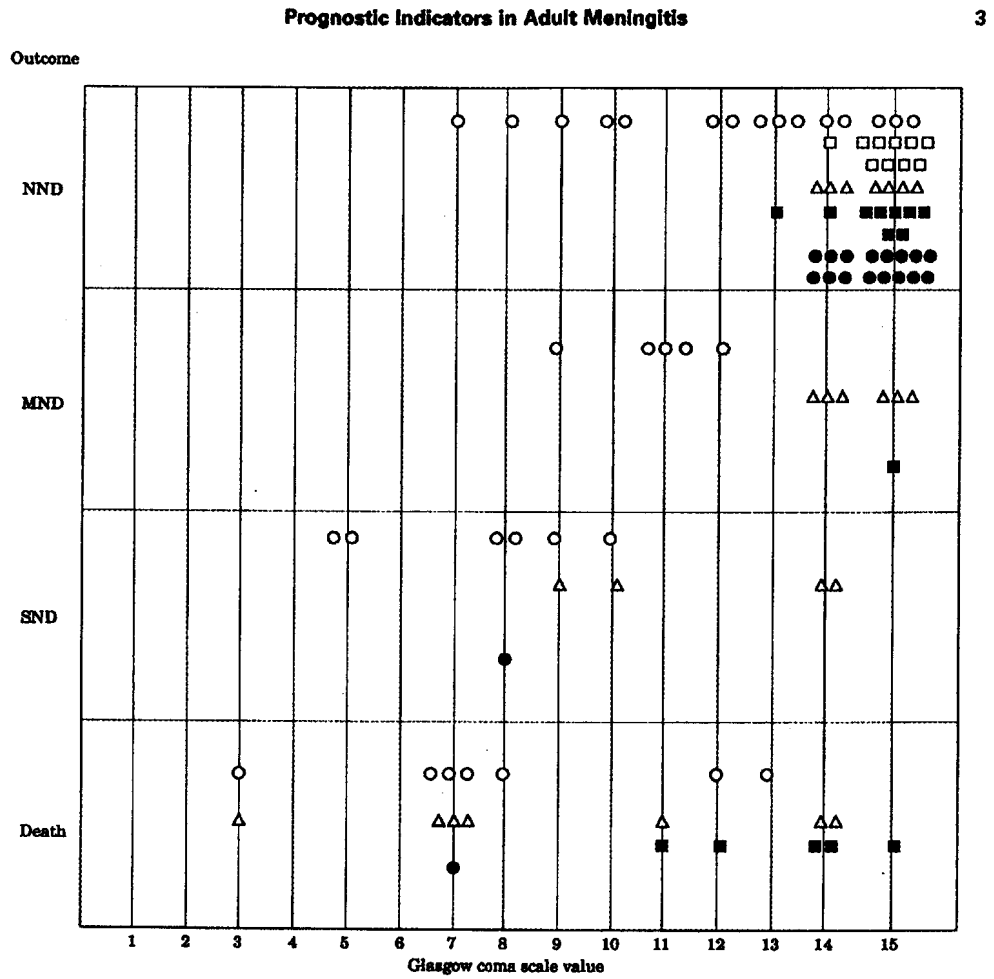
## Results

Figure 1 illustrates the outcome categories and the Glasgow Coma Scale scores. In 65 patients, a Glasgow Coma Scale value of more than 12/15 was found ( $> 12/15$ ). Eighteen patients had values between 9 and 12; (9 - 12 including 9 and 12), and 16 less or equal to 8 ( $\leq 8$ ). After treatment, 75,3 % were healthy of the group who had a Glasgow Coma Scale value of  $> 12$  at admission, while 12,3 % of that group had a minor neurological deficit, 3,1 % a severe neurological deficit and 9,3 % died. In the group with Glasgow Coma Scale values between 9 and 12, the values were 27,7 %, 27,7 % 22 % and 22 % respectively. In patients with a Glasgow Coma Scale value of  $\leq 8$  12 % had no neurological deficit, none had a minor neurological deficit, while 29 % had a severe neurological deficit, and 59 % died.

All ten patients in the viral meningitis group recovered without neurological sequelae as one would expect. In this group the lowest Glasgow Coma Scale value at admission was 14/15 (this was found in only one patient - an elderly gentleman who was slightly confused at admission but improved rapidly).



Figure 1



- - Viral meningitis
- - Bacterial meningitis
- - Uncertain/other
- - Cryptococcal meningitis
- △ - TB meningitis

Of the 33 patients in the bacterial meningitis group, 15 recovered fully, five had a minor neurological deficit, six a severe neurological deficit and seven died (21 %). All patients who had a Glasgow Coma Scale value of  $\leq 8$  either died or had severe neurological deficits except two patients: in one, severe diabetic ketoacidosis might have contributed to the low initial Glasgow Coma Scale value of 7/15. One patient with bacterial meningitis died in spite of an initial good Glasgow Coma Scale value (13/15) - he had an additional biochemical disorder with hyperkalemia and probable subsequent ventricular fibrillation.

In the 24 patients with TB meningitis, seven recovered without neurological deficits, six suffered minor deficits, four severe deficits and seven patients (30 %) died. Of the patients with cryptococcal meningitis (15 patients), nine recovered without deficits, while one had a minor neurological deficit and five died (30 %). An interesting trend was observed in these chronic meningitis subgroups (TB and cryptococcal meningitis): even high Glasgow Coma Scale values of 14/15 were associated with an adverse outcome in 50 % of patients, while only one of ten patients (10 %) with a Glasgow Coma Scale value of  $< 14$  survived without sequelae.

The summary statistics for the outcome categories are shown in Table 2. It was found by a non-parametric one-way analysis of variance (Kruskal-Wallis) that, with respect to mean Glasgow Coma Scale values, significant differences were present among the outcome categories no neurological deficit, minor neurological deficit, severe neurological deficit and death. By making use of pair-wise comparison in particular, it was found that neither the two groups NND and MND nor the two groups SND and D differed; however, the favourable outcome groups as a whole (NND and MND) were significantly different from the adverse outcome groups (SND and D) as a whole ( $P < 0,0001$ ).

## Discussion

The Glasgow Coma Scale is widely known; it is objective and easy to assess in patients with a variety of disorders. It effectively reflects the degree of impaired consciousness and coma. The vague terminology that is often applied to patients with impaired consciousness may lead to confusion, and an objective scale may facilitate consultations between referral and tertiary hospitals and can certainly lead to a more accurate determination

of prognosis. As was expected, the Glasgow Coma Scale value at admission was shown to be an accurate prognostic indicator in patients with meningitis in this study.

In patients with chronic meningitis (mainly tuberculous and cryptococcal) even a slight degree of impairment of consciousness- reflected by a Glasgow Coma Scale value of 14/15 - probably indicates the severity and duration of the disease, thus possibly accounting for the relatively more grave prognosis, even with a high Glasgow Coma Scale value. This finding was later additionally tested in a subgroup of 46 patients with cryptococcal meningitis and will be discussed in more detail under "Prognostic factors in cryptococcal meningitis".

In conclusion it was found that a Glasgow Coma Scale value of  $> 12$  was associated with a good neurological outcome in 88 % of patients. A Glasgow Coma Scale value of  $\leq 8$ , however, predicted an unfortunate outcome in 88 % of patients. In the chronic meningitis subgroup a higher Glasgow Coma Scale value seemed to be a prerequisite for a good outcome.

Table 2

SUMMARY STATISTICS IN OUTCOME CATEGORIES				
	Outcome category	N	Median	Range
Age	NND	56	30	14-75
	MND	13	26	15-64
	SND	11	28	21-46
	D	20	35.5	15-70
GCS	NND	56	15	7-15
	MND	13	14	9-15
	SND	11	9	5-14
	D	20	9.5	3-15
CSF-N (/mm <sup>3</sup> )	NND	56	4.2	0-17 050
	MND	13	201	0-33 000
	SND	11	2136	0-16 010
	D	20	114	4-48 130
CSF-P (mg/l)	NND	56	1240	310-8562
	MND	13	2160	180-9090
	SND	11	5870	1440-13 320
	D	20	2210	200-17 700
CSF-Gl (mmol/l)	NND	56	2.25	0-5.1
	MND	13	1.6	0-6.4
	SND	11	0.3	0.1-3.4
	D	20	0.9	0.1-5.2
<p>NND : No neurological deficit;  MND : Minor neurological deficit;  SND : Severe neurological deficit;  D : Death;  CSF- N : Neutrophil count;  CSF- P : Protein level;  CSF- Gl : Glucose level;</p>				

### **1.1.2 Age, CSF-neutrophil count, CSF-protein and glucose levels as prognostic indicators in patients with meningitis**

#### **Introduction and survey of the literature**

Several studies have indicated that age less than one year or greater than 40 years as well as a very high CSF-protein level in patients with bacterial meningitis have been associated with an unfavourable prognosis (Hodges and Perkins 1975, Weiss *et al.*, 1967). In one study of 349 cases of bacterial meningitis (Hodges and Perkins 1975), it was found that more than one-third of patients with a CSF protein value of > 500 mg/100 ml died showing a statistical difference for mortality between patients with lower protein values and those with high values. This was also found in an older study, which reported on prognostic factors in pneumococcal meningitis (Weiss *et al.*, 1967). In the same study of 349 episodes of meningitis a trend towards decreased survival in patients with low CSF leucocyte counts was seen but this did not reach statistical significance. This trend was also seen with very low CSF-glucose levels but once again not statistically

significant. In another study of 493 cases of bacterial meningitis, however, no correlation could be found between very high CSF-protein levels and mortality (Durand *et al.*, 1993). The CSF-neutrophil count and CSF-glucose levels have variable prognostic significance in different studies (Hodges and Perkins 1975). In tuberculous meningitis, extremes of age (< 5 years, > 50 years) have been associated with an adverse prognosis (Kennedy and Fallon 1979, Berenguer *et al.*, 1992, Berger 1994), as have very high CSF protein levels (> 300 mg/dl) (Haas *et al.*, 1977, Weiss and Flippin 1965).

### Methods and patients

In our study of 100 adult patients with various types of meningitis the age, CSF-neutrophil counts and CSF-protein and glucose levels were also evaluated as possible prognostic factors. The methods and patients were the same as for the evaluation of the Glasgow Coma Scale as prognostic indicator in meningitis and the summary statistics are also shown in Table 2.

Table 2

SUMMARY STATISTICS IN OUTCOME CATEGORIES				
	Outcome category	N	Median	Range
Age	NND	56	30	14-75
	MND	13	26	15-64
	SND	11	28	21-46
	D	20	35.5	15-70
GCS	NND	56	15	7-15
	MND	13	14	9-15
	SND	11	9	5-14
	D	20	9.5	3-15
CSF-N (/mm <sup>3</sup> )	NND	56	4.2	0-17 050
	MND	13	201	0-33 000
	SND	11	2136	0-16 010
	D	20	114	4-48 130
CSF-P (mg/l)	NND	56	1240	310-8562
	MND	13	2160	180-9090
	SND	11	5870	1440-13 320
	D	20	2210	200-17 700
CSF-Gl (mmol/l)	NND	56	2.25	0-5.1
	MND	13	1.6	0-6.4
	SND	11	0.3	0.1-3.4
	D	20	0.9	0.1-5.2

NND : No neurological deficit;  
MND : Minor neurological deficit;  
SND : Severe neurological deficit;  
D : Death;  
CSF- N : CSF Neutrophil count;  
CSF- P : CSF Protein level;  
CSF- Gl : CSF Glucose level;



## Results

In this study the outcome categories (No neurological deficit (NND), minor neurological deficit (MND), severe neurological deficit, (SND), and death (D)) did not differ significantly with respect to age, CSF-neutrophil count or CSF-glucose level. However, the outcome groups did differ significantly with respect to the protein level in the CSF, in particular in outcome categories NND and SND ( $P = 0,0025$ ). Thus, a very high CSF protein level was associated with a bad outcome.

## Discussion

Studies evaluating prognostic factors in meningitis have often shown that extremes of age are associated with a worse prognosis (Hodges and Perkins 1975, Sigurdardóttir *et al.*, 1997). In our study no pediatric cases were included, and most patients with meningitis were in the younger age groups with median ages < 40 years in all the outcome categories. This probably accounts for the fact that age was not associated with prognosis in this study.

However, the outcome categories did differ significantly with regard to the CSF-protein levels, with very high levels associated with a worse prognosis, as was also shown in previous studies (Hodges and Perkins 1975, Weiss *et al.*, 1967). The median CSF protein levels of the SND group and the D group were 5870 and 2210 mg/L respectively. The statistical difference was not as marked as with the Glasgow Coma Scale where the p-value was  $<0,0001$ .

## **1.2 ELECTROENCEPHALOGRAPHY (EEG) AS PROGNOSTIC INDICATOR IN PNEUMOCOCCAL MENINGITIS**

### **SUMMARY**

#### **Background**

This study aimed to evaluate possible prognostic factors in the EEG's of patients presenting with pneumococcal meningitis.

#### **Methods and patients**

Twelve patients presenting with pneumococcal meningitis underwent EEG studies within 48 hours of admission. EEG's were graded from normal (grade 0) to grossly abnormal (grade 4).

#### **Results**

A grade 2 dysfunction occurred in one patient, while six patients showed a grade 3 abnormality and five patients a grade 4 abnormality on EEG. None of the patients with a grade 4 dysfunction recovered.

## Conclusions

Polymorphic delta activity (grade 4 abnormality) on the EEG of patients with pneumococcal meningitis seems to predict a poor outcome.

## Introduction and survey of the literature

Electroencephalography (EEG) in clinical practice seems to have limited value in patients with meningitis. Certain signs in a visually analysed EEG may have prognostic implications - but one recent study showed that electroencephalography did not add significant contributions to information derived from clinical evaluations alone (Pike *et al.*, 1990). The literature regarding EEG's in meningitis is relatively old, showing mild abnormalities in aseptic meningitis (Gibbs *et al.*, 1962) and more pronounced abnormalities in bacterial meningitis (Turrel and Roseman 1955). In children, up to 25 % have initial seizures when presenting with bacterial meningitis (Turrel and Roseman 1955), while seizures as a presenting feature of meningitis are rare in adults.

The aim of this evaluation was to determine possible prognostic factors in the EEG's of patients with pneumococcal meningitis.

### Methods and Patients

As part of our study investigating EEG's - both visually analysed (VEEG) and quantitative EEG's (QEEG) - as possible diagnostic aids in groups of patients with meningitis (discussed in detail under "The Electroencephalogram as diagnostic aid in meningitis") a subgroup of 12 patients with pneumococcal meningitis was investigated regarding prognostic signs on EEG. Within 48 hours of admission the patients underwent EEG studies. The electrodes were applied according to the International 10 - 20 system and secured by adhesive paste; impedances were less than 5 kOhm. Nihon-Kohden models 4221, 4418 or 7210 were used for the performance of the EEG's. Both bipolar and common reference montages were utilized. Eye movement recordings from the outer canthus electrodes were referred to M2.

An experienced electroencephalographer, who had no knowledge of the clinical data, analysed the EEG's. The EEG's were graded from normal

(grade 0) to grossly abnormal (grade 4) according to a classification system largely incorporating the Mayo Clinic System (Mayo Clinic and Mayo Foundation 1991). In this system, grade 0 is normal, grade 1 shows 6 - 7 Hz theta activity; grade 2 has 4 - 5 Hz theta and/or delta activity in < 20 % of the recording; grade 3 shows intermittent rhythmic delta activity (IRDA) and/or delta in > 20 % of the EEG recordings and grade 4 comprises persistent polymorphic non-reactive delta activity (PDA).

The final outcome of the patients (no neurological deficit (NND), minor neurological deficit (MND), severe neurological deficit (SND) and death (D)) was then correlated with the initial EEG rating.

## Results

None of the 12 patients had normal (grade 0) or slightly slowed (grade 1) EEGs. Only one patient was categorized as a grade 2 dysfunction, while a grade 3 dysfunction was seen in six patients, and grade 4 dysfunction occurred in five patients. Of the five patients with a grade 4 dysfunction, none recovered without sequelae - two died, two had severe neurological

deficits and one a minor neurological deficit. Contrary to this group, all patients with a grade 3 dysfunction recovered completely (Figure 2).

## Discussion

Generally, a correlation is seen between the degree of slowing on EEG and cerebral responsiveness measured by impairment of consciousness in patients. The finding of Glasgow Coma Scale values of  $\leq 8$  predicting a bad prognosis has been discussed in the section on Glasgow Coma Scale as prognostic factor, and the correlation between Glasgow Coma Scale values and EEG grading versus outcome will be further discussed in the section entitled "The Electroencephalogram as diagnostic aid in meningitis".

Figure 2

EEG GRADING VS. OUTCOME IN 12 PATIENTS WITH PNEUMOCOCCAL MENINGITIS.					
Outcome	D			xx	
	SND			xx	
	MND	x		x	
	NND		xxx		
			xxx		
		1	2	3	4

EEG grade

- NND : No neurological deficit  
MND : Minor neurological deficit  
SND : Severe neurological deficit  
D : Death



## Conclusion

Thus, although the number of patients evaluated by EEG to determine possible prognostic importance of electroencephalography in meningitis in this study is very small, there is a trend towards adverse outcome in patients with pneumococcal meningitis where the EEG shows polymorphic delta activity (grade 4 dysfunction).

# **1.3 BRAIN CT SCAN AS PROGNOSTIC TOOL IN**

## **MENINGITIS**

### **SUMMARY**

#### **Background**

The indications and value of radiological studies in patients with meningitis are controversial and CT brain scans are often only done when complications are suspected. This part of the Pretoria Academic Hospital meningitis study aimed to investigate CT brain scan findings in patients with bacterial, tuberculous and cryptococcal meningitis to evaluate the CT brain scan as a possible prognostic tool.

#### **Methods and patients**

The CT brain scans of 26 patients with TB meningitis, 33 with bacterial meningitis, and 21 patients with cryptococcal meningitis were analysed and compared to the ultimate outcome of the patients.

## Results

In TB meningitis the presence of infarcts was associated with an adverse outcome in 80 % of patients; diffuse edema, while only occurring in two patients, was fatal in both; hydrocephalus/enlarged ventricular system was the most common CT abnormality, but predicted a bad prognosis in only 55 % of patients.

In bacterial meningitis CT brain scans showed a wide spectrum of abnormalities, including gliosis, meningeal enhancement, infarcts etc., and no specific sign indicated a bad prognosis. However, the two patients with infarcts on brain scanning both died - but more patients will have to be evaluated to determine the significance of this observation.

In cryptococcal meningitis, a retrospective analysis of 21 CT scans showed normal scans in 13 patients of whom five had an unfortunate outcome. No single finding stood out as a bad prognostic sign.

## Conclusion

A worse prognosis occurred in patients with TB meningitis who had infarcts on CT scanning; in bacterial and cryptococcal meningitis no single factor seemed to indicate a bad prognostic sign.

## Introduction and survey of the literature

The value of performing a CT/MRI scan of the brain in patients with meningitis has been debated. However, brain imaging studies are frequently used when complications of meningitis are suspected; e.g., hydrocephalus, effusions, abscesses, etc., or when predisposing factors for the development of meningitis such as CSF leaks are sought. In a study by Durand (Durand *et al.*, 1993), 31 % of patients had abnormalities on CT scan related to the meningitis (bacterial), with hydrocephalus/enlarged ventricles occurring most commonly (13/87 - 15 %). Patients with focal signs had significantly more abnormalities on CT scans than those without focal signs. Ventricular enlargement and collection of fluid subdurally were also the most common findings in children in another study (Stovring and Snyder 1980). Another recent study from Iceland (Sigurdardóttir *et al.*,

1997), analysing data of 132 episodes of bacterial meningitis over 20 years, showed abnormalities on CT scan in one-third of patients who underwent CT scanning, most commonly edema or low-density lesions. However, as in the study by Durand (Durand *et al.*, 1993), the relationship between abnormal scans and outcome of the patients was not further investigated.

In chronic meningitis, hydrocephalus and infarcts are commonly seen on CT scanning and contrast-enhancing meninges, particularly the basal meninges, are also often found. In addition, ring-enhancing lesions (tuberculomas) are frequently seen in TB meningitis (Berger 1994, Daris *et al.*, 1993). Some retrospective studies have evaluated CT scans/MRI in tuberculous meningitis looking for prognostic indicators, but these studies have mostly been in children (Jinkins 1991). Ventriculomegaly and/or infarcts were found to be indicators of an adverse prognosis in one study evaluating nine children with intracranial tuberculosis (Wallace *et al.*, 1991).

Thus, not many studies have evaluated the CT scan/MRI as a possible prognostic tool in meningitis in adults. In our study of adults with bacterial,

tuberculous and cryptococcal meningitis, CT scans were performed and the relationship between an adverse prognosis in patients and abnormal brain CT scans was investigated.

### Methods and patients

As part of this study 37 consecutive adult patients with bacterial and 30 patients with TB meningitis were evaluated in the period from March 1994 to the end of February 1998. Most patients underwent CT scanning of the brain within 24 hours of admission; however, in some patients brain scans could not be performed due to either technical problems or to the patient's demise before the scan could be done. The CT brain scans of patients with cryptococcal meningitis were reviewed retrospectively from 1994 to 2000 in 21 patients. The diagnosis of the specific type of meningitis was made for bacterial meningitis only when the cultures were positive, for cryptococcal meningitis when antigen and/or Indian ink/culture were positive, and for tuberculous meningitis when the following criteria were met: When either CSF cultures for tuberculosis were positive, or Ziehl-Neelssen staining showed acid-fast bacilli, or post mortem confirmed

caseating granulomas with meningeal exudates, the patient was classified as definite tuberculous meningitis. All other patients who had extraneural tuberculosis or improved on anti-tuberculous treatment with characteristic clinical and CSF findings (lymphocytic predominance, high protein, low glucose values) were classified as highly probable tuberculous meningitis. Those patients with only suggestive CSF findings but without further proof of tuberculosis - often because the patient passed away before any tests could be done and post mortem examinations could not be performed for various reasons - were excluded from the study. Details of the patient numbers in the different categories for the total TB meningitis group are given in Chapter 2. A group of patients where the diagnosis was uncertain, (mostly suspected bacterial meningitis with negative cultures), was excluded from this analysis.

## Results

In the subgroup of 30 patients who presented with TB meningitis, 26 patients had CT brain scans shortly after admission. In this group of patients hydrocephalus/enlarged ventricles occurred in 11/26 (42 %) patients, meningeal enhancement was seen in six patients (23 %), while

granulomas and brain edema occurred in four and two patients respectively (15 % and 7,5 %). More than one abnormality on the scan was seen in seven patients (27 %).

The outcome of the patients with tuberculous meningitis is shown in Table 3. Severe neurological deficit and death were grouped together as an adverse outcome, while no neurological deficit and minor neurological deficit were grouped together as a good outcome. Fifty five percent of patients (6/11) with hydrocephalus had a bad outcome; enhancement occurred equally in patients irrespective of outcome. The presence of infarcts on CT scan was associated with an adverse outcome in particular - 80 % of patients with an infarct had a bad outcome (4/5 patients). The presence of edema seemed to be a particularly bad prognostic sign as both patients who showed edema on brain scan died. The presence of granulomas did not seem to influence the outcome - 25 % of patients with granulomas had a poor outcome, compared to 55 % of patients without granulomas (but possibly with other abnormalities), who had an adverse outcome. When two abnormalities occurred on the CT scan, (e.g., hydrocephalus + infarct) 71 % of patients had an adverse outcome (5/8 patients).





Table 3

CT SCAN FINDING	TOTAL CASES	ADVERSE OUTCOME (%)	
Granulomas	Present: 4	1	25 %
	Absent: 22	11	55 %
Enhancement	Present: 7	3	43 %
	Absent: 19	9	47 %
Hydrocephalus	Present: 11	6	55 %
	Absent: 15	6	40 %
Infarct	Present: 5	4	80 %
	Absent: 21	8	38 %
Edema	Present: 2	2	100 %
	Absent: 24	10	42 %
2 Abnormalities	Present: 8	5	63 %
	Absent: 18	7	39 %

In the subgroup of 37 patients with bacterial meningitis seen during the study period, CT scans were performed in 33 patients. The CT scans showed a spectrum of abnormalities, including evidence of old trauma, ependymitis, enhancement of meninges, infarcts, subdural effusions, mastoiditis, sinusitis and hydrocephalus. The results are shown in Table 4.

Since such a large spectrum of abnormalities was found, the number of patients in each category is small and no finding can conclusively be noted as an adverse prognostic sign. Thus CT findings in bacterial meningitis in our study were either due to old injuries, or are readily reversible with treatment. Interestingly, however, the presence of infarcts on CT scan of the brain (seen in two patients) - most probably a sign of quite a longstanding infectious process - was fatal in both, while edema in adults with bacterial meningitis did not seem to be associated with a bad prognosis as in tuberculous meningitis. Therefore, although no specific sign on CT scan points to a bad prognosis in bacterial meningitis, except possibly the presence of infarcts, it was notable that a normal CT scan was associated with a good outcome in 90 % of patients.

Table 4

CT SCANS IN BACTERIAL MENINGITIS		
CT SCAN FINDING	NUMBER OF PATIENTS	ADVERSE OUTCOME
Normal	12	1 (8 %)
Ependymitis	6	3 (50 %)
Meningeal enhancement	6	2 (33 %)
Evidence of previous trauma	7	3 (43 %)
Edema	4	1 (25 %)
Infarct	2	2 (100 %)
Subdural effusions	1	1 (100 %)
Hydrocephalus	1	1 (100 %)
Mastoiditis/Sinusitis/ Cerebritis	2	1 (50 %)
Superior sagittal sinus thrombosis	1	0 (0 %)

The patients with cryptococcal meningitis were collected retrospectively from 1994 to 2000 (please also refer to section 1.4: An analysis of clinical, CSF and prognostic findings in South Africa HIV-positive patients with cryptococcal meningitis). CT brain scans were available in 21 patients; 13 scans were normal (62 %) and five of these patients had an unfortunate outcome (38 %). Diffuse cerebral atrophy was seen in four patients (of whom 2 (50 %) had a poor outcome). Infarcts occurred in only two patients on CT scan, of whom one died. Surprisingly, hydrocephalus was seen in only one patient, who subsequently died. The findings are shown in Table 5.



Table 5

<b>CT BRAIN SCANS IN CRYPTOCOCCAL MENINGITIS</b>		
<b>CT Scan finding</b>	<b>Number of Patients</b>	<b>Adverse outcome</b>
<b>Normal</b>	<b>13</b>	<b>5 (38 %)</b>
<b>Atrophy</b>	<b>4</b>	<b>2 (50 %)</b>
<b>Infarct</b>	<b>2</b>	<b>1 (50 %)</b>
<b>Hydrocephalus</b>	<b>1</b>	<b>1 (100 %)</b>

## Conclusion

In tuberculous meningitis the presence of infarcts was associated with an adverse prognosis in 80 % of patients; diffuse cerebral edema was uniformly fatal, and hydrocephalus/enlarged ventricles predicted an adverse outcome in only 55 % of patients.

In bacterial meningitis a wide spectrum of abnormalities on CT scanning was seen, making evaluation of possible prognostic findings difficult in a relatively small group of patients. However, a normal brain scan was associated with a good outcome in 90 % of patients with bacterial meningitis.

In cryptococcal meningitis more than 60 % of patients had normal brain scans but this did not necessarily predict a good prognosis as almost 40 % of patients with normal scans still had an unfortunate outcome. No single CT brain scan finding stood out as a specific prognostic sign in cryptococcal meningitis.

Larger number of patients needs to be studied to verify the above findings.

1.4 **AN ANALYSIS OF CLINICAL, CSF AND PROGNOSTIC  
FINDINGS IN SOUTH AFRICAN HIV-POSITIVE  
PATIENTS WITH CRYPTOCOCCAL MENINGITIS**

**SUMMARY**

**Background**

An exponential increase in cases with chronic meningitis has been noted in South Africa together with the HIV-epidemic. In particular, the incidence of cryptococcal meningitis has soared in recent years.

**Methods and Patients**

This retrospective study evaluated 44 HIV-positive subjects with cryptococcal meningitis, reviewing the clinical CSF and prognostic findings in these patients.

## Results

The results showed a trend towards higher morbidity/mortality in those patients older than 40 years, those with acellular CSF and those with an initial depressed level of consciousness.

## Conclusion

A higher age, acellular CSF and depression of consciousness seem to be associated with a worse outcome in South African patients with cryptococcal meningitis.

## Introduction

Since the advent of HIV an enormous increase in cases with cryptococcal meningitis has been seen worldwide. In South Africa in particular, the increase over the last five years has been exponential. A recent study (Schutte *et al.*, 2000) at the Pretoria Academic Hospital reported an increase of cases with cryptococcal meningitis from 6 % of meningitis cases in 1994/5 to 31 % in 1997/98. Increasing prevalence of cryptococcal



meningitis has also been reported in other studies from Southern Africa (Bergemann and Karstaed 1996).

After an episode of cryptococcal meningitis, HIV-positive patients require life-long prophylactic anti-fungal therapy to prevent relapses. Since the treatment and prophylaxis are often expensive, this is not always possible in developing countries. In the world literature some prognostic factors in cryptococcal meningitis have been addressed recently: in one study (Saag 1992) the most important predictor of early mortality in cryptococcal meningitis was the mental state of the patient at admission; in another (Zuger *et al.*, 1986) an antigen titer of  $> 1:105$ , a low CSF leucocyte count of  $< 20/\text{mm}^3$  and an age  $< 35$  years appeared to be predictive of mortality in cryptococcal meningitis. Following these, some institutions have considered palliative treatment in patients with so-called bad prognostic signs. However, at the Department of Neurology at the Pretoria Academic Hospital, anecdotal reports indicated that patients with cryptococcal meningitis frequently recover completely in spite of "bad" prognostic signs. Thus, the aim of this study was to analyse the clinical and cerebrospinal fluid findings in HIV-positive patients with cryptococcal meningitis in our

population and compare them and the outcomes with those of the world literature.

## Methods and patients

Adult patients with cryptococcal meningitis presenting to the neurology ward of the Pretoria Academic Hospital were reviewed from 1994 to 2000. During this study period, 52 patients with cryptococcal meningitis were identified; of these, useful and complete data were available in 46 patients. The age of the patients, CSF biochemistry and cell-counts, as well as the Glasgow Coma Scale at admission were assessed and correlated with the ultimate outcome of the patients. In all patients HIV-testing was performed. The CD4-counts, CSF-Adenosine deaminase levels and CT brain scans, while not always routinely performed, were available in a large number of cases and also evaluated as possible prognostic indicators. In the statistical analysis, Chi square tests were used to calculate p-values, and odds ratios were also analysed to further clarify possible differences between groups when the p-value was large.

## Results

Of the 46 cases identified with cryptococcal meningitis only two patients were HIV-negative. The findings of these two patients have been omitted from the reported results. The male - to - female ratio was almost 1:1. - 23 males and 21 females were seen with cryptococcal meningitis. Nineteen patients died, and three had a severe neurological deficit at discharge (i.e., either bedridden, or severely incapacitated) - they were grouped together as having an adverse outcome (50 % of patients). There was no difference between males and females regarding outcomes: 10 females and 12 males had adverse outcomes. The ages of the patients ranged from 24 to 55 years (mean: 35 years), and the age means for the group with adverse outcome and a good outcome were 35,4 years, and 34,6 years respectively. Seventeen patients were <35 years old; of these 8 (47 %) had an adverse outcome. Nine patients were  $\geq 40$  years and of these five (56 %) had an adverse outcome. There was no statistical difference between age < 35 years vs. age > 35 years for bad outcome ( $p = 0,75$ ; OR 0,83 (0,21; 3,29)).

The CSF-glucose/serum-glucose values were  $< 50\%$  in 18/20 patients with a good outcome and 18/21 with an adverse outcome. The mean glucose value of patients with good outcome was 2,0 mmol/L compared to the mean glucose value of 1,8 of the patients who had an adverse outcome. The CSF protein value was raised ( $> 450$  mg/L) in 80 % of patients (37/46) with a range of 150 - 7 681 mg/l (mean 1435). Raised protein levels occurred in 19/22 patients with a good outcome and 17/22 patients with an adverse outcome. The mean was 1499 mg/L for the former group and 1067 mg/L for the latter, thus showing a trend towards lower values in the group with an unfortunate outcome. However, there was no statistical difference between the groups of patients with a raised CSF protein level vs. a normal CSF protein level regarding outcome ( $p = 0,69$  - Fisher 2-tailed test; OR 0,254 (0,08; 3,18)). The CSF- white cell count was  $< 20/\text{mm}^3$  in 27/44 patients (61 %); of these 15/27 (56 %) had an unfortunate outcome. Acellular CSF occurred in 14 patients of whom 9 (64 %) had an adverse outcome. There was a trend towards lower CSF lymphocyte counts in the adverse outcome group where the mean lymphocyte count was  $16/\text{mm}^3$  compared to  $41,3/\text{mm}^3$  of the group with a good outcome. However, statistically there was no difference regarding outcome between the group

of patients with acellular CSF compared to those with CSF pleocytosis ( $p = 0,19$ ; OR 0,35 (0,54; 10,75)).

The Glasgow Coma Scale values ranged from 9 - 15 (mean 13,9), with a mean of 14,5 in the group with a good outcome and 13,3 in the group with an adverse outcome. In the group of patients with a GCS value of  $\leq 13$  (11 patients), nine patients had an unfortunate outcome (82 %); if a GCS of  $\leq 14$  was taken as cut-off value, 72 % of patients had an adverse outcome. However, even in the group of patients with a GCS of 15/15 one-third (8/24) of patients eventually had a bad outcome.

The CSF-ADA levels were available in 31 patients and ranged from 0,8 - 17 IU/L. The adverse outcome groups showed a trend toward lower ADA values with a mean of 6,7 IU/L compared to the group with a good outcome where the mean ADA levels were 7,8 IU/L. In total 20/31 (65 %) patients had ADA values of  $> 6$  IU/L and seven patients had values of  $> 10$  IU/L.

CD4-counts were available in 35 patients with 34/35 (97 %) showing values of  $< 200 \times 10^6/L$ . In 20 patients a CD4-count of  $< 50$  was found; of these an equal number (i.e., 50 %) had good and adverse outcomes. Even when a CD4-count of  $< 20 \times 10^6/L$  was taken as cut-off value, only 5/8 patients had a bad outcome. The peripheral white cell count was  $< 10 \times 10^9/L$  in 38/42. Details of the ranges and means for the groups are shown in Table 6 and 7.

CT brain scans were available in 21 patients with 13 scans reported as normal (five patients with normal scans had an unfortunate outcome). Cerebral atrophy occurred in four patients (two had a poor outcome) and infarcts were seen in only two patients of whom one died. Hydrocephalus was seen in one patient who subsequently died (please refer to section 1.3).

Table 6

DATA OF PATIENTS WITH GOOD OUTCOME IN CRYPTOCOCCAL MENINGITIS								
Age	Sex	L	N	CSF Glu/S-Glu	Pro	WCC	ADA	GCS
31	M	5	2	3,1 - 4,9	840	8,4	/	15
62	F	12	0	1,0 - 6,8	1140	3,9	3,8	15
32	M	24	0	2,5 - 7,1	180	8,6	6,4	15
30	F	134	6	0,6 - 5,3	840	2,5	7,0	14
28	F	18	0	2,2 - 8	2120	2,5	3,8	14
35	M	5	10	2,3 - 6,9	2059	4,1	10,2	11
32	M	0	0	0,4 - 7,3	1085	10,1	11,4	15
40	F	0	0	2,4 - 4,1	452	5,5	5,6	15
35	F	0	0	2,4 - 4,9	330	9,4	6,0	15
36	M	36	12	0,4 - /	4484	3,0	17	15
29	M	42	0	1,9 - 6,6	618	3,1	6,9	-
45	M	85	61	2,0 - 5,8	2260	4,31	13,7	14
36	M	189	30	1,2 - 4,7	7681	4,5	9,8	15
35	M	85	36	2,0 - 5,2	1579	3,4	8,1	-
37	F	12	0	2,7 - 6,1	842	2,2	7,9	15
46	F	7	13	3,9 - 12,1	300	3,34	3,13	15
36	M	6	0	1,8 - /	982	2,8	8,3	15
26	F	275	0	2,0 - 8,2	942	7,9	8,4	13
29	F	1	10	2,4 - 5,0	587	4,4	/	15
43	M	7	333	1,6 - 5,5	1330	/	5,8	15
31	F	0	0	2,1 - 5,0	335	0,8	/	15
26	F	6	0	1,9 - 4,9	953	7,7	9,2	15
43	F	0	0	2,0 - 5,2	1075	5,4	3,97	15

Table 7

DATA OF PATIENTS WITH ADVERSE OUTCOME IN CRYPTOCOCCAL MENINGITIS								
Age	Sex	L	N	CSF Glu/S-Glu	Pro	WCC	ADA	GCS
52	F	24	18	1,6 - 4,2	310	20	3,2	12
35	M	0	12	3,2 - 7,1	400	6,0	3,7	14
35	M	0	0	2,9 - 7,1	250	7,8	2,3	11
40	M	0	0	2,9 - 6,9	526	11,3	-	14
36	M	12	6	0,6 - 5,0	2598	4,1	14,9	15
36	F	0	0	1,3 - 7,1	937	6,7	6,4	15
36	F	6	0	3,1 - 2,4	281	5,9	1,6	12
42	M	0	0	1,4 - 5,1	918	5,9	-	-
40	F	12	0	0,8 - 8,8	1982	2,9	13,4	-
35	M	12	0	2,5 - 7,4	876	5,8	5,8	15
25	F	0	0	1,4 - 5,5	1478	7,4	-	9
33	F	0	0	2,0 - 6,0	830	8,75	-	15
28	M	6	0	2,4 - 7,0	732	6,8	8,4	12
45	M	30	12	0,1 - 4,8	727	-	7,89	15
33	F	8	31	0,5 - 6,9	1921	13,1	-	10
30	F	156	0	2,0 - 5,5	1650	4,9	10,2	13
26	F	18	6	1,1 - 7,2	1175	19	-	14
24	M	0	0	2,5 - 4,3	845	2,05	-	14
38	F	0	48	6,4	447	2,8	2,13	15
39	M	0	0	3,3 - 6,5	384	5,3	-	15
55	M	0	0	2,2 - 5,6	671	4,6	-	13
37	M	59	72	0,8 - 6,2	2859	4,3	-	15
31	F	27	105	1,5 - 5,9	986	8,6	7,5	12



## Discussion

Contrary to other studies, an age  $< 35$  years was not found to be a bad prognostic sign in our group of patients (47 % adverse outcome). An age  $> 40$  years was associated with a bad outcome in 55 % of our patients. Furthermore, low CSF - white cell counts of  $< 20$  occurred equally in patients with good and adverse outcomes, making this no reliable prognostic sign in our group of patients. However, complete acellularity in the CSF (9/14 patients) was associated with a bad prognosis in 64 % of our patients. The level of consciousness, as reflected by the Glasgow Coma Scale value showed a degree of correlation with the outcome of the patients: almost three-quarter of patients with a GCS value of  $\leq 14$  had an adverse outcome. However, even a value of 15/15 was no guarantee of a good outcome - one-third of patients who had a GCS of 15 on admission still had an unfortunate outcome.

Interestingly, very low CD4-counts were no immediate indicator of a bad prognosis, occurring in both adverse and good outcome groups.

Brain CT scans were mostly normal; hydrocephalus was fatal in the one patient where it occurred, and cerebral atrophy was present in four patients of whom two died. The number of patients in this study is too small to make deductions about prognosis on CT scanning.

### Conclusion

Thus, in summary, in our study an age > 40 years was associated with a higher morbidity/mortality, as was acellularity in the CSF, and a GCS value of  $\leq 14$  on admission. These differences, however, did not reach statistical significance, possibly due to the small numbers. We would therefore at present advocate treating all patients with cryptococcal meningitis irrespective of clinical, CSF or special investigations, until further studies have clarified the so-called bad prognostic signs.

## Chapter 2

### THE IMPACT OF HUMAN IMMUNODEFICIENCY

### VIRUS (HIV) ON MENINGITIS

#### SUMMARY

##### Background

The increase in HIV infections in South Africa is alarming. The aim of this prospective 4-year study was to evaluate the rising incidence of HIV-related admissions due to meningitis at the Pretoria Academic Hospital (PAH) adult neurology ward and to investigate the spectrum of meningitis during this time.

##### Patients and Methods

Adults with meningitis presenting at the PAH neurology ward from March 1994 through February 1998 were included. HIV-antibody status was

determined and patients were assigned to five categories: bacterial, tuberculous, viral and cryptococcal meningitis, as well as an uncertain category.

## Results

Over the 4-year study period 141 patients with meningitis were seen. Of these, 44 were HIV-positive (31 %), with TB meningitis occurring in 16 (36 %), cryptococcal meningitis in 22 (50 %) and acute bacterial meningitis in three (7 %). In the first 2 years of the study, 14 % of patients were HIV-positive; this figure rose to 44 % in the 3<sup>rd</sup> year, and 57 % in the final year. The spectrum of meningitis also changed; bacterial meningitis remained relatively stable at about 25 % of the total; TB meningitis almost doubled from 16 % in the 1<sup>st</sup> year to 31 % in the last year of the study; viral meningitis initially occurred in 8 % of patients and later in 3 % of cases, while cryptococcal meningitis showed the most significant increase from 6 % of cases in 1994/5 to 31 and 26 % respectively in the last two years of the study.

## Conclusion

Over a 4-year period the HIV-epidemic was responsible for a marked shift in the spectrum of meningitis towards chronic infections such as TB and cryptococcal meningitis at the PAH.

## **2.1 CHANGES IN THE SPECTRUM OF MENINGITIS DUE TO HIV-INFECTION**

### **Introduction and survey of the literature**

During the first decade of the AIDS epidemic, South Africa was probably protected by political as well as geographical and social barriers and therefore lagged behind other African countries in the number of HIV cases. In the early 1980's HIV-infection was mainly seen in homosexual white males and the spread to the heterosexual population was relatively slow. Unfortunately, in the last fifteen years the scenario has changed considerably and HIV is now a major health threat in the country. The Doyle model is the most well known of models predicting the extent of the AIDS epidemic in South Africa (Editorial SAMJ 1996). According to this model, between 18 and 27 % of South Africans will be infected with HIV by 2010 - a frightening proposition.

Even though potent antibiotic therapies have been developed over the past decade, meningitis remains an ominous disease with a high morbidity and

mortality, especially in developing countries. Furthermore, the HIV-epidemic in South Africa has changed the face of many hospital wards over the past five years. It is well known that HIV-infection is a specific risk factor for developing intracranial tuberculosis, including tuberculous meningitis in particular (Bishburg *et al.*, 1986). Thus, admissions due to HIV-related infections, especially meningitis, are increasing in parallel to the HIV-seropositivity of the general population.

One recent study from the Chris Hani-Baragwanath Hospital (Bergemann and Karstaed 1996) looked mainly retrospectively (8 months) and prospectively (4 months) at the spectrum of meningitis in a population with a high prevalence of HIV-infection. In this study tuberculous meningitis was the most common cause of meningitis at 25,4 %, followed by bacterial meningitis in 22,5 % of cases, viral meningitis in 14,1 % and cryptococcal meningitis in 13 %. Although only 68 % of patients were tested, almost 40 % of these were HIV-positive. This study predicted a change in the spectrum of meningitis towards a predominance of tuberculous and cryptococcal meningitis.

Our prospective study, which formed part of the ongoing meningitis project at the Pretoria Academic Hospital, was performed to investigate the constantly rising incidence of HIV-related admissions due to meningitis at the Pretoria Academic Hospital's adult neurology ward over a four-year period and to evaluate the spectrum of meningitis seen during this time.

### Methods and patients

All adult patients presenting with meningitis at the neurology ward of the Pretoria Academic Hospital from March 1994 to the end of February 1998 were included in this study. At the time of the study the Pretoria Academic Hospital was a 1000 bed urban academic and general hospital acting as a referral hospital from Pretoria and surrounding areas, including a large part of the northern regions of South Africa. Due to changes in the referral system, more patients from peripheral hospitals were seen during the first year of the study.

The specific criteria for inclusion in the study were: headache with or without neck stiffness, coupled with an active CSF and an age above 13



years. The HIV-antibody status was tested in all patients as far as possible.

Patients were assigned to five categories: Bacterial, tuberculous, viral and cryptococcal meningitis, as well as an uncertain category.

The final diagnosis of bacterial meningitis was only made when CSF cultures were positive; in this way, some patients were initially treated for bacterial meningitis on clinical suspicion (high CSF-neutrophil counts, high protein and low glucose levels) but were later shifted to the "uncertain" category because of a lack of microbiological proof.

The final diagnosis of tuberculous meningitis was made when CSF cultures were positive or evidence of TB was found in other sites with active CSF, or when the patient's clinical and CSF findings were compatible with TB meningitis and the patient responded to anti-tuberculous treatment.

Viral meningitis was only diagnosed when CSF findings were typical, a repeat lumbar puncture did not show an increase in neutrophils, and the patient

showed clinical improvement within 24 hours. The final diagnosis of cryptococcal meningitis was made when the CSF cultures were positive for Cryptococcus neoformans, although Indian ink staining and cryptococcal latex agglutination were also performed on most patients.

Whenever the diagnosis remained uncertain or when patients had received antibiotics before admission for any reason, e.g., otitis, sinusitis, etc., they entered the "uncertain" category and were treated as for bacterial meningitis. In selected "uncertain" cases, TB treatment was added. In the statistical analysis, the proportions of patients were compared using Chi Square tests.

## Results

### Patients and etiology

Between 1994 and 1998 141 patients with meningitis were evaluated. The majority of patients were Black (102/141, 72%), while 36 Caucasians and three of mixed ancestry were seen. Bacterial meningitis occurred in 26 % of patients (37/141), 23 % (33/141) had tuberculous meningitis, while only 6 % (8/141) had viral meningitis. Cryptococcal meningitis occurred in 17 % of patients (24/141) and 39 patients (28 %) were assigned to the "uncertain" category. The details of the etiology, male : female ratio, age, HIV status and mortality are shown in Table 8.

During the four years 44 HIV-positive patients with meningitis were seen (31 %). Seventy-five percent of the patients were Black (38/44). Cryptococcal meningitis was the most commonly occurring form of meningitis - 22/44 patients (50 %) with HIV had cryptococcal meningitis compared to 16/44 (36 %) of cases with tuberculous and 3/44 (7 %) with acute bacterial meningitis. The detail of the spectrum of meningitis in HIV-positive patients is shown in Table 9.



Table 8

ETIOLOGY, MALE: FEMALE RATIO, AGE, HIV-STATUS AND MORTALITY IN 141 PATIENTS WITH MENINGITIS					
	TBM (n = 33;23 %)	ABM (n = 37;26 %)	CRY M (n = 24;17 %)	AVM (n = 8;6 %)	UNCERTAIN (n = 39;28 %)
M:F	17:16	31:6	14:10	5:3	16:23
Age (mean)	15-48 (29)	15-68 (36)	25-62 (37)	16-65 (31)	15-81 (35)
HIV- positive	16/33 (48 %)	3/37 (8 %)	22/24 (92 %)	0	3 (8 %)
Mortality	9/33 (27 %)	8/37 (22 %)	9/24 (38 %)	0	2 (5 %)

TBM: Tuberculous meningitis, ABM: Acute bacterial meningitis, CRY M: Cryptococcal meningitis, AVM: Acute viral meningitis.



Table 9

SPECTRUM OF MENINGITIS IN HIV-POSITIVE PATIENTS	
	No of cases
M : F	24:20
TBM	6/44 (36 %)
Cry M	22/44 (50 %)
ABM	3/44 (7 %)
Other ("uncertain")	3/44 (7 %)
Mortality	11/44 (25 %)
TBM: Tuberculous meningitis, ABM: Acute bacterial meningitis, CRY M: Cryptococcal meningitis.	

The three Caucasian patients with HIV all had cryptococcal meningitis and were homosexual males. The three HIV-positive patients of mixed ancestry all had tuberculous meningitis.

The overwhelming majority of patients had apparently been unaware of their HIV-positive serostate (41/44 patients, 93 %). At that stage of the meningitis study CD4-counts were not performed routinely; however, in 15 patients with cryptococcal meningitis, the CD4-counts ranged from 3,2 to  $188 \times 10^6/L$  (mean 86, 4), and in 13 patients with TB meningitis the values ranged from 6,6 to  $340 \times 10^6/L$  (mean 147).

From March 1994 to the end of February 1995 - the first year of the study - 51 adult patients with meningitis were evaluated. Seropositivity for HIV occurred in 8/49 patients (16 % HIV-positive). Table 10 illustrates the spectrum of meningitis for this period.



Table 10

ETIOLOGY AND DISTRIBUTION OF MENINGITIS				
	March 1994 - Feb 1995	March 1995 - Feb 1996	March 1996 - Feb 1997	March 1997 - Feb 1998
	No of patients (%)	No of patients (%)	No of patients (%)	No of patients (%)
Bacterial Meningitis	14 (27 %)	7 (28 %)	7 (24 %)	9 (26 %)
Tuberculous meningitis	8 (16 %)	8 (32 %)	6 (21 %)	11 (31 %)
Viral Meningitis	4 (8 %)	1 (4 %)	2 (7 %)	1 (3 %)
Cryptococcal meningitis	3 (6 %)	3 (12 %)	9 (31 %)	9 (26 %)
"Uncertain"/ and other type of meningitis	22 (44 %)	6 (24 %)	5 (17 %)	6 (14 %)

Twenty-two patients were classified as "uncertain"; four had been treated with antibiotics before admission, four had parameningeal infections (e.g., sinusitis, otitis) and active CSF, and five were probable viral meningitis cases but had already been started on antibiotics by the first attending physician. In seven patients, the CSF findings were compatible with bacterial meningitis with high neutrophil counts, high protein and low glucose levels, but the CSF cultures were negative. These patients probably could also have been classified as bacterial meningitis. Of the other patients in the "uncertain" group, one patient was later diagnosed as cysticercal meningitis and one as having carcinomatous meningitis.

Of the HIV-positive patients, tuberculous meningitis occurred in five patients, cryptococcal meningitis in two, and one patient had meningitis due to a Streptococcus Group B infection. Thus, a chronic form of meningitis occurred in 7/8 (88 %) of HIV-positive patients during the first year of the study.



Twenty-five adults with meningitis were admitted in the period from March 1995 to February 1996. Again, 16 % of patients were HIV-positive (4/21). Table 10 also illustrates the spectrum of meningitis for the second year of the study. All HIV-positive - patients had chronic meningitis - two were diagnosed with tuberculous and two with cryptococcal meningitis. Meningitis of "uncertain" etiology occurred in six patients: one had a parameningeal infection together with active CSF, and five had probable viral meningitis but had already received their first dose of antibiotics by the physician who initially assessed them.

During the third year of the study from March 1996 to February 1997, a total of 29 patients with meningitis were seen. A marked increase in HIV-positive patients was now seen - 12/29 (44 %), were HIV-positive. Table 10 again illustrates the data of the patients. Of the patients categorized as "uncertain", parameningeal infections occurred in two patients, two probably had viral meningitis, but had been treated with antibiotics, and one was treated for both bacterial and tuberculous meningitis, although microbiological proof was not found. In the HIV-positive patients, chronic meningitis occurred in 10/12 patients; nine had cryptococcal and one

tuberculous meningitis. In addition, one patient had bacterial meningitis due to a S.pneumoniae infection and one probably had viral meningitis.

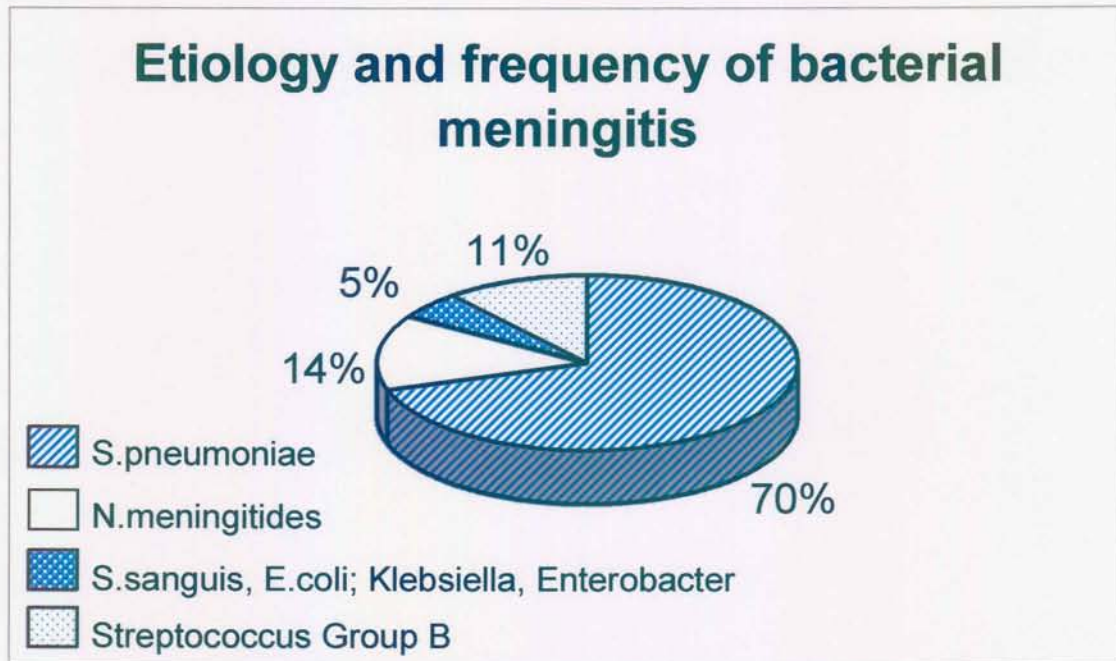
In the period from March 1997 to February 1998, the last year of this specific study, 36 patients with meningitis were assessed. By this time, even more patients were HIV-positive: 20/35 patients (57 %) were found to be HIV-positive - at least every second patient now admitted with meningitis thus had HIV-infection. The spectrum of meningitis is also reflected in table 10 for this year. In the group of patients with meningitis of "uncertain" etiology, six patients were included. Of these, two had a CSF picture compatible with bacterial meningitis but cultures were sterile, three probably had viral meningitis but had already received antibiotics, and one patient was treated for both bacterial and tuberculous meningitis even though cultures were negative. Chronic meningitis occurred in 17 of the 20 HIV-positive patients (85 %) - eight had tuberculous and nine cryptococcal meningitis; one patient had a pneumococcal infection, one had probable viral meningitis, and one was treated for both tuberculous and bacterial meningitis since CSF findings were ambiguous.



In total, tuberculous meningitis occurred in 33/141 patients (23 %). Of these, 20/33 (61 %) had definite proof of tuberculosis with either CSF cultures positive or proof of tuberculosis in another site together with typical CSF findings. In the remaining patients cultures were negative, but the clinical picture improved on anti-tuberculous treatment. Of the HIV-positive patients, sixteen had tuberculous meningitis - 10/16 (63 %) had microbiological proof of tuberculosis. This figure is similar to the positive identification of tuberculosis in the group of patients who were HIV-negative: 17/33 patients with tuberculous meningitis were HIV-negative and positive proof for tuberculosis was obtained in 10/17 (59 %).

The overwhelming majority (70 %) of patients with bacterial meningitis had pneumococcal infections. The etiology and frequencies of bacterial meningitis are shown in figure 5.

Figure 5

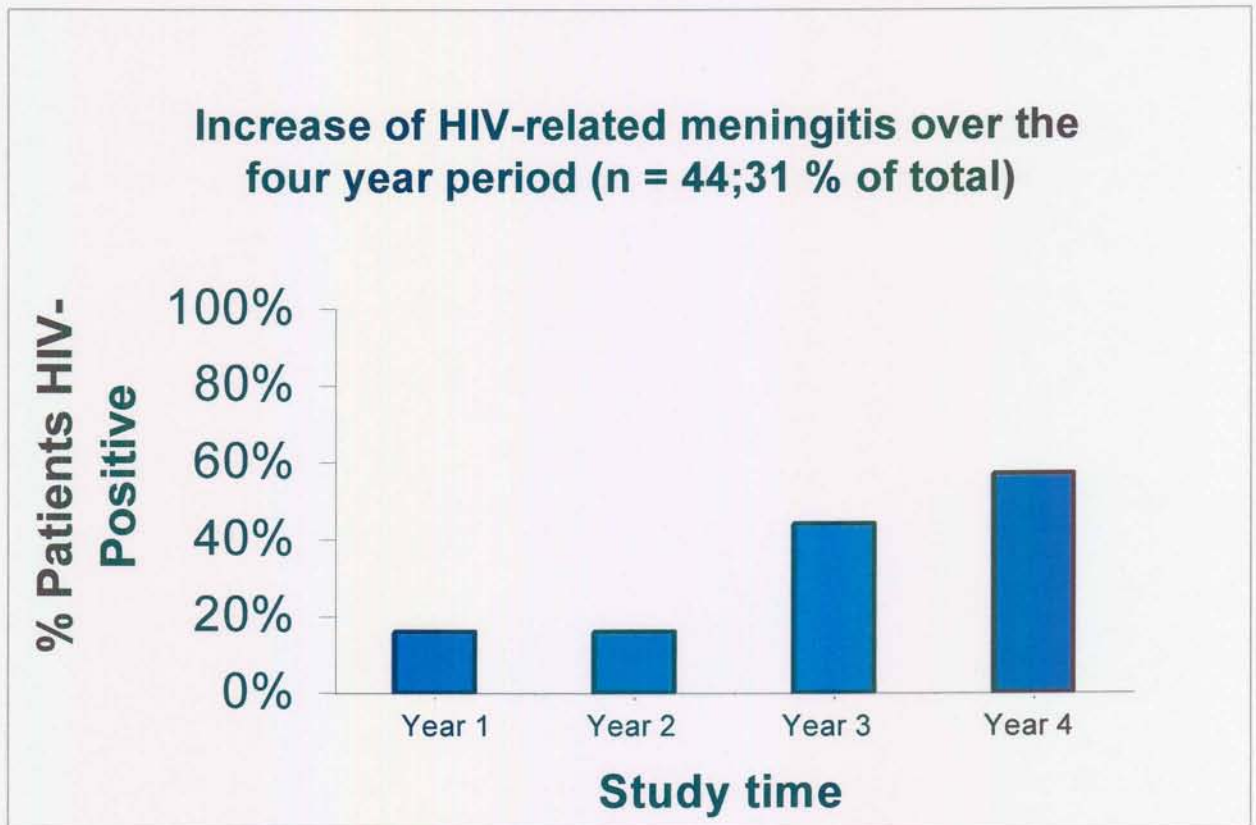


In the three HIV-positive patients with bacterial meningitis, a pneumococcal infection was the cause in two and Streptococcus group B in one.

#### Four-year spectrum

When the spectrum of meningitis over the 4-year study period is analysed, it can be seen that bacterial meningitis remained relatively stable at almost 30 % of the total. (Had one included the seven probable cases of bacterial meningitis for the first year of the study, this figure would have been higher at 40 %; for the first year this would have made the "uncertain" category much smaller at 28 %). Tuberculous meningitis almost doubled from 16 % in the first year to 31 % in the last year of the study; viral meningitis initially occurred in 8 % of patients and in only 3 % of cases by the last year of the study. Cryptococcal meningitis, however, showed the most significant increase from 6 % of total meningitis cases in 1994/5 to 31 and 26 % respectively in the last two years of the study. Figure 6 shows the yearly increase in HIV-positive cases.

Figure 6



## Mortality

Over the 4-year study period 27/141 patients (19 %) died. Of these 27 patients, 11 were HIV-positive and ten HIV-negative, and in six the HIV-status could not be determined - this was mostly because patients died before the test could be done. Thus, 25 % (11/44) of HIV-positive patients died, eight due to cryptococcal meningitis and three as a result of tuberculous meningitis. When comparing the mortality of the HIV-positive and the HIV-negative group, the HIV-positive patients had a mortality more than double that of the HIV-negative/not tested group (11/98: 11 %); but due to the small numbers this did not reach statistical significance.

## Discussion

In developed countries, the incidence of HIV-infection has been declining over the last few years. Unfortunately the epidemic in developing countries is still expanding at an alarming rate (Editorial SAMJ 1996, Bergemann and Karstaedt 1996). In 1994 the highest HIV-positive rates in pregnant women in South Africa were seen in Kwa-Zulu-Natal at 14,35 % (Editorial SAMJ 1996). From these surveys the estimated doubling time was 15,5 months and the highest prevalence was in the 20 - 25 year age group. Thus,

taking into account that the time interval between infection with the HIV and the development of AIDS is around 10 years, it is interesting to note that the mean age of patients with cryptococcal meningitis in this study is, indeed, 37 years. With the increase in prevalence it is expected that people will become infected at a younger age, and the mean age of patients with HIV and cryptococcal/tuberculous meningitis will probably decrease considerably.

In the very short time interval of four years - from 1994 to 1998 - the incidence of HIV-related admissions due to meningitis has increased from one in six patients to more than one in two patients at the Pretoria Academic Hospital. This obviously has grave implications for the future costs of the health sector.

Together with the dramatic increase in HIV seropositivity of the general population, the spectrum of meningitis has shifted over the past four years. A recent South African study from the Chris Hani-Baragwanath Hospital did predict an increase in the incidence of tuberculous and cryptococcal meningitis due to the HIV-epidemic and speculated that the incidence of



pneumococcal meningitis might also increase (Bergemann and Karstaedt 1996). In the Pretoria Academic Hospital study the most noteworthy increase has been in cryptococcal meningitis - from 6 % of all meningitis admissions during the first year of the study to 26 % in the final year. Tuberculous meningitis admissions almost doubled in the study period - from 16 % to 31 %. A high risk of bacteraemia due to *S pneumoniae* has been reported (Redd *et al.*, 1990) in HIV-positive patients, and there have been predictions of an overwhelming increase in bacterial meningitis in the South African context (Bergemann and Karstaedt 1996). However, this study does not substantiate these predictions presently. Overall, only three HIV-positive patients (7 %) had acute bacterial meningitis, of which two were due to a pneumococcal infection.

The vast majority of patients in this study were apparently unaware of their HIV-status (41/44). The episode of meningitis apparently brought the positive serostate to their attention for the first time. In addition, 38/41 patients first presented with an AIDS-defining illness in the form of tuberculous or cryptococcal meningitis. As was expected, the CD4-counts that had been performed showed very low values - with an interesting

tendency towards counts of below  $100 \times 10^6/L$  in the group of patients with cryptococcal meningitis. In this group extremely low values were seen with 4/15 patients having CD 4 counts of less than 20. Once again it needs to be emphasized that these patients apparently first needed serious medical attention when they presented with their episode of meningitis.

Despite adequate treatment, mortality rates for meningitis remain high worldwide. For pneumococcal meningitis mortality rates of 25 % are not unusual; depending on the study, mortality rates range from 17 to 59 % (Quaade and Kirstensen 1962, Carpenter and Petersdorf 1962). At the Pretoria Academic Hospital the specific mortality for pneumococcal meningitis was 23 % - this relatively high mortality rate might be a reflection of the often-late presentation of many of the patients, as well as the small number of ICU beds available for medical patients.

Mortality rates for tuberculous meningitis usually vary from between 15 and 50 % in different studies (Durand *et al.*, 1993, Manchanda and Lal 1966). Higher mortality rates have also been reported occasionally and in one

recent study (Vechoor *et al.*, 1996) it was found that a positive HIV-serostate did not influence mortality in tuberculous meningitis: 53 % of the patients with HIV-infection in the study died, compared to 30 % of those without HIV-infection ( $p = 0,43$ ). Our observations seem to support this finding as 19 % of patients with tuberculous meningitis and HIV died within six to eight weeks, compared to the 35 % of patients with tuberculous meningitis who were HIV-negative/not tested.

Contrary to tuberculous meningitis, it has been reported that cryptococcal meningitis in HIV-positive patients is associated with a much higher morbidity and mortality than in HIV-negative patients. In a recent study from Durban (Moosa and Coovadia 1997) it was found that 64 % of HIV-positive patients with cryptococcal meningitis died compared to 9 % of HIV-negative patients. In addition, most HIV-positive patients died within the first two weeks of therapy. Most of the HIV-positive patients who died in the Pretoria Academic Hospital study had cryptococcal meningitis, but no comparison could be made between the HIV-positive and HIV-negative groups with cryptococcal meningitis as the number of HIV-negative

cases with cryptococcal meningitis was too small. Interestingly, the three patients with HIV and bacterial meningitis all recovered completely.

The male : female ratio in our bacterial meningitis patient population remains somewhat puzzling. Of patients with bacterial meningitis, 84 % were male; of patients with pneumococcal meningitis 81 % were male. A slight male predominance in pneumococcal infection has been reported in the world literature (Schlech *et al.*, 1985, Bohr *et al.*, 1983). In the study from the Chris Hani-Baragwanath Hospital, the male - to - female ratio was 2 : 1 for pneumococcal bacteraemia but the marked majority of males in our study remains noteworthy. It is also remarkable that four of the five females with pneumococcal meningitis were above 55 years of age, while all male patients except one, were below 55 years of age. Complex migrational patterns of South African men have been suggested as underlying factors but the higher incidence of alcoholism and head injuries in male South Africans compared to females might also play a role. However, all these arguments remain speculative at present. In all of the other forms of meningitis - tuberculous, cryptococcal, as well as HIV-related cases of meningitis - the male : female ratios were approximately 1 : 1.

Thus in conclusion, it may be stated that over a four-year period the HIV epidemic was responsible for a marked shift in the spectrum of meningitis towards chronic infections such as cryptococcal and tuberculous meningitis as seen at a large urban academic and general hospital in South Africa.



## **2.2 COMPARISON OF CLINICAL, CEREBROSPINAL FLUID AND PATHOLOGICAL FINDINGS AND OUTCOME IN HIV-POSITIVE AND HIV-NEGATIVE PATIENTS WITH TUBERCULOUS MENINGITIS**

### **SUMMARY**

#### **Background**

The early diagnosis of TB meningitis remains difficult. In South Africa, the HIV-epidemic has shifted the spectrum of meningitis towards chronic infections (mainly TB and cryptococcosis). This prospective study aimed to analyse clinical, CSF and pathological findings and outcomes in TB meningitis evaluating whether HIV infection significantly influences the characteristic findings.

#### **Methods and patients**

Forty consecutive patients with TB meningitis presenting at the Pretoria Academic Hospital were evaluated clinically and CXR's, CT brain scans, CSF

profiles, HIV and routine blood tests were analyzed. Post-mortems were performed in seven patients and outcomes were assessed after treatment.

## Results

Twenty patients were HIV-positive and 17 negative (three not tested). History and clinical findings were similar in both groups. The mean Glasgow Coma Scale (GCS) on admission was 13 in both groups, while CXR's showed abnormalities consistent with TB in 9/17 with HIV and 7/15 without, with abnormal CT brain scans in 15/19 patients with HIV and 12/16 without. Dilated ventricles and infarcts occurred more commonly in HIV-positive patients. The CSF results showed similar results in the groups. Post-mortem examinations in three HIV-positive patients showed weakly formed granulomas and extensive endarteritis and infarcts. Outcomes were similar in the two groups, but a low Glasgow Coma Scale value on admission was a better prognostic indicator than the CD4-count in HIV-positive patients.

## Conclusion

HIV infection does not significantly alter clinical and CSF findings in TB meningitis in our South African study but ventricular dilatation and infarcts

are more frequent in HIV-positive patients. The GCS gives a better indicator of prognosis than the CD4-count.

## Introduction and survey of the literature

Tuberculosis remains an endemic disease in South Africa and case notification rates are presently at least 194 per 100 000 population (Weyer and Fourie 1989). A definite epidemiologic association has been found between HIV-infection and tuberculosis since HIV affects predominantly those cellular immune mechanisms that are essential for maintaining resistance against M.tuberculosis. Thus, an even higher prevalence of active tuberculosis is expected in South Africa with subsequent high incidences of tuberculous meningitis - which has been classified as an AIDS-defining illness since 1987. In addition, diagnosing tuberculous meningitis when the patient first presents is still very difficult and more often than not patients have to be treated empirically on clinical suspicion before proof of tuberculosis is obtained. Characteristically, tuberculous meningitis develops insidiously, with cerebrospinal fluid findings showing a lymphocytic pleocytosis, elevated protein levels and low glucose values with



often high adenosine deaminase levels. Unfortunately, exceptions to these characteristic findings are often seen of which only a few are quoted here: in one study from India (Virmani *et al.*, 1975) six patients in whom acid-fast bacilli were isolated from the cerebrospinal fluid in spite of complete absence of cellular response were reported, and in another study (Roberts 1981) the delay in instituting antituberculous therapy because of a high percentage of polymorphonuclear leukocytes in the CSF was reported. These studies were performed before the HIV-era.

More recently, studies have looked at tuberculous meningitis in HIV-infected patients in a mostly retrospective manner. One study from Spain (Berenguer *et al.*, 1992) identified 37 HIV-positive patients with tuberculous meningitis from their records and compared them to patients without HIV-infection. They found similar presentations, clinical manifestations, cerebrospinal fluid results and mortality in the two groups, also commenting that CD4-counts  $< 200 \times 10^6/L$  and a long duration of illness ( $> 2$  weeks pre-admission) were associated with a poor prognosis. Another study (Dube *et al.*, 1997) retrospectively compared a group of 15 patients with HIV-infection with 16 patients who were HIV-negative with tuberculous meningitis. All findings were similar in the two groups including

mortality. However, an increased incidence of intracerebral mass lesions in HIV-infected patients (60 % versus 14 % in the HIV-negative group) was found. Another recent study (Yechoor *et al.*, 1996) reported a higher incidence of hypoglycorrhagia in HIV-positive patients with tuberculous meningitis while another report emphasized the occurrence of acellular CSF in HIV-positive patients with tuberculous meningitis (Laguna *et al.*, 1992).

In our five-year study we aimed to evaluate patients with and without HIV-infection and tuberculous meningitis, analysing clinical and cerebrospinal fluid findings and possible prognostic factors.

### Methods and patients

Forty consecutive adults with proven or clinically probable tuberculous meningitis presenting at the Pretoria Academic Hospital, Neurology ward in the period from March 1994 to June 1999, were included in the study. The criteria for the diagnosis of tuberculous meningitis were as follows: When either CSF cultures for tuberculosis were positive (n = 16), or Ziehl-Neelssen staining showed acid-fast bacilli (n = 0), or post mortem confirmed caseating granulomas with meningeal exudates (n = 8), the patient was



classified as definite tuberculous meningitis. All other patients who had extraneural tuberculosis or improved on anti-tuberculous treatment with characteristic clinical and CSF findings (lymphocytic predominance, high protein, low glucose values) were classified as highly probable tuberculous meningitis (n = 13). Those patients with only suggestive CSF findings but without proof of tuberculosis - often because the patient passed away before any tests could be done and post mortem examinations could not be performed for various reasons - were excluded from the study.

After admission, patients were evaluated clinically, which included history taking and a full neurological assessment also incorporating an evaluation of the Glasgow Coma Scale, and chest X-rays, CT brain scans, CSF profiles and HIV and routine blood tests were analysed. In addition, post mortem examinations were performed in seven patients.

## Results

Over the five-year period of the study, 40 patients were included. Of these 20 were HIV-positive (50 %), 17 HIV-negative (43 %) and in three

patients no HIV-test had been performed since the patients had passed away soon after admission.

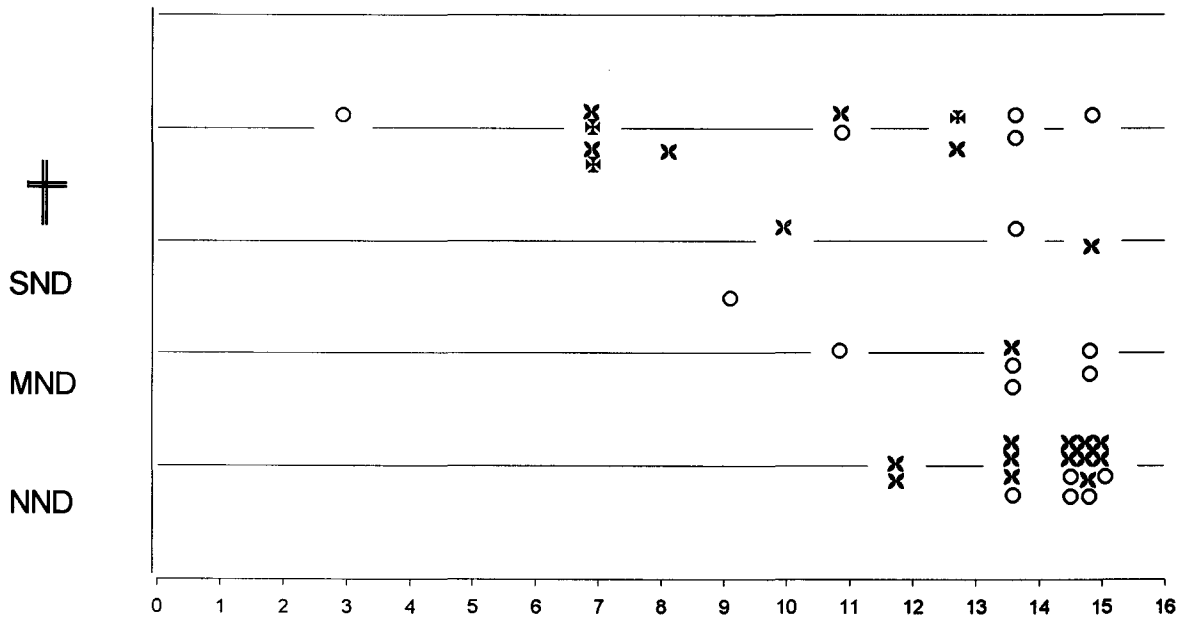
When analysing the history, it was found that most patients had been unwell for almost two weeks (range: two days to three weeks). There was no difference between the HIV-positive and the HIV-negative groups - in HIV-positive patients the average time of disease had been nine days, and in HIV-negative patients 11 days. However, some patients reported somewhat vaguely of having felt unwell for one to two weeks; for these patients the arbitrary value of 10 days was taken when calculating the average. In all patients where a history was obtainable, headache had been a prominent complaint (37/37) and neck stiffness was an universal finding. Febrileness occurred equally in both groups - 75 % of both HIV-positive and HIV-negative patients were febrile on admission. The two patients with a temperature of  $< 36^{\circ}\text{C}$  both passed away.

Once again the Glasgow Coma Scale value was determined as a measurement of the level of consciousness of the patients on admission. The values ranged from 3 to 15 with a mean of 13 in both groups. A Glasgow Coma Scale value of 8 or less was associated with a bad prognosis - all patients

who had a low Glasgow Coma Scale ( $\leq 8$ ) died (six patients). The details of the results of the Glasgow Coma Scale against outcome are shown in Figure 7.

Figure 7

**GCS ON ADMISSION vs. OUTCOME AFTER TREATMENT IN PATIENTS WITH TB  
 MENINGITIS**



† Death

**SND** - Severe neurological deficit

**MND** - Minor neurological deficit

**NND** - No neurological deficit

**GCS** - Glasgow Coma Scale

x HIV-positive

o HIV-negative

⌘ HIV not tested

In contrast to the bad prognosis with a low Glasgow Coma Scale, a value of 14 - 15 was associated with a good neurological outcome (no or minor neurological deficit) in 80 % of patients (20/25). Of these patients, nine were HIV-negative and eleven were HIV-positive. In total, good neurological outcomes were found in 65 % of HIV-positive patients (13/20) and 59 % of HIV-negative patients (10/17) -  $p = 0,69$ ; Chi square test. Interestingly, HIV-positive patients were more than twice as likely to suffer no neurological deficit at discharge than HIV-negative patients - 60 % (12/20) patients with HIV had no neurological deficit compared to 29 % (5/17) of HIV-negative patients ( $p = 0,06$ ; Chi square test). Even though this observation did not reach statistical significance, it showed a trend toward better outcome in the short term in the HIV-positive group. The two groups were similar with regard to adverse outcome (severe neurological deficit or death): 7/17 (41 %) of HIV-negative and 8/20 (40 %) of HIV-positive patients had an unfortunate outcome ( $p = 0,7$ ; Chi square test).

Chest X-rays were abnormal and in keeping with tuberculosis (either old TB, or active) in 50 % of patients (16/32) - nine were HIV-positive and seven HIV-negative (two were not tested). Therefore, HIV-negative and HIV-

positive patients were equally likely to have an abnormal chest X-ray (HIV-positive abnormal chest X-ray: 9/17 - 53 %; HIV-negative abnormal 7/15 - 47 %;  $p = 0,72$ ; Chi square test). Table 11 shows the results of the chest X-rays. A diffuse pulmonary infiltrate was the most common abnormality, which seemed to occur more commonly in HIV-positive individuals (4: 1); miliary TB occurred in three HIV-positive patients and in three HIV-negative patients.

Abnormalities on CT scan of the brain were found in a very high percentage of patients. In total, 79 % of patients had abnormalities on CT scan (30/38 patients). In the HIV-positive group 15/19 (79%) were abnormal compared to the 12/16 (75 %) abnormal in the HIV-negative patients -  $p = 0,78$ , Chi square test. In addition, all three patients whose HIV-state was unknown, had abnormalities on CT scan. Table 12 shows the results of the CT brain scans.



Table 11

RESULTS OF CHEST X-RAYS IN PATIENTS WITH TB MENINGITIS			
	HIV-positive (N = 17)	HIV-negative (N = 15)	HIV not tested (N = 3)
Miliary TB	3	3	-
Infiltrate	4	1	2
Effusion	1	1	-
Bronchopneumonia	1	2	-
Old TB/pleural thickening	-	2	-
Normal	8	8	1

(Note: Some patients had more than one abnormality on CXR).

Table 12

RESULTS OF CT BRAIN SCANS IN PATIENTS WITH TB MENINGITIS			
	HIV- positive	HIV- negative	HIV not tested
Hydrocephalus/enlarged ventricles	10	6	3
Meningeal enhancement	3	5	
Infarction	8	1	1
Granulomas	2	3	
Edema	1	1	
Normal	4	4	

(Note: Some patients had more than one abnormality on CT scan).

In a high proportion of patients, hydrocephalus/an enlarged ventricular system was demonstrated (total: 19/38, 50 %), including 10 HIV-positive patients, six HIV-negative patients and three patients where the HIV was not tested. Of these 19 patients, 12/19 (63 %) had an adverse outcome with 10 deaths and two severe neurological deficits. The occurrence of infarcts on CT scan was also noteworthy as eight HIV-positive patients showed evidence of an infarct on scan, compared to only one HIV-negative patient. Meningeal enhancement was seen in three HIV-positive and five HIV-negative patients, and granulomas were seen in two HIV-positive and three HIV-negative patients. When comparing the Glasgow Coma Scale on admission with the CT scans (which were mostly performed within 24 hours of admission), it can be seen that all patients with normal scans (8/28, 29 %) had Glasgow Coma Scale values of 14 or 15. However, when evaluating all 25 patients with Glasgow Coma Scale values of 14 - 15 an abnormal scan was still found in 15 (60 %) - including five patients with granulomas and six with hydrocephalus/dilated ventricles.

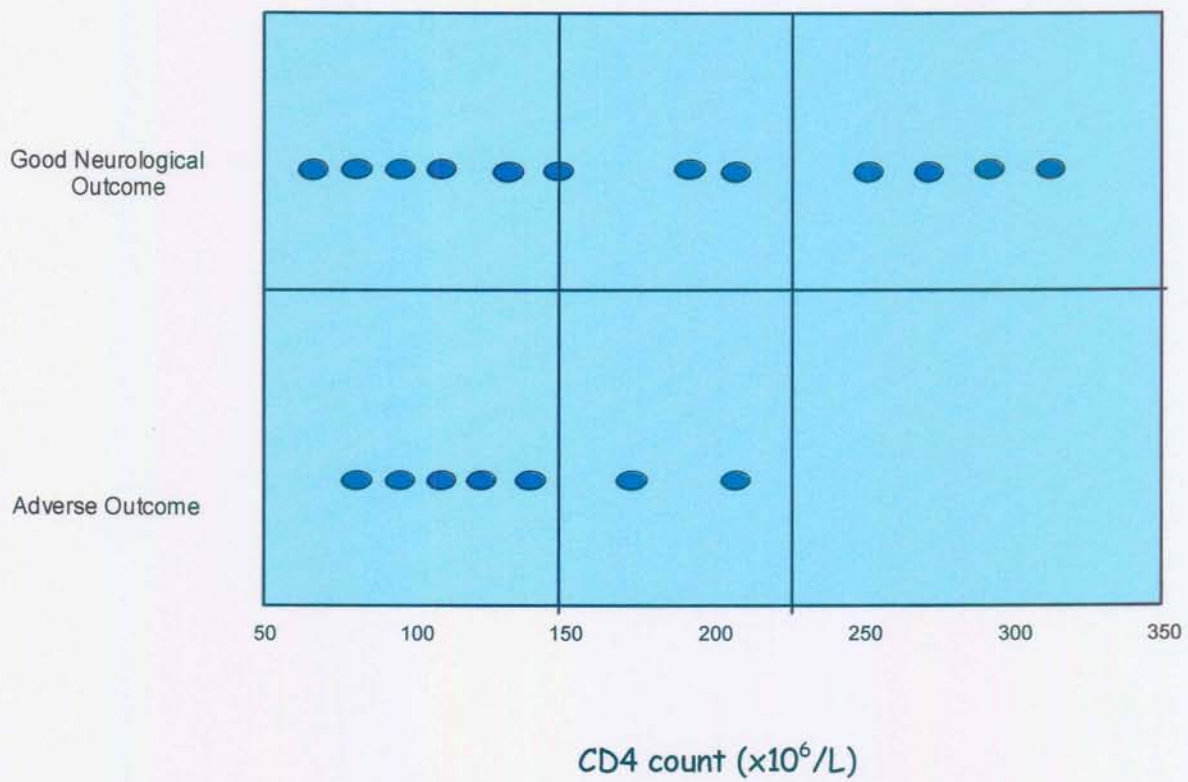
The CD4-counts were performed only in HIV-positive patients and ranged from 6,6 to  $473 \times 10^6/L$  (mean CD4-count:  $180 \times 10^6/L$ ). Adverse neurological outcomes (death/severe neurological deficit) occurred in 5/11

patients with CD4-counts of  $< 150 \times 10^6/L$  - thus more than half of patients with CD4 - counts  $< 150$  had good outcomes. No patient with a CD4-count of  $> 250 \times 10^6/L$  died. The results of the CD4-counts versus outcome in patients with TB meningitis are shown in Figure 8.



Figure 8

CD count vs. outcome in HIV-positive patients with TB meningitis



In the HIV-positive group the serum white cell counts ranged from  $2,2 \times 10^9/L$  to  $16,4 \times 10^9/L$  (mean 6,2) and in the HIV-negative groups from  $1,6 \times 10^9/L$  to  $14,4 \times 10^9/L$  (mean 8,2). In 19/20 (95 %) of HIV-positive patients the serum white cell count was  $< 11 \times 10^9/L$  compared to 14/17 (82 %) of HIV-negative patients ( $p = 0,21$ ; Chi square test).

Table 13 shows the results of the CSF analysis. There was no statistical difference (unpaired t - test; Welch correction) for any of the values in the two groups of patients. However, the HIV-positive group did show a trend towards higher CSF-lymphocyte counts. Another noteworthy fact was the measurement of the ADA-levels in the two groups. In 18 seropositive patients, the ADA values ranged from 2,5 to 28,5 IU/L with a mean of 12,6; compared to 15 HIV-negative patients where the values ranged from 3,3 to 25,1 IU/L (mean 13,5) -  $p = 0,67$  (Welch unpaired test).

Table 13

CSF ANALYSIS OF PATIENTS WITH TB MENINGITIS					
	CSF-L (Mean)	CSF-N (Mean)	CSF-P (Mean)	CSF-G (Mean)	CSF-ADA (Mean) n = 33
HIV +ve (n = 20)	0 - 385 (164)	0 - 293 (69)	1210 - 11522 (2880)	0,6 - 6,4 (1,9)	2,5 - 28,5 (12,6) (n = 18)
HIV -ve (n = 17)	0 -275 (96)	0 - 442 (87)	200 - 9220 (3476)	0,8 - 5,2 (1,7)	2,2 - 25,1 (13,5) (n = 15)
P (Welch unpaired t- test)	0,07	0,62	0,51	0,66	0,67
HIV +ve : HIV-positive HIV -ve : HIV-negative CSF-L : CSF Lymphocyte count (/mm <sup>3</sup> ) CSF-N : CSF Neutrophil count (/mm <sup>3</sup> ) CSF-P : CSF Protein value (mg/L) CSF-G : CSF Glucose value (mmol/L) CSF-ADA : CSF Adenosine deaminase level (IU/L)					

Of seven patients in whom post mortem examinations were performed, three were HIV-positive and four were HIV-negative. In the HIV-positive cases only the brain was examined but full examinations were performed on HIV-negative cases. In one seropositive case necrosis of brain tissue on the base of the brain with involvement of temporal lobes, the corpora mammilaria and the optic chiasm was found. Extensive meningo-encephalitis was also present with a dense inflammatory infiltrate of plasma cells and lymphocytes together with weakly formed granulomas and tuberculous bacilli. Both of the other two HIV-positive patients showed hydrocephalus - one with right-sided uncal and cerebellar tonsillar herniation and communicating hydrocephalus presumably due to obstruction of the basal cisterns; the other with diffuse slight dilatation of the whole ventricular system. Infarcts were seen in both patients: one in the area of the left basal ganglia with tuberculous endarteritis and weakly formed granulomas on histology, and the other in the areas around the longitudinal fissure with caseating necrosis and evidence of tuberculous endarteritis as well. Chronic inflammatory exudates were also present in both patients in the subarachnoid space.



In the HIV-negative patients, hydrocephalus was also found in two patients with uncus herniation in both, and tonsillar herniation additionally in one patient. In all four HIV-negative patients a chronic basal inflammatory exudate was found subarachnoidally, with tuberculous granulomas and areas of focal cortical involvements, but no infarcts. Proof of tuberculosis in other organs (e.g., kidney, liver, lungs), was found in all HIV-negative patients.

## Discussion

In many countries the prevalence of tuberculosis is increasing presently. At least three million patients die of tuberculosis annually - this makes tuberculosis the most common infectious cause of death worldwide (Zumba *et al.*, 2000). In addition, the HIV-epidemic in South Africa is still expanding at an alarming rate, and HIV-infection is at present the most important predisposing factor for the development of tuberculosis. Thus it was estimated that in 1999 at least one million HIV-related cases of tuberculosis would occur, causing almost a third of the expected 2,5 million AIDS-related deaths (Zumba *et al.*, 2000). Even more ominous at present is the occurrence of multi-drug resistant tuberculosis, which may pose a

serious threat to human health both in developed and less-developed countries.

One complication of tuberculosis is the development of meningitis, not only in children but increasingly so in adults co-infected with the human immunodeficiency virus. Even in HIV-negative patients, tuberculous meningitis is difficult to diagnose and with the decrease in immunity in HIV it was feared that tuberculous meningitis could be missed or that the characteristic findings would be obscured. Some studies have looked at the differences between HIV-positive and HIV-negative patients with tuberculous meningitis but these have been mostly retrospective analyses of TB meningitis patient data files. One recent study (Yechoor *et al.*, 1996) from Houston, Texas, reviewed a 12-year period of adults with tuberculous meningitis. Of 31 patients, 65 % (20/31) were HIV-positive; both HIV-positive and HIV-negative patients had similar findings on CT scan, CSF-analysis and chest X-rays. In this specific study cumulative rates of occurrence for 100 000 persons over the study period of 12 years were estimated at 1,72 for people without HIV-infection and 400 for those with HIV-infection. In a multivariate regression analysis an increased mortality was found in Black patients and those in whom corticosteroids had not been

used. In another study (Topley *et al.*, 1998) the clinical features, laboratory findings and radiological features of 40 children with tuberculous meningitis were studied; of these, 10 children were HIV-positive. When comparing the groups, the HIV-infected children were younger, had a shorter duration of symptoms, and 70 % of them were Mantoux-negative compared to the 23 % Mantoux-negative HIV-negative children. CT brain scans showed a higher incidence of ventricular enlargement, gyral enhancement and atrophy in the HIV-positive group. Clinical features were similar in both groups, but HIV-positive children had a considerably worse outcome with 30 % mortality rate in this group (HIV-negative : 0 %).

Our study incorporated only adults with tuberculous meningitis and the data was collected prospectively. In addition, some previously unreported tests have been performed in this study, and some differences from findings of the world literature have been found.

Tuberculous meningitis usually develops insidiously (Berger 1994). Compared to other studies our patients were symptomatic for a relatively

short time - on average less than two weeks. In the Texas study of patients (Yechool *et al.*, 1996) of patients with tuberculous meningitis 14/17 had symptoms within one month of admission and three patients had symptoms present for longer than one month. In our study, no patient had reported symptoms for more than three weeks. The most common presenting symptom was headache, and a low-grade temperature occurred in 75 % of both HIV-positive and HIV-negative patients. It has been stated before that purely tuberculous meningitis alone rarely causes a temperature of  $>39^{\circ}\text{C}$  (Tandon *et al.*, 1988); certainly in our study this proved true as no patient had a reported temperature of  $>39^{\circ}\text{C}$ .

In this study a definite correlation was found between staging of the disease according to the Glasgow Coma Scale at admission and outcome of the patient after treatment. Other studies have found similar results when comparing the level of consciousness with eventual outcome of patients (Smith 1964). Using the Glasgow Coma Scale as a measurement of the level of consciousness of patients holds several advantages. It is an accurate scale, it is well known to medical staff and it is objective to use. A GCS value of  $\leq 8$  was associated with an adverse outcome in all patients.

Contrary to this, a GCS value of 14 - 15 predicted a good neurological outcome in 80 % of patients. While the findings in the HIV-positive and HIV-negative groups of patients were similar, it was interesting to note that HIV-positive individuals were twice as likely to be completely neurologically intact than HIV-free patients.

It must be noted however, that other similar studies in the literature did not find a correlation between stage of disease and outcome (Yechoor *et al.*, 1996). The old staging method developed in 1948 by the British Medical Research Council (MRC Report 1948) is still widely used and may cause confusion. Stage III (advanced) tuberculous meningitis is, for example, defined as "the presence of stupor or coma, severe neurological deficits, seizures or abnormal movements" - stupor and coma are relatively vague terms, and abnormal movements may be caused by quite a small lesion (infarct) in the area of the basal ganglia, and thus not necessarily be implicated in a bad prognosis as such. The same holds true for convulsions, which may occur as a result of e.g., hyponatremia due to inappropriate ADH secretion.

Meningeal enhancement or exudates in the sub-arachnoid cisterns, a classic finding in tuberculous meningitis, is typically seen in approximately 60 % of patients in different studies (Berger 1994). Our study found a lower incidence of enhancement - 8/38 patients (21 %) had obvious enhancement on CT-scan. Hydrocephalus/dilated ventricles, however, was seen in 18 of our patients (47 %) - a similar figure as in other studies where hydrocephalus is reported to occur in between 38 and 76 % of patients with tuberculous meningitis. Of the patients with hydrocephalus/dilated ventricles in our study, an adverse outcome was found in 12 (67 %). One retrospective study in children, showed that the presence of ventriculomegaly and/or an infarct on scan was associated with sequelae, while tuberculomas alone were not necessarily predictive of a poor neurological outcome (Wallace *et al.*, 1991). Another paediatric study found that all patients who died had compound parenchymal/meningeal lesions on CT scan (Jenkins 1991). In contrast, one retrospective study in patients with tuberculous meningitis found the presence of ventricular enlargement alone, or basal enhancement, not to constitute a bad prognostic sign (Bullock and Welchman 1982). Infarcts, (27 % of patients in our study), are also reported in the literature as occurring in between 20 and 28 % of patients with tuberculous meningitis (Berger 1994). However, in our study the HIV-

positive patients were much more likely to have an infarct on CT scan than the HIV-negative patients (8 : 1). Granulomas are reported to occur in 10 - 16 % (Berger 1994, Davis *et al.*, 1993) of patients with tuberculous meningitis and some studies of HIV-positive patients with tuberculous meningitis have reported an even higher incidence of 60 % (Dube *et al.*, 1992). Our study showed an incidence of 13 % of granulomas with no significant difference between the two groups. Basal lucencies (edema/infarction) was reported in one study from Durban (Bullock and Welchman 1982) as present in 32 % cases - this was a rare finding seen in our study in only two patients (5 %). It was noteworthy that this seemed to be a bad prognostic sign as both our patients with edema died, as was also reported in the study of Bullock and Welchman from Durban.

Interestingly, a high Glasgow Coma Scale value on admission was not predictive of a normal scan - this is an important finding since radiology departments are sometimes reluctant to perform urgent scans on alert-looking patients. This study clearly shows that 60 % of patients with a GCS value of 14 - 15 (which implies a completely normal - looking patient or one

who e.g., only seems slightly confused), had abnormalities on CT scan. These findings lead to neurosurgical consultations in at least five patients.

The CD4-counts in the HIV-positive patients in our study were low. Counts of  $< 200 \times 10^6/L$  were found in 63 % of patients but there was no correlation between the CD4-count and outcome in our study. This is in contrast with some other studies (Berenguer 1992), which found an illness of  $> 14$  days and CD4-counts  $< 200 \times 10^6/L$  to be associated with a bad prognosis. However, in our study it is noteworthy that no patient with a CD4-count of  $> 200$  died. The serum white cell counts were normal in the majority of patients, although there was a propensity to lower counts in the HIV-infected patients (mean 6,2 versus  $8,2 \times 10^6/L$  in non-infected patients).

In patients with tuberculous meningitis abnormalities on chest X-rays occur in 25 % to 50 % (Berger 1994) of patients and more often in children (50 - 90 %) (Lincoln *et al.*, 1994). This is in keeping with findings in our study where 51 % of patients had an abnormal chest X-ray - with miliary TB as



the most common finding (17 %) at a slightly lower incidence compared to other studies (25 - 50 %) (Berger 1994).

Analysis of cerebrospinal fluid is essential for the diagnosis of tuberculous meningitis. The reported median cerebrospinal fluid white cell counts range from 63 to 283 cells/mm<sup>3</sup> (Traub *et al.*, 1984, Barrett-Connor 1967); extremes have been reported with normal CSF white cell counts (Berger 1994) and even values of > 4000/mm<sup>3</sup> (Karandanis and Shulman 1976). Mostly, the cells are lymphocytes after the acute phase has passed. In our study the range of CSF lymphocytes (0 - 285/mm<sup>3</sup> in HIV-positive patients - mean 164) was comparable to that of HIV-negative patients, but interestingly, the mean of 96 was much lower in the HIV-negative group (p = 0,07). None of the patients had acellular cerebrospinal fluid in our study. The CSF protein value is usually elevated in tuberculous meningitis - one study of 20 patients with AIDS and tuberculous meningitis (Yechoor *et al.*, 1996) reported 2/19 patients with normal CSF protein levels, while another large study (Berenguer 1992) reported a normal CSF protein in 43 % of patients. This has not been our experience, as all our 20 patients with HIV-

infection and tuberculous meningitis had high CSF protein levels, with a range of 1210 to 11522 mg/L.

One recent study of 31 patients with tuberculous meningitis (Yechoor *et al.*, 1996) showed a higher incidence of hypoglycorrhagia in HIV-infected patients (50 % versus 24 % of HIV-negative patients). In our study no such difference was found: 75 % of HIV-positive and 80 % of HIV-negative patients had CSF - glucose values of < 2,2 mmol/L. Adenosine deaminase levels have been shown to be high in tuberculous meningitis but sensitivity and specificity are between 73 % - 100 % and 71 % - 99 % respectively (Mann *et al.*, 1982, Ribera *et al.*, 1987, Coovadia *et al.*, 1986). Adenosine deaminase levels may also be elevated in bacterial meningitis (Chawla *et al.*, 1991) but in previous studies, it has been suggested that a higher cut-off point for ADA values might improve the diagnostic yield for tuberculous meningitis. In our study, 20/33 (60 %) of patients had values > 10 IU/L. The mean ADA levels of 12, 6 and 13,5 IU/L in the HIV-positive and HIV-negative groups respectively were similar in the two groups, and 85 % of patients in total had values of > 6. No previous studies comparing ADA levels in HIV-positive and HIV-negative patients could be found.

In our study, definite proof of tuberculosis was found to the same extent in the HIV-positive and HIV-negative group i.e., cultures yielding M.tuberculosis, Ziehl-Neelssen staining positive and post mortem indicative of tuberculosis. This was also found in a recent study by Yechoor (Yechoor 1996 *et al.*) where findings of 11 HIV-negative adults with tuberculous meningitis were compared to those of 20 HIV-positive patients with tuberculous meningitis. In the Pretoria Academic Hospital study three cases of highly probable tuberculous meningitis had cervical or axillary lymphnode biopsies, which confirmed the diagnosis of tuberculosis (This is further discussed under "lymphnode biopsy as an aid in the diagnosis of tuberculous meningitis".)

Thus, this study confirmed that clinical, cerebrospinal fluid and radiographic findings are similar in both HIV-infected and HIV-negative patients. The Glasgow Coma Scale value at admission was a better prognostic indicator in all patients than the CD4-counts in HIV-positive individuals.

## Chapter 3

### DIAGNOSTIC AIDS IN MENINGITIS

#### INTRODUCTION

In clear-cut cases the specific diagnosis of meningitis is not difficult. Ideally, a bacterial cause of meningitis will show organisms on gram staining, a positive capsular antigen test and a polymorph predominant pleocytosis with high protein and low glucose levels on cerebrospinal fluid analysis (Karandanis and Shulman 1976, Spanos *et al.*, 1989). Viral meningitis should typically show few cells - mostly lymphocytes - with normal glucose and possibly slightly raised protein levels (Karandanis and Shulman 1989). However, the reality shows that many cases have ambiguous findings. Added to this is the fact that chronic meningitis, especially tuberculous meningitis, can show a variety of cerebrospinal fluid results, which may not resemble the classic lymphocytic pleocytosis with high protein and low glucose values described in chronic infections (Kennedy and Fallon 1979). Partially treated bacterial meningitis and in some cases even viral meningitis, may have similar cerebrospinal fluid findings.

It is with this in mind that we evaluated some tests that might help to make an early diagnosis of a specific type of meningitis.

### 3.1 POLYMERASE CHAIN REACTION IN TUBERCULOUS MENINGITIS

#### SUMMARY

##### Background

Polymerase chain reaction testing for tuberculosis is a promising test for diagnosing tuberculous meningitis and sensitivities of up to 80 % have been reported in the literature.

##### Methods and Patients

We evaluated the PCR for TB in the CSF of 10 patients with suspected tuberculous meningitis presenting at the Pretoria Academic Hospital Neurology Unit from 1994 to 1996.

## Results

In only 20 % (2/10) of cases the PCR for tuberculosis was positive in the CSF; in the remaining eight patients with negative PCR, four had positive CSF cultures for TB, in one a lymphnode biopsy yielded proof of TB together with CSF findings characteristic of TB, one showed miliary TB on CXR and meningeal enhancement with granulomas on CT brain scan together with typical CSF findings, and the other two patients had characteristic clinical and CSF findings and improved on anti-TB treatment.

## Conclusion

Thus it was found that PCR in our laboratory is at present an unreliable test for the exclusion of TB meningitis.

## Introduction and survey of the literature

Tuberculous meningitis is difficult to diagnose. Often, CSF stains are negative for acid-fast bacilli, and cultures for M.tuberculosis are negative or take such a long time that patients have to be treated on clinical suspicion for tuberculous meningitis. Recently, polymerase chain reaction has been applied to specimens of cerebrospinal fluid to detect DNA of

M.tuberculosis. Sensitivities of up to 75 % - 80 % have been reported (Shankar *et al.*, 1991, Kaneko *et al.*, 1990). The test looked very promising and we decided to evaluate polymerase chain reaction for M.tuberculosis in ten patients to determine the sensitivity and specificity for our laboratory and our patients in tuberculous meningitis.

### Methods and patients

From March 1994 to November 1996 the polymerase chain reaction for tuberculosis was performed on the CSF of 10/15 patients with suspected tuberculous meningitis presenting to the neurology unit of the Pretoria Academic Hospital. In addition, CSF cultures for M.tuberculosis were performed on all patients, as well as cell counts, protein, and glucose levels. Of these patients, post mortem examinations were performed in four and lymphnode biopsies in three patients.

The PCR was performed at the microbiological laboratory of the Pretoria Academic Hospital as part of the routine work-up of patients with meningitis.

## Results

In 2/10 (20 %) cases the PCR for M.tuberculosis was positive in the cerebrospinal fluid. In these two patients CSF cultures were also positive for tuberculosis, and in the one patient the post mortem also confirmed tuberculous meningitis. Of the eight cases where the PCR for tuberculosis was negative, four CSF cultures were positive for M.tuberculosis, in one a lymphnode biopsy yielded proof of tuberculosis in addition to CSF findings characteristic of tuberculous meningitis, and one patient had miliary tuberculosis on chest X-ray and meningeal enhancement with granulomas on CT scan of the brain. The other two cases had characteristic CSF and clinical findings of tuberculous meningitis and improved on anti-tuberculous treatment.

## Discussion

In this study, only 20 % of patients with tuberculous meningitis had a positive PCR for M.tuberculosis in the cerebrospinal fluid. While the number of patients is small it is obvious that a negative PCR unfortunately cannot be used to rule out tuberculous meningitis. The possibility exists that this is a laboratory specific finding and that once the technique is



refined; the sensitivity of PCR testing will be improved. For the time being, PCR for tuberculosis in the CSF is an unreliable test that should be interpreted with caution in our patients.

## **3.2 LYMPHNODE BIOPSY AS AN AID TO**

### **DIAGNOSE INTRACRANIAL**

### **TUBERCULOSIS**

#### **SUMMARY**

##### **Background**

Intracranial tuberculosis is difficult to diagnose and patients are often treated on clinical suspicion. Lymphnode biopsies may provide easy access to histology in cases with suspected intracranial tuberculosis.

##### **Methods and Patients**

This report describes seven patients with intracranial tuberculosis (TB): six with tuberculous meningitis and one with intracranial tuberculomas. In all cases the diagnosis was confirmed by excision biopsy of a enlarged cervical or axillary lymphnode.

## Results

The biopsies showed caseating granulomas with/without acid fast bacilli, confirming the diagnosis of TB within 48 h of admission.

## Conclusion

Lymphnode biopsies may be an effective and practical aid in diagnosing intracranial TB. A definite diagnosis of TB can thus be made rapidly in patients with suspected intracranial TB.

## Introduction and survey of the literature

Diagnosing intracranial tuberculosis, i.e., tuberculous meningitis or tuberculomas, is notoriously difficult. The diagnosis is very often based on clinical suspicion and response to anti-tuberculous treatment rather than microbiological evidence. Lymphnode biopsies have been performed to diagnose pulmonary tuberculosis (Kapur and Judd 1967), but no reports in the literature could be found where lymphnode biopsies aided in the diagnosis of intracranial tuberculosis.

In this study we report seven patients, six with tuberculous meningitis and one with only intracranial tuberculomas, whose diagnosis of tuberculosis was confirmed within two days by lymphnode biopsies.

### Case reports

Patient 1, a 29-year-old female, complained of two to three weeks of headache, neck pain and fever. She was fully alert on admission without focal neurological signs. She had obvious neck stiffness, a temperature of 38.5°C and cervical and axillary lymphadenopathy. The cerebrospinal fluid findings were as follows: protein 2060 mg/L, chloride 115 mmol/L, glucose 1,4 mmol/L (serum-glucose 6,8 mmol/L), 251 lymphocytes /mm<sup>3</sup> and 10 neutrophils/mm<sup>3</sup>. The gram stain, capsular antigen and cryptococcus antigen tests were all negative, and culture did not yield any growth. Polymerase chain reaction for tuberculosis in the CSF was negative and the adenosine deaminase levels were 8,3 units/L. The patient tested positive for the human immunodeficiency virus (HIV), with a CD 4 - count of 110 × 10<sup>6</sup>/L. On chest X-ray a reticulonodular pattern was seen as is commonly found in miliary tuberculosis, and the PPD was strongly positive at 15 mm. On CT scan of the brain a small granulomatous lesion was visible in the right parietal

area. A biopsy of a soft mobile, rubbery cervical lymphnode of 1 cm was performed and on histology acid - fast bacilli and caseating granulomas were seen. This confirmed the diagnosis of tuberculosis within 48 hours of the patient's admission. She subsequently received anti-tuberculous treatment and recovered fully.

Patient 2 was a 20-year-old man who complained of headache, neck stiffness and fever for the previous 10 days. On examination, he was neurologically intact, but had neck stiffness, a temperature of 38 °C and cervical lymphadenopathy. On CSF analysis, the protein level was 3270 mg/L, chloride 100 mmol/L, glucose 1,1 mmol/L (serum-glucose 6,8 mmol/L), lymphocytes 220/mm<sup>3</sup>, and neutrophils 18/mm<sup>3</sup>. The CSF - ADA level was 16,4 units/L, and gram staining, capsular antigen tests as well as cryptococcus antigen and culture were negative. No abnormalities were detected on chest X-ray and CT brain scan. The PPD was positive (13 mm). A cervical lymphnode of approximately 1,5 cm diameter was biopsied, revealing caseating granulomas but no acid-fast bacilli were reported on the specimen.

Patient 3 was a male of 32 years who had a history of two weeks of headache together with neck stiffness and fever. He presented to the neurology department after a tonic-clonic convulsion. He had fever and neck stiffness and loose, rubbery enlarged lymphnodes were palpable in the axillary and cervical regions. The rest of the neurological examination was normal. The cerebrospinal fluid showed a protein level of 1970 mg/L, chloride 116 mmol/L, glucose 3,9 mmol/L (serum-glucose 5,2 mmol/L), ADA 10,6 units/L, with 12 lymphocytes/mm<sup>3</sup> and no neutrophils. The capsular antigen tests, as well as cryptococcus antigen, gram stain and culture were negative. The patient was HIV-positive with a CD4-count of 100 × 10<sup>6</sup>/L. The chest X-ray revealed an interstitial pattern, and basal meningeal enhancement and a lacunar infarct in the posterior limb of the left internal capsule were seen on CT brain scan. A biopsy of a 1,5 x 2cm axillary lymphnode was taken, and caseating granulomas together with acid-fast bacilli were reported on histology. The patient improved on anti-tuberculous treatment and M.tuberculosis was cultured eight weeks later from the CSF.

Patient 4, a 56-year-old man, initially presented with both focal and generalized convulsions, and a left hemiparesis. He had no clinical signs of

meningeal involvement but the CT scan of the brain showed multiple granulomatous lesions. Cervical and axillary lymphadenopathy was present. Cerebrospinal fluid analysis revealed a protein level of 1000 mg/L, chloride 120 mmol/L, glucose 2,9 mmol/L (serum glucose 5,0 mmol/L), ADA 0,7 units/L and one lymphocyte and 10 neutrophils/mm<sup>3</sup>. The PCR for tuberculosis was negative. On chest X-ray, a reticulonodular pattern was seen. Two rubbery, mobile 1 - 2 cm axillary lymphnodes were biopsied, showing caseating granulomas and acid-fast bacilli. The patient did well on anti-tuberculous treatment and M.tuberculosis was eventually also cultured from the sputum.

Patient 5, a male of 40 years, complained of three months of weight loss and malaise. In the two weeks before admission he developed progressive headache and neck pain. On examination, he was alert with terminal neck stiffness and a low-grade temperature of 37.6°C with palpable 1 - 2 cm large cervical and axillary lymphnodes, which were firm but mobile. The cerebrospinal fluid findings were as follows: protein 2190 mg/L, chloride 121 mmol/L, glucose 1,0 mmol/L (serum glucose 3,4 mmol/L), together with 384 lymphocytes/mm<sup>3</sup>. Gram stain, capsular and cryptococcal antigen tests were negative, as was the PCR for tuberculosis. Culture yielded no growth and

the ADA level was high at 38,5 units/L. The patient was found to be HIV-positive with a CD 4 - count of  $149 \times 10^6/L$ . The CT scan of the brain was within normal limits but the chest X-ray showed a reticulonodular pattern. Within 24 hours of admission, a right axillary lymphnode biopsy was performed, showing caseating granulomas typical of tuberculosis. Acid-fast bacilli were also seen on special staining. The patient improved rapidly on anti-tuberculous treatment. Eight weeks later, M.tuberculosis was cultured from the CSF.

Patient 6, was a 17 year-old female who was HIV-negative and complained of a one week history of malaise and headache. On examination she had generalized lymphadenopathy, with large lymphnodes cervically. On CT scan of the brain, meningeal enhancement was seen, while the chest X-ray showed evidence of miliary tuberculosis. The CSF examination showed the following: culture, antigens negative, protein 1860 mg/L, glucose 1,0 mmol/L (serum-glucose 5,6 mmol/L) with 24 neutrophils/mm<sup>3</sup> and no lymphocytes, ADA 9,1 units/L. A biopsy of a lymphnode revealed tuberculous lymphadenitis and several weeks later a sputum specimen result returned with proven tuberculosis. The patient improved markedly on anti-tuberculous treatment.



Patient 7 was a HIV-positive 39 year-old man with a 2-week history of progressive headache and neck pain. On admission he was well oriented and the temperature was 38 °C. Lymphnodes were palpable in the axillary and inguinal areas. The CT brain scan showed early hydrocephalus with prominent temporal horns of the lateral ventricles but the chest X-ray was within normal limits. On CSF analysis the protein was 2960 mg/L, the glucose 0,7 mmol/L (serum-glucose 5,5 mmol/L), the ADA 16,4 units/L with 128 lymphocytes/mm<sup>3</sup> and 55 neutrophils/mm<sup>3</sup>. The PCR for tuberculosis was negative in the CSF, as were all antigen tests and cultures. An inguinal lymphnode biopsy revealed multiple weakly formed granulomas with necrosis and giant cells and the patient improved dramatically on anti-tuberculous treatment.

## Discussion

In this study six patients with tuberculous meningitis and one with only intracranial tuberculomas are described. On all the patients the diagnosis of tuberculosis was confirmed on histology by excision biopsy of enlarged lymphnodes (cervical/axillary/inguinal) showing acid-fast bacilli and/or

caseating granulomas. The difficulty of diagnosing tuberculous meningitis has been reported in the literature (Berger 1994, Roberts 1981). Often the diagnosis is based on vague "clinical and laboratory data compatible with tuberculosis" without bacteriological confirmation or histological support. Newer tests i.e., TB-antigen and polymerase chain reaction, are often unreliable as was also found in the four patients in whom the test was performed in our study and was found to be negative. The chest X-ray was suggestive of tuberculosis in five of the seven patients, but sputum was difficult to obtain in all cases and it is well described that it can actually be negative even in miliary tuberculosis.

Previous studies have reported lymphnode biopsies to be helpful in diagnosing pulmonary tuberculosis (Kapur and Judd 1967). To our knowledge this is the first report where lymphnode biopsies have aided in the diagnosis of intracranial tuberculosis. In this study the lymphnode biopsies were able to rapidly (within 24 - 48 hours) confirm the diagnosis of mycobacterial infection in our patients, thus leading to earlier and specific treatment. In all our patients other causes of chronic meningitis (e.g., cryptococcal meningitis) were excluded, and all patients improved on anti-tuberculous treatment.

In four patients acid-fast bacilli were seen on special staining in the histological specimens of the lymphnodes, and M.tuberculosis bacilli were eventually also cultured from the sputum or CSF in four patients. Unfortunately, no cultures were taken from the lymphnodes; however, subsequent lymphnode specimens will be sent for microscopy, culture and possibly sensitivity studies as susceptibility testing is becoming increasingly important in an era of multi-drug resistant tuberculosis, especially coupled with HIV-infection.

Four of our patients were seropositive for HIV. It is not clear whether tuberculous lymphadenopathy is more common in HIV-positive patients with intracranial tuberculosis than in HIV-negative individuals and more studies are needed to clarify this issue.

### 3.3 THE VALUE OF ADENOSINE DEAMINASE ISO-ENZYMES IN THE DIAGNOSIS OF TUBERCULOUS MENINGITIS

#### SUMMARY

##### Background

Adenosine deaminase (ADA) exists as two iso-enzymes, ADA<sub>1</sub> and ADA<sub>2</sub>. It appears that the ADA<sub>2</sub> iso-enzyme originates mainly from monocytes and macrophages. In tuberculous pleural effusions most of the ADA activity consists of ADA<sub>2</sub>. The aim of this prospective study was to analyse ADA iso-enzymes in the CSF of patients with meningitis to investigate whether the expected rise of the ADA<sub>2</sub> iso-enzyme would occur in tuberculous meningitis.

##### Methods and Patients

ADA iso-enzyme analysis was performed on the CSF of 15 patients with tuberculous and 11 patients with bacterial meningitis by an automated

kinetic enzyme coupled assay in the presence and absence of a specific ADA inhibitor.

## Results

The ratio of  $ADA_2/ADA_{Total}$  was  $> 0,8$  in 14/15 patients with tuberculous meningitis. In bacterial meningitis the ratio was  $\leq 0,8$  in 10/11 patients.

## Conclusion

The  $ADA_2$  iso-enzyme is the major contributor to increased ADA activity in the CSF of patients with tuberculous meningitis, probably reflecting the monocyte - macrophage origin of the ADA.

## Introduction and survey of the literature

Many studies have reported on the importance of an elevated adenosine deaminase (ADA) value in the cerebrospinal fluid of patients with tuberculous meningitis (Ribera *et al.*, 1987, Coovadia *et al.*, 1986). The enzyme is mainly associated with T-lymphocytes (Sullivan *et al.*, 1977) in humans and high plasma concentrations of ADA have been found in systemic infections where cell mediated responses are elicited. In addition, elevated ADA values have been found in tuberculous infections of pleural, pericardial

and peritoneal cavities (Ungerer *et al.*, 1994). In the cerebrospinal fluid high levels of ADA were reported to have a sensitivity of 100 % and a specificity of 99 % in diagnosing tuberculous meningitis in 21 patients of one study (Ribera *et al.*, 1987). The levels stayed high through the first three weeks of treatment. Interestingly, one report looked at ADA levels (Ena *et al.*, 1988) in AIDS patients with tuberculous meningitis and found that in spite of T-cell depletion the levels were still elevated. Other studies showed less dramatic sensitivities and specificities for diagnosing tuberculous meningitis by elevated ADA levels (with a 73 % sensitivity reported in one study, and specificity of 71 % in another study) (Mann *et al.*, 1982, Ribera *et al.*, 1987, Coovadia *et al.*, 1986). Another recent study showed that ADA levels were raised in both tuberculous and bacterial meningitis, and no definite demarcation in the levels could be found between the two types (Chawla *et al.*, 1991). Our own studies have also mirrored these findings (unpublished results): in four of seven patients with proven pneumococcal meningitis, for example, the ADA levels were > 6 units/L confirming that high ADA levels are not specific for tuberculous meningitis.

Adenosine deaminase is the catalysing enzyme for the deamination of adenosine (or deoxyadenosine) to inosine (or deoxyinosine) and ammonia.

For ADA, two iso-enzymes exist, namely ADA<sub>1</sub> and ADA<sub>2</sub>. Both iso-enzymes are encoded by different gene loci (Hirschhorn and Ratech 1980). The ADA<sub>1</sub> iso-enzyme has been found in all cells, including lymphocytes and monocytes, but the ADA<sub>2</sub> iso-enzyme is primarily present in monocytes (Ungerer *et al.*, 1994). Prominent rises in ADA<sub>2</sub> - activity would be expected in chronic infections, with mostly monocyte-macrophage activation. In tuberculous pleural effusions, it has been shown that ADA<sub>1</sub> and ADA<sub>2</sub> iso-enzymes contribute independently to ADA elevations: in tuberculous effusions, most of the measured ADA activity is due to the ADA<sub>2</sub> iso-enzyme, probably reflecting monocyte-macrophage origin (Ungerer *et al.*, 1994).

In a prospective study of patients with meningitis, it was thus investigated whether ADA<sub>2</sub> activity was predominant in the cerebrospinal fluid of patients with chronic infections, specifically tuberculous meningitis.

### Methods and patients

The cerebrospinal fluid of 15 consecutive patients with tuberculous meningitis and 11 patients with bacterial meningitis presenting to the adult

neurology ward of the Pretoria Academic Hospital, was investigated. The biochemistry laboratory personnel performing the ADA determination were unaware of the specific diagnosis of the patients.

Of the patients with tuberculous meningitis, 7 were male and 8 female and the ages ranged from 15 - 45 years. All patients were Black. Patients were symptomatic for between five days to more than two weeks before first presentation to the hospital and first ADA determination. In the group of patients with bacterial meningitis, nine patients were male and two female, their ages ranging from 18 - 65 years. Patients were symptomatic for two days (six patients) to five days (one patient), before ADA analysis was performed.

The method for determining ADA activity together with ADA iso-enzymes was as follows: ADA and iso-enzymes were determined by an automated kinetic enzyme coupled assay in the presence and absence of a specific ADA<sub>1</sub> inhibitor, namely erythro - 9 - (2 - hydroxy - 3 - nonyl) adenine. This specific method has been described previously (Oosthuizen *et al.*, 1993). One-way analysis of variance (ANOVA) statistical method was used to determine whether the groups of cerebrospinal fluid differed significantly,



and linear association tests (Pearson) were also performed to establish whether correlations between ADA<sub>1</sub> and ADA<sub>2</sub> and lymphocyte/ neutrophil counts in the CSF respectively were present.

## Results

The diagnosis of tuberculosis was made according to standard criteria, including characteristic CSF findings and clinical findings, as well as histology and positive cultures. The criteria for the diagnosis of tuberculosis were: Presence of acid-fast bacilli on CSF staining, positive culture and/or PCR for tuberculosis in the CSF, proof of tuberculosis at another site together with characteristic clinical and CSF findings; and typical CSF findings (protein > 500 mg/L, CSF glucose/serum glucose < 50 % or CSF glucose < 2,2 mmol/L and a lymphocytic pleocytosis), together with response to antituberculous treatment. The laboratory findings of the patients with tuberculous meningitis are shown in Table 14.

Table 14

CSF FINDINGS IN TB MENINGITIS						
N	L	CSF Glu-S Glu	P	ADA <sub>T</sub>	ADA <sub>2</sub>	ADA <sub>2</sub> /ADA <sub>T</sub>
270	42	0,9 - 6,2	3400	3,5	3,2	0,91
55	128	0,7 - 5,5	2960	7,5	6,1	0,81
77	108	0,8 - 5,7	1850	10,5	9,9	0,94
12	470	1,5 - 5,2	2300	10,5	9,7	0,92
0	244	6,4 - 1,6	3000	16,5	14,3	0,87
0	385	1,0 - 3,43	2190	22,2	20,6	0,93
*24	134	1,9 - 7,8	200	6,4	4,4	0,7
385	275	0,8 - 12,1	2300	15,5	13,1	0,85
0	647	2,2 - 7,9	1400	10,4	10,2	0,98
36	18	1,1 - 4,5	3645	14,8	14,0	0,94
10	251	1,4 - 6,8	2060	17,7	17,6	0,99
61	97	1,0 - ?	3649	38,67	37,0	0,95
85	12	2,5 - 4,6	6415	14,9	13,7	0,92
323	293	2,6 - 6,3	4177	27,2	23,9	0,88
48	256	2,1 - 6,8	2434	22,0	21,9	0,99

N:	Neutrophils (/mm <sup>3</sup> )
L:	Lymphocytes (/mm <sup>3</sup> )
CSF Glu-S Glu:	CSF glucose - serum glucose (mmol/L)
P:	Protein (mg/L)
ADA <sub>T</sub> :	ADA Total (u/L)
ADA <sub>2</sub> :	ADA <sub>2</sub> isoenzyme (u/L)

\* CSF is ventricular fluid collected when external drain was inserted; diagnosis of TB was confirmed at post mortem in this patient.

The patients with bacterial meningitis were mostly diagnosed with S.pneumoniae infection. In eight patients S.pneumoniae was cultured from the CSF, in two N.meningitides and in one a Streptococcus Group B. These results are shown in Table 15.

The ratios of the ADA<sub>2</sub> iso-enzyme over the total ADA values were calculated for every patient. In the patients with tuberculous meningitis the ratio of ADA<sub>2</sub>/ADA<sub>total</sub> was > 0,8 in 14/15. This was in contrast to the ratio in patients with bacterial meningitis, which was ≤ 0.8 in 10/11 patients. Statistical analysis shows that at the 0,05 level of significance, there is a significant difference of the ADA<sub>2</sub>/ADA<sub>total</sub> ratios between the groups (p < 0,0001).

Table 15

CSF FINDINGS IN BACTERIAL MENINGITIS						
N	L	CSF Glu-S Glu	P	ADA <sub>T</sub>	ADA <sub>2</sub>	ADA <sub>2</sub> /ADA <sub>T</sub>
672	250	0,1 - 8,9	4298	10	5,2	0,52
684	24	2,1 - 7,1	4991	6,7	2,2	0,33
138	0	0,1 - 13,5	17200	9,8	8,6	0,88
1311	30	0,3 - 16,4	17700	9,4	7,5	0,79
600	75	1,6 - 8,3	1310	56,4	25,4	0,45
5894	507	1,3 - 5,1	5720	4,6	2,1	0,45
2200	110	0,1 - 17,2	5870	3,8	1,5	0,39
2536	208	1,9 - 5,5	2370	27,5	7,3	0,26
6313	12	0,1 - 6,3	3910	5,1	3,9	0,76
12100	22	0,2 - 9,5	5810	6,3	2,5	0,39
4620	110	1,3 - 4,8	2120	15,8	9,9	0,63

N:	Neutrophils (/mm <sup>3</sup> )
L:	Lymphocytes (/mm <sup>3</sup> )
CSF Glu-S Glu:	CSF glucose - serum glucose (mmol/L)
P:	Protein (mg/L)
ADA <sub>T</sub> :	ADA Total (u/L)
ADA <sub>2</sub> :	ADA <sub>2</sub> isoenzyme (u/L)

Three patient values of  $ADA_2/ADA_{total}$  stand out from the rest. One patient with tuberculous meningitis had an  $ADA_2/ADA_{total}$  ratio of  $< 0,8$ . In this patient marked hydrocephalus had been found and the CSF specimen was taken when an external drain was placed in theatre. The diagnosis of tuberculosis was later confirmed at post mortem. Two patients with bacterial meningitis had high ratios (0,88 and 0,79): In both patients the CSF protein levels had been exceptionally high - 17 000 and 17 700 mg/L - which possibly could have affected measurement of ADA.

## Discussion

The  $ADA_2$  iso-enzyme was found to be the major contributor to the total ADA activity in the CSF of adults with tuberculous meningitis. In tuberculous meningitis the median  $ADA_2$  iso-enzyme contribution to the total ADA activity was 90 % compared to 51 % in bacterial meningitis.

At present the origin of ADA activity in the CSF of patients with tuberculous meningitis is uncertain. However, studies based on the occurrence of iso-enzymes in body fluids of patients with tuberculosis suggests a monocyte-macrophage origin. The  $ADA_1$  iso-enzyme was found

to be responsible for all the ADA activity in lymphocytes in a recent study (Sullivan *et al.*, 1977). In chronic meningitis the increased ADA activity - mostly due to ADA<sub>2</sub> iso-enzyme activity - probably is of monocyte-macrophage origin, and not of lymphocyte or neutrophil origin. Linear correlation tests (Pearson) also showed no correlation between ADA<sub>1</sub> or ADA<sub>2</sub> activity and neutrophils or lymphocytes in the cerebrospinal fluid in this study.

Thus, in conclusion, as in tuberculous infections of the pleura or peritoneum, the ADA<sub>2</sub> iso-enzyme is the major contributor to increased ADA activity in the CSF of patients with tuberculous meningitis.

### 3. 4 ADENOSINE DEAMINASE ISO-ENZYMES IN OTHER FORMS OF MENINGITIS

#### SUMMARY

##### Background

The tuberculous meningitis, a chronic form of meningitis, the ADA<sub>2</sub> - iso-enzyme was found to be the major contributor to CSF-ADA activity. Since cryptococcal meningitis is also a chronic infection with predominantly monocyte - macrophage activation, it was postulated that the ADA<sub>2</sub> - iso-enzymes would also be the main contributor to CSF-ADA activity in this disease.

##### Methods and Patients:

The CSF of 13 patients with cryptococcal meningitis presenting at the adult neurology ward of the Pretoria Academic Hospital, was investigated. Total ADA and iso-enzyme activities were analysed in the CSF.

## Results

In all 13 patients the ratio  $ADA_2/ADA_{TOTAL}$  in the CSF was  $> 0,8$ .

## Conclusion

Thus ADA2 iso-enzyme activity is indeed the major contributor to the total ADA in the CSF of patients with cryptococcal meningitis.

## Introduction and survey of the literature

Following the above study where iso-enzymes were determined in the CSF of patients with tuberculous and bacterial meningitis, it was postulated that the results should be similar in other forms of chronic meningitis. Thus it is expected that the  $ADA_2$  iso-enzyme would also be the major contributor to total ADA activity in the CSF of patients with, e.g., cryptococcal meningitis.

Cryptococcal meningitis usually poses no diagnostic dilemma as Indian ink staining, and capsular antigen tests are readily available and sensitive. The organism is also easily and rapidly cultured. Therefore, the ADA iso-enzymes determination would probably not be of the same diagnostic value as in tuberculous meningitis.



## Methods and patients

In addition to the previous study, the CSF of 13 patients with cryptococcal meningitis was investigated and the total ADA activity as well as the ADA iso-enzymes were analysed. Of the patients with cryptococcal meningitis, six were male and six female. All patients were Black, the ages ranging from 28 to 62 years. The time elapsed since onset of symptoms and CSF evaluations ranged from two days in one patient to two months (one patient) with most patients presenting after one to two weeks of symptoms.

## Results

The results of the CSF analysis are shown in Table 16.

The ADA values ranged from 1,58 to 14,0 IU/L (mean: 8,1) and the total ADA levels were raised in 10/13 patients. In all 13 patients, the  $ADA_2/ADA_{TOTAL}$  ratio was  $> 0,8$ . CSF lymphocyte counts ranged from 0 to 189/mm<sup>3</sup> (mean: 30) and the neutrophil count from 0 to 849 (mean: 75).

## Conclusion

This study confirmed that the ADA<sub>2</sub> iso-enzyme is the major contributor to total ADA activity in the CSF of patients with another form of chronic meningitis, i.e., cryptococcal meningitis. As in tuberculous meningitis, the increased ADA activity, mostly ADA<sub>2</sub>-activity, is probably from monocyte and macrophage origin as would be expected in a chronic infection.

Table 16

CSF FINDINGS IN CRYPTOCOCCAL MENINGITIS						
N	L	CSF Glu-S Glu	P	ADA <sub>T</sub>	ADA <sub>2</sub>	ADA <sub>2</sub> /ADA <sub>T</sub>
2	5	3,1 - 4,9	480	8,1	7,0	0,86
0	12	1,0 - 5,1	1 140	5,5	4,7	0,85
18	24	1,6 - 4,8	310	3,3	3,2	0,97
12	0	3,2 - 7,1	400	4,7	4,7	1,0
10	5	2,3 - 6,9	2 059	10,2	9,1	0,89
0	0	0,4 - 7,3	1 085	10,0	8,9	0,89
0	42	1,9 - 6,6	618	6,97	6,12	0,88
0	6	3,1 - 2,4	281	1,58	1,44	0,91
61	85	2,0 - 5,8	2 260	14,0	13,54	0,97
849	0	0,0 - ?	3 165	9,5	8,9	0,94
30	189	1,2 - 4,7	76 81	10,89	9,96	0,91
0	12	2,7 - 6,1	842	7,6	7,4	0,97
0	12	0,8 - 8,8	1 982	13,4	13,15	0,98
<p>N : Neutrophils (/mm<sup>3</sup>)</p> <p>L : Lymphocytes (/mm<sup>3</sup>)</p> <p>CSF Glu-s Glu : CSF glucose - serum glucose (mmol/L)</p> <p>P : Protein (mg/L)</p> <p>ADA<sub>T</sub> : ADA Total (IU/L)</p> <p>ADA<sub>2</sub> : ADA<sub>2</sub> isoenzyme (IU/L)</p>						

### **3.5 THE ELECTROENCEPHALOGRAM AS DIAGNOSTIC AID IN MENINGITIS**

#### **DISCRIMINATION BETWEEN VIRAL AND NON-VIRAL MENINGITIS BY VISUALLY ANALYSED AND QUANTITATIVE ELECTRO-ENCEPHALOGRAPHY**

#### **SUMMARY**

##### **Background**

A prospective study was conducted to assess the ability of the visually analysed electroencephalogram (VEEG), the quantitative EEG (QEEG) and the Glasgow Coma Scale (GCS) to discriminate between patients with viral and nonviral meningitis.

##### **Methods and Patients:**

The 55 subjects, aged 14 - 75 years, fell into one of the following categories: viral ( $n = 12$ ), bacterial ( $n = 19$ ), tuberculous ( $n = 16$ ) or cryptococcal ( $n = 8$ ) meningitis. EEG recordings and Glasgow Coma Scale (GCS) scores were obtained within 48 hours of admission to hospital.

## Results

The sensitivity of the VEEG and QEEG for the prediction of patients with nonviral meningitis (true positives in this context) attained reasonably high values of 70 % and 80 %, respectively. In contrast, the sensitivity of the GCS was only 38 %. Each of the three tests achieved high degrees of consistency in this regard with positive predictive values of 94 % or better. The specificity for each of the three tests was high, 100 % of the VEEG and the GCS and 82 % for the QEEG indicating a high probability for the correct prediction of viral meningitis (true negatives). The consistency of this prediction was, however, poor due to negative predictive values of only 53 % for the QEEG, 48 % for the VEEG and 32 % for the GCS.

The QEEG results did not reveal any obvious advantages over the VEEG. Rather the assessment of the occurrence of particular VEEG abnormalities

showed that patients with delta abnormalities had a very high probability of nonviral meningitis. At the other end of the spectrum, all normal VEEGs occurred in viral meningitis.

## Conclusion

In important respects the predictive ability of the EEG was superior to that of the GCS. While there was statistically significant agreement between the VEEG and GCS, the degree of agreement was poor. This study indicates that the EEG is a valuable and probably underestimated test in the acute phase of meningitis and provides complementary information to the GCS.

## Introduction and survey of the literature

Not many studies have evaluated the EEG in meningitis during the past twenty years. Earlier studies showed no or mild abnormalities in viral meningitis (Gibbs *et al.*, 1962) and more pronounced abnormalities in bacterial meningitis (Turrell and Roseman 1955). Some signs in visually analysed EEG's (VEEG) may be associated with a particularly good or bad

prognosis (Soulas 1977) but at least one recent study concluded that VEEG only contributes minimally to routine clinical assessments in meningitis (Pike *et al.*, 1990). Quantitative EEG (QEEG) has not been used previously in evaluating patients with meningitis, and studies on adults with meningitis and EEG findings are rare, possibly due to the findings of less marked abnormalities in adults compared to children (Gibbs *et al.*, 1962, Turrell and Roseman 1955).

In this study, which was part of the prospective meningitis study at the Pretoria Academic Hospital, the extent to which the VEEG and QEEG discriminated between viral meningitis (no treatment required) and non-viral meningitis (i.e., urgent treatment required for bacterial, fungal, or tuberculous infection) in adults. The EEG was also compared to the Glasgow Coma Scale of the patient.

### Methods and patients

Fifty-five adult patients with meningitis were evaluated in this prospective study. The patients' ages ranged from 14 to 75 years (median 30 years) with 20 females and 35 males. Twelve patients were diagnosed with viral

meningitis with clinical and CSF findings compatible with aseptic meningitis (lymphocytic pleocytosis, normal to mildly elevated CSF protein levels, normal to mildly depressed CSF glucose levels in an awake patient with routine capsular antibody tests, gram staining and cultures negative). Acute bacterial meningitis occurred in 19 patients, with cultures mostly positive for S.pneumoniae or N.meningitides. Tuberculous meningitis was diagnosed in 16 patients with CSF and clinical findings typical of tuberculous meningitis with the patient improving on anti-tuberculous treatment or when CSF cultures were positive for M.tuberculosis, or when CSF and clinical findings were compatible with tuberculous meningitis and evidence of tuberculosis was found in another site. Cryptococcal meningitis occurred in eight patients and was diagnosed by positive CSF culture and/or capsular antigen tests. In an additional 30 patients, diagnosis was uncertain and these patients were not included in this study.

VEEG's were performed according to the International 10 - 20 systems with Nihon-Kohden models (4221, 4418, 7310), and both bipolar and common reference montages were included with eye movements recorded from the outer canthus and referred to M<sub>2</sub>. The electroencephalographer analysing the data was blind to the clinical diagnosis of the patients. All VEEG's were



graded from 0 (normal) to 4 (persistent polymorphic, non-reactive delta (PDA), with grade 1 showing 5 - 7 Hz theta activity, grade 2, 4 - 5 Hz theta and/or delta of < 20 % of the recording, and grade 3 intermittent rhythmic delta (IRDA) and/or delta in > 20 % of the recordings.

The QEEG's were also performed on Nihon Kohden systems (4418 or 7310) using Stellate Systems Rhythm® version 3,0 programs. Results of the spectral analysis were divided into four frequency bands: Delta (0,75 - 3,75 Hz), theta (4 - 7,75 Hz), alpha (8 - 13 Hz) and beta (13,25 - 31 Hz) and results were shown on an amplitude ( $\mu V$ ) scale with both absolute and relative values. The ratio of the alpha amplitude to the combined delta/theta amplitude from the six recorded derivations was chosen for statistical analysis.

## Results

The VEEG grades 0 - 2 (normal to moderately abnormal) were compared to VEEG grades 3 - 4 (markedly to severely abnormal), postulating that 0 - 2 would indicate viral meningitis, and 3 - 4 non-viral meningitis. Thus the sensitivity of the VEEG for predicting non-viral meningitis was 70 %

(30/43) and the specificity was 100 % (12/12); the positive predictive value was 100 % (30/30) with a negative predictive value of 48 % (12/25).

On the QEEG's the parieto-occipital mean ratios were used for analysis - the mean parieto-occipital ratio was significantly higher in non-viral (mean  $\pm$  SD = 4,22  $\pm$  2,62) than in the viral (mean  $\pm$  SD = 1,67  $\pm$  0,75) meningitis groups, (two-sample t - test:  $t = 5,4$ ,  $P = < 0,001$ ).

The QEEG ratio of alpha/theta plus delta from parieto-occipital deviations was evaluated to find an optimal cut-off point for the differentiation of viral from non-viral meningitis. Patients with a ratio of  $\leq 2,1$  were thus classified as viral and  $\geq 2,1$  as non-viral. Taking this QEEG variable, the sensitivity for the prediction of non-viral meningitis, was 80 % (32/40) with a specificity of 82 % (9/11), a positive predictive value of 94 % (32/34), and a negative predictive value of 53 % (9/17).

Again Glasgow Coma Scale scores of 13 - 15 (relatively intact) were compared to scores of 3 - 12 (markedly to severely abnormal). The sensitivity of the Glasgow Coma Scale in predicting non-viral meningitis was 38 % (16/42) with a specificity of 100 % (12/12), a positive predictive value

of 100 % (16/16) and a negative predictive value of 32 % (12/38). A statistical significant (but relatively poor) degree of agreement was found between VEEG grade of abnormality and the Glasgow Coma Scale (refer to article for details).

Particular VEEG findings were found to relate to certain categories of meningitis, e.g., Delta activity for > 20 % of the EEG recordings, IRDA and PDA were only seen in non-viral meningitis (Table 17).

Table 17

THE OCCURRENCE OF PARTICULAR VEEG FINDINGS IN RELATION TO THE CATEGORY OF MENINGITIS			
		Meningitis	
VEEG	N	Viral	Non-viral
Normal	6	6	0
Theta	12	5	7
Delta < 20 %	7	1	6
Delta > 20 %	4	0	4
IRDA	19	0	19
PDA	7	0	7

IRDA: Intermittent rhythmic delta activity  
PDA: Polymorphic delta activity

## Discussion

The sensitivity of the VEEG and QEEG for predicting patients with non-viral meningitis was quite high (70 and 80 % respectively) with very high positive predictive values of 94 % or more. The Glasgow Coma Scale showed a sensitivity of only 38 %, but also a high positive predictive value - thus if a patient had one or more abnormal test result, the probability of non-viral meningitis was very high.

Specificities of the VEEG and Glasgow Coma Scale were 100 % with 82 % for the QEEG, but negative predictive values were relatively poor - 53 % for QEEG, 48 % for VEEG and 32 % for Glasgow Coma Scale, mostly due to overlap between relatively normal tests in patients with viral and non-viral meningitis.

In patients with cerebral dysfunctions a correlation between EEG and measures of impairment of consciousness is usually found (Sharbrough 1993): This was also seen in our patients where a significant correlation was seen between VEEG grading and Glasgow Coma Scale score, but the degree of agreement was relatively poor due to numerous patients with high

Glasgow Coma Scale scores but quite severely abnormal EEGs. Thus, the EEG can be considered as helpful in the early stage of differentiating viral from non-viral meningitis, particularly the early chronic types such as tuberculous meningitis, where CSF findings may be confusing and may actually mimic a viral infection.

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## ADDENDUM

# A Prospective Study of Glasgow Coma Scale (GCS), Age, CSF-Neutrophil Count, and CSF-Protein and Glucose Levels as Prognostic Indicators in 100 Adult Patients with Meningitis

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**Background:** the Glasgow coma scale (GCS) is an objective measurement of a patient's level of consciousness and has prognostic implications in traumatic head injuries. Morbidity and mortality of patients with meningitis have been related amongst others to level of consciousness, hypoglycorrhachia, extremes of age, and high CSF protein values. In this prospective study of 100 patients the correlation between the GCS, age, CSF-neutrophil count and CSF-glucose and protein levels and the eventual outcome of the patients was assessed.

**Methods:** in 100 consecutive patients with meningitis (bacterial, viral, tuberculous, cryptococcal and other) the GCS, age, CSF-neutrophil count and CSF-protein and glucose levels were determined at admission. After treatment the outcome of the patient was assigned to one of four categories: healthy, minor and severe neurological deficits and death.

**Results:** from a non-parametric one-way analysis of variance it was found that with respect to mean GCS-values significant differences were present among the outcome categories ( $P < 0.0001$ ). The outcome categories did not differ significantly with respect to age, CSF-neutrophil count or CSF-glucose level, but did differ significantly with respect to the CSF-protein level ( $P < 0.0025$ ). Additionally, 88% of patients with a GCS value of  $> 12$  had a good neurological outcome, while 88% of those with a GCS value of  $\leq 8$  had a poor outcome.

**Conclusion:** a good correlation between both the GCS and CSF-protein level at admission and the outcome of patients with meningitis was found, with the GCS value being a better prognostic indicator than high CSF protein levels.

## Introduction

The Glasgow coma scale, originally described in 1974 by Teasdale and Jennett,<sup>1</sup> is a practical, objective measurement of a patient's level of consciousness without using vague terms such as 'stupor' or 'lethargy'. Furthermore, the GCS is useful in predicting the outcome of patients with severe head injuries, with a score of less than 8 indicating a poor prognosis.<sup>2</sup> In patients with hypoxia, cerebrovascular disease or metabolic disease,<sup>3</sup> it was shown that certain aspects of the GCS were associated with a poor outcome.

The morbidity and mortality of patients with meningitis have been related to the level of consciousness,<sup>4,11</sup> but no reports could be found where the GCS count was prospectively correlated to the outcome of patients with acute or chronic meningitis. In a recent special report by the Research Committee of the BSSI,<sup>11</sup> retrospective analysis showed that absence of eye opening, no verbal response and no response to pain was associated with a

high mortality. Hypoglycorrhachia, exceptionally high CSF protein values, early-onset seizures, increasing age and absence of nuchal rigidity have all been implicated as unfavourable prognostic factors in patients with meningitis.<sup>5,10,12</sup> In this prospective study of 100 adult patients with meningitis, the patient outcome categories were

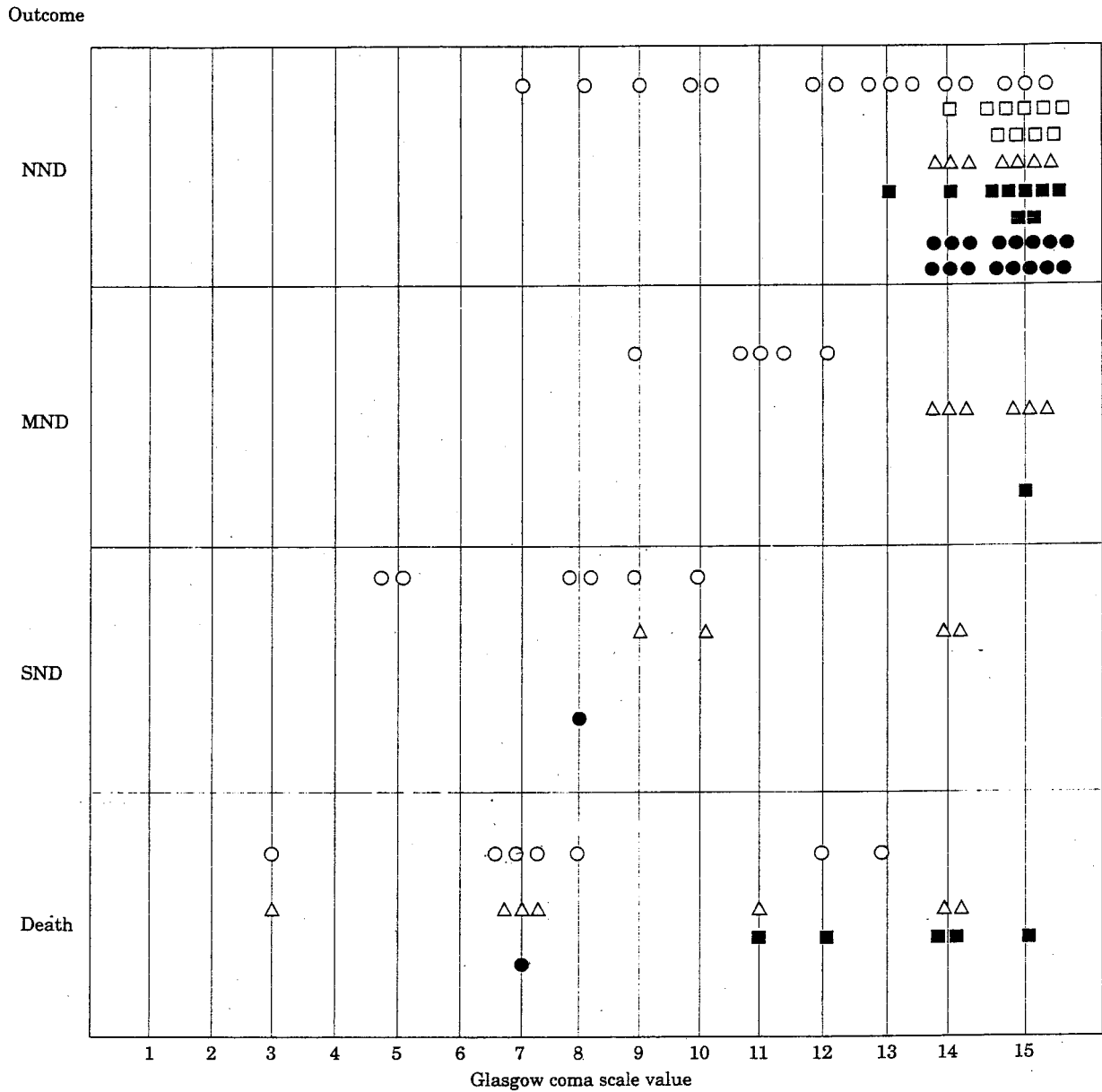
Table 1. Glasgow coma scale.

Eyes open	Spontaneously	4
	To verbal command	3
	To pain	2
	No response	1
Best motor response	Obeys	6
	Localizes	5
	Flexion-withdrawal	4
	Flexion-abnormal	3
	Extension	2
	No response	1
Best verbal response	Oriented	5
	Disoriented	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
		15

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Table II. Patient outcome categories versus Glasgow coma scale.



compared to determine whether they differed significantly with respect to the GCS value at admission, the age of the patients, the CSF-neutrophil count, the CSF-protein and the CSF-glucose levels.

#### Patients and Methods

In 100 consecutive adult patients with meningitis the GCS (Table I) was determined at admission. The cases included the following types of meningitis: 33 patients

with bacterial meningitis (24 with *Streptococcus pneumoniae*, four with *Neisseria meningitidis*, and one each of *Escherichia coli*, *Enterobacter* spp., beta hemolytic streptococcus, group B *Streptococcus* and *Klebsiella pneumoniae*), 24 patients with TB meningitis, 15 patients with Cryptococcal meningitis, 10 with viral meningitis, and 18 with meningitis of unknown aetiology (seven had CSF findings in keeping with bacterial meningitis but cultures were sterile, four had otitis, sinusitis or pneumonia with meningeal signs and symptoms and active CSF, and seven had clinical and CSF findings compatible with viral men-

Table III. Summary statistics in outcome categories.

	Outcome category	N	Median	Range
Age	NND	56	30	14-75
	MND	13	26	15-64
	SND	11	28	21-46
	D	20	35.5	15-70
GCS	NND	56	15	7-15
	MND	13	14	9-15
	SND	11	9	5-14
	D	20	9.5	3-15
CSF-N (/mm <sup>3</sup> )	NND	56	4.2	0-17 050
	MND	13	201	0-33 000
	SND	11	2136	0-16 010
	D	20	114	0-48 130
CSF-P (mg/l)	NND	56	1240	310-8562
	MND	13	2160	180-9090
	SND	11	5870	1440-13 320
	D	20	2210	200-17 700
CSF-Gl (mmol/l)	NND	56	2.25	0-5.1
	MND	13	1.6	0-6.4
	SND	11	0.3	0.1-3.4
	D	20	0.9	0.1-5.2

NND, no neurological deficit; MND, minor neurological deficit; SND, severe neurological deficit; D, death; CSF-N, CSF-neutrophil count; CSF-P, CSF-protein level; CSF-Gl, CSF-glucose level.

ingitis but had been started on antibiotics by the attending physician). After adequate treatment of the specific type of meningitis, the outcome of the patient was assigned to one of four categories: no neurological deficit (NND); minor neurological deficit (MND), i.e. some neurological sequelae but could return to former level of functioning; severe neurological deficit (SND), i.e. severe deficit prohibiting former level of functioning; death (D).

### Results

A GCS value of more than 12 was found in 65 patients, 19 had values between 9 and 12, and 16 less or equal to 8. Of the group with a GCS >12, 75.3% were healthy after treatment, 12.3% had a minor neurological deficit, 3.1% a severe neurological deficit and 9.3% died. In the group with GCS values between 9 and 12, the percentage values were 26.3%, 26.3%, 26.3% and 21.1%, respectively, and in the group with a GCS value of  $\leq 8$  the values were 12.5%, 0%, 25% and 62.5%, respectively (Table II).

In the viral meningitis group, (10 patients) all patients recovered without neurological sequelae, as is expected. The lowest GCS value at admission was 14/15 (one patient).

In the bacterial meningitis group (33 patients) 15 recovered fully, five had a minor neurological deficit, six a severe neurological deficit, and seven died. All patients with a GCS value of  $\leq 8$  either died or had severe

neurological deficits except two patients: in one, severe diabetic ketoacidosis probably contributed to the low initial GCS value (7/15); the other, with a GCS of 13/15 who died, had a biochemical disorder with hyperkalemia and subsequent ventricular fibrillation.

In the TB meningitis group (24 patients), seven recovered without sequelae; six had minor neurological deficits, four severe neurological deficits and seven died. In the Cryptococcal meningitis group (15 patients) nine recovered fully; one had a minor neurological deficit, and five died. Interestingly, in this chronic meningitis subgroup (TB and Cryptococcal meningitis) even GCS values of 14/15 were associated with a poor outcome in 6/12 patients, while only one of 10 patients with a GCS value of <14 survived without sequelae.

The summary statistics for the outcome categories are shown in Table III. From a non-parametric one-way analysis of variance (Kruskal-Wallis), it was found that with respect to mean GCS-values significant differences were present among the outcome categories (NND, MND, SND, D) ( $P < 0.0001$ ). In particular, by making use of pairwise comparison, it was found that neither NND and MND nor SND and D differed; however, the favourable outcome groups (NND and MND) were significantly different from the adverse outcome groups (SND and D). In this study the outcome categories did not differ significantly with respect to age, CSF-neutrophil count or CSF-glucose level. However, the outcome groups differed significantly with respect to the protein level ( $P = 0.0025$ )



in the CSF, in particular in outcome categories NND and SND.

### Discussion

There has been an ongoing search for clinical parameters to determine the prognosis of patients with meningitis. Extremes of age, a very short duration of illness,<sup>5,6</sup> as well as a long duration of symptoms,<sup>4,7</sup> the presence of coma, and a number of CSF findings,<sup>5,10,12</sup> have all been associated with a poor outcome.

The GCS is widely known, objective and easy to assess in patients and reflects the depth of impaired consciousness and coma.<sup>1</sup> The use of an objective scale facilitates consultations between referral and tertiary hospitals and can lead to a more accurate determination of prognosis. As was expected, the GCS value at admission was shown to be an accurate prognostic indicator in patients with meningitis in this study. Although the outcome categories also differed significantly with respect to the CSF-protein values, this difference was not as marked as with the GCS value.

In chronic meningitis even a slight degree of impairment of consciousness (GCS 14/15) probably reflects the severity and duration of the disease, thus possibly accounting for the relatively more grave prognosis even with a high GCS value.

In conclusion, it was found in this study that a GCS value of >12 was associated with a good neurological outcome in 88% of patients. A GCS value of ≤ 8 predicted

a poor outcome in 88% of patients. In addition, the GCS value at admission was found to be a better prognostic indicator than high CSF-protein levels. However, in the chronic meningitis subgroup a higher GCS value seemed to be a prerequisite for a good outcome.

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# The Impact of HIV on Meningitis as Seen at a South African Academic Hospital (1994 to 1998)

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## Summary

**Background:** The increase in HIV infections in South Africa is alarming. The aim of this prospective 4-year study was to evaluate the rising incidence of HIV-related admissions due to meningitis at the Pretoria Academic Hospital (PAH) adult neurology ward and to investigate the spectrum of meningitis during this time.

**Patients and Methods:** Adults with meningitis presenting at the PAH neurology ward from March 1994 through February 1998 were included. HIV antibody status was determined and patients were assigned to five categories: bacterial, tuberculous, viral and cryptococcal meningitis, as well as an uncertain category.

**Results:** Over the 4-year study period 141 patients with meningitis were seen. Of these, 44 were HIV-positive (31%), with TB meningitis occurring in 16 (36%), cryptococcal meningitis in 22 (50%) and acute bacterial meningitis in three (7%). In the first 2 years of the study, 14% of patients were HIV positive; this figure rose to 44% in the 3rd year, and 57% in the final year. The spectrum of meningitis also changed: bacterial meningitis remained relatively stable at about 25% of the total; TB meningitis almost doubled from 16% in the 1st year to 31% in the last year of the study; viral meningitis initially occurred in 8% of patients and later in 3% of cases, while cryptococcal meningitis showed the most significant increase from 6% of cases in 1994/5 to 31 and 26% respectively in the last 2 years of the study.

**Conclusion:** Over a 4-year period the HIV epidemic was responsible for a marked shift in the spectrum of meningitis towards chronic infections such as TB and cryptococcal meningitis at the PAH.

## Key Words

HIV · Meningitis · Chronic infections

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## Introduction

Even though potent antibiotic therapies have been developed over the past decades, meningitis remains a frighten-

ing disease with a high morbidity and mortality, particularly in developing countries. In addition, the HIV epidemic in South Africa has changed the face of many hospital wards and units over the 4 years. It is well known that HIV infection is a risk factor for the development of tuberculous meningitis (TBM) in particular [1]. Admissions due to HIV-related infections, especially meningitis, are thus increasing parallel to the HIV seropositivity in the general population [2]. In 1994 the point prevalence rate of HIV infections in South African antenatal clinic attenders was 7.6%; this had risen to 14.2% by 1996 (data from Department of Health, RSA). The highest levels of HIV infections are found in the eastern provinces of South Africa.

This prospective study, which forms part of an ongoing meningitis project at the Pretoria Academic Hospital (PAH), was performed to evaluate the rising incidence of HIV-related admissions due to meningitis at the PAH's adult neurology ward over a 4-year period and to investigate the spectrum of meningitis seen during this time.

## Patients and Methods

Patients with meningitis presenting at the adult neurology ward of the Pretoria Academic Hospital from the beginning of March 1994 to the end of February 1998 were included in this study. The PAH is a 1,000-bed urban academic and general hospital and acts as a referral hospital for Pretoria and surrounding areas as well as a large part of the northern regions of South Africa. Because of changes in the referral system, more patients from peripheral hospitals were seen in the 1st year of the study. The neurology department admits patients directly from casualty or outpatient departments and primarily looks after patients with meningitis in the ward. The specific criteria for inclusion were headache with or without meningism together with an active CSF, and an age above 13 years. HIV-antibody status was determined in all patients as far as possible.

The patients were assigned to five categories: bacterial, tuberculous (TB), viral and cryptococcal meningitis, as well as an uncertain category.

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The final diagnosis of bacterial meningitis was only made when CSF cultures were positive; in this way, some patients were initially treated for bacterial meningitis on clinical suspicion (high CSF neutrophil counts, high protein and low glucose levels) but were later shifted to the "uncertain" category because of a lack of microbiological proof.

The final diagnosis of tuberculous meningitis was made when CSF cultures were positive or evidence of TB was found in other sites with active CSF, or when the patient's clinical and CSF findings were compatible with TB meningitis and the patient responded to antituberculous treatment.

Viral meningitis was only diagnosed when CSF findings were typical, a repeat lumbar puncture did not show an increase in neutrophils, and the patient showed clinical improvement within 24 h. The final diagnosis of cryptococcal meningitis was made when the CSF cultures were positive for *Cryptococcus neoformans*, although India ink staining and cryptococcal latex agglutination were also performed on most patients.

Whenever the diagnosis remained uncertain or when patients had received antibiotics before admission for any reason, eg, otitis, sinusitis, etc., they entered the "uncertain" category and were treated as for bacterial meningitis. In selected "uncertain" cases, TB treatment was added. In the statistical analysis, the proportions of patients were compared using chi-square tests.

## Results

### Patients and Etiology

Over the 4-year study period 141 patients with meningitis were seen. Of these, 102 were black, 36 Caucasian, and three of mixed ancestry. Bacterial meningitis occurred in 37 patients (26%), 33 (23%) had TBM, eight (6%) viral meningitis and 24 (17%) cryptococcal meningitis. 39 (28%) patients were assigned to the "uncertain" category (Table 1).

A total of 44 HIV-positive patients was seen (31%), the vast majority being heterosexual black patients (38/44, 75%). TBM occurred in 16/44 (36%), cryptococcal meningitis in 22/44 (50%) and acute bacterial meningitis in 3/44 (7%) (Table 2). The three Caucasian HIV-positive patients were homosexual males with cryptococcal meningitis, while the three patients of mixed ancestry with HIV had TBM.

	TBM (n = 33; 23%)	ABM (n = 37; 26%)	CRY M (n = 24; 17%)	AVM (n = 8; 6%)	Uncertain (n = 39; 28%)
M : F	17 : 16	31 : 6	14 : 10	5 : 3	16 : 23
Age (mean)	15-48 (29)	15-68 (36)	25-62 (37)	16-65 (31)	15-81 (35)
HIV-positive	16/33 (48%)	3/37 (8%)	22/24 (92%)	0	3 (8%)
Mortality	9/33 (27%)	8/37 (22%)	9/24 (38%)	0	2 (5%)

TBM: tuberculous meningitis, ABM: acute bacterial meningitis, CRY M: cryptococcal meningitis, AVM: acute viral meningitis

Table 2

Spectrum of meningitis in HIV-positive patients.

	No. of cases
M : F	24 : 20
TBM	16/44 (36%)
CRY M	22/44 (50%)
ABM	3/44 (7%)
Other ("uncertain")	3/44 (7%)
Mortality	11/44 (25%)

TBM: tuberculous meningitis, ABM: acute bacterial meningitis, CRY M: cryptococcal meningitis

In 41/44 patients the episode of meningitis first brought to their attention that they were HIV positive. Most patients claimed that they had been healthy and well until then. CD4 counts were not performed routinely on HIV-positive patients; however, in 13 patients with TBM where the counts were performed, the values ranged from 6.6 to 340 × 10<sup>6</sup>/l (mean 147), and in 15 patients with cryptococcal meningitis from 3.2 to 18.8 × 10<sup>6</sup>/l (mean 86.4).

In the first year of the study (March 1994 to end February 1995), 51 adult patients with meningitis were seen. Of these, HIV seropositivity was found in 8/49 patients (16% HIV positive). The spectrum of meningitis for this period is illustrated in table 3. 22 patients were classified as "uncertain" – of these, four had parameningeal infections with active CSF, four had received antibiotics before admission and five were probably viral meningitis cases but had already been started on antibiotics by the first attending physician. Seven patients had CSF findings compatible with bacterial meningitis (high neutrophil counts, high protein and low glucose levels) but CSF cultures were negative – thus, these patients could possibly also have been classified as bacterial meningitis. One patient was later diagnosed as having cysticercal meningitis and one as having carcinomatous meningitis. Of the patients who were HIV positive, five had TBM and two cryptococcal meningitis, and one patient had meningitis due to a *Streptococcus* group B infection. Thus, 7/8 HIV-positive patients had a form of chronic meningitis.

During the 2<sup>nd</sup> year of the study from March 1995 to February 1996, 25 patients with meningitis were admitted. Of these, 4/21 were HIV positive (16%). The spectrum of meningitis is shown in table 3. All patients who were HIV positive had chronic meningitis – two had tuberculous and two cryptococcal meningitis. Six patients had meningitis of "uncertain" etiology; one had a parameningeal infection with



active CSF, and five probably had viral meningitis but had already received antibiotics from the first attending physician.

In the period from March 1996 to February 1997, 29 patients with meningitis were seen. HIV seropositivity was found in 12/27 patients (44%) – a marked increase in comparison to the previous year. The data of the patients are also shown in table 3. Five patients were categorized as “uncertain:” two had parameningeal infections, two probably had viral meningitis but had been treated with antibiotics, and one was treated for both bacterial and tuberculous meningitis although microbiological proof was not found. In the HIV-positive group, chronic meningitis was found in 10/12 patients (nine cryptococcal, one tuberculous); one had bacterial meningitis (pneumococcal) and one probably had viral meningitis.

During the last year of the study from March 1997 to February 1998, 36 patients with meningitis were seen and included in the study. 20/35 patients (57%) were found to be HIV positive – at least every second patient admitted with meningitis thus was HIV positive. Table 3 also shows the spectrum of meningitis for this year. Six patients had meningitis of “uncertain” etiology; of these, two patients had CSF findings in keeping with bacterial meningitis but cultures were sterile, three probably had viral meningitis but had already received antibiotics, and one patient was treated for both bacterial and tuberculous meningitis even though all cultures were sterile. Of the 20 patients who were HIV positive, chronic meningitis was found in 17 (85%) – eight had TBM and nine cryptococcal meningitis; one patient had bacterial meningitis due to *Streptococcus*

Table 3  
 Etiology and distribution of meningitis.

	March 1994 – Feb 1995	March 1995 – Feb 1996	March 1996 – Feb 1997	March 1997 – Feb 1998
	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
Bacterial meningitis	14 (27%)	7 (28%)	7 (24%)	9 (26%)
Tuberculous meningitis	8 (16%)	8 (32%)	6 (21%)	11 (31%)
Viral meningitis	4 (8%)	1 (4%)	2 (7%)	1 (3%)
Cryptococcal meningitis	3 (6%)	3 (12%)	9 (31%)	9 (26%)
“Uncertain” and other type of meningitis	21 (44%)	6 (24%)	5 (17%)	5 (14%)

*pneumoniae*, while one probably had viral meningitis and one was treated for both tuberculous and bacterial meningitis because of ambiguous CSF and clinical findings.

Of the 33/141 (23%) patients with TBM, 20/33 (61%) had definite proof of tuberculosis with either CSF cultures positive or proof of tuberculosis in another site in addition to typical CSF findings. The remaining patients had negative cultures but improved on antituberculous treatment. 16 patients with TB meningitis were HIV positive; 10/16 (63%) did have microbiological proof of TB. Thus, the incidence of positive identification of TB was the same ( $p = 0.89$ ) in the TBM groups with or without HIV infection [17/33 HIV negative with TB meningitis, positive proof for TB in 10/17 (59%)].

The etiology and frequencies of bacterial meningitis are illustrated in figure 1. In the three HIV-positive patients with bacterial meningitis, a pneumococcal infection was the cause in two and *Streptococcus* group B infection in one.

#### Mortality

Of the 141 patients with meningitis seen over the 4-year period, 27 died (mortality: 19%). Of these 27 patients, ten were HIV negative, 11 were HIV positive and in six patients the HIV status was not determined – in most cases because the patient died before the test could be done. Thus 11/44 HIV-positive patients died (25%), eight as a result of cryptococcal meningitis and three due to TBM. The mortality in the HIV-infected group of patients was more than double that of the HIV-negative/not tested group (11/98: 11%), but due to the small numbers this did not reach statistical significance ( $p = 0.06$ ).

#### Four-Year Spectrum

When analyzing the spectrum of meningitis over the 4-year period (Table 3), it can be seen that bacterial meningitis remained relatively stable at about 25% of the total;

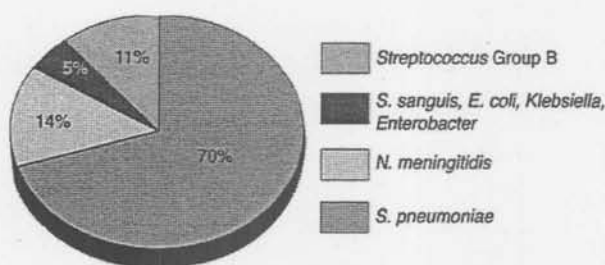


Figure 1  
 Etiology and frequency of bacterial meningitis.

TBM almost doubled from 16% in the 1st year to 31% in the last year of the study; viral meningitis was initially seen in 8% of patients and by the end of the study period in 3% of cases, while cryptococcal meningitis showed the most significant increase from 6% of total meningitis cases in 1994/5 to 31 and 26%, respectively, in the last 2 years of the study. The yearly increase in HIV-positive cases is shown in figure 2.

### Discussion

While the incidence of HIV infection in developed countries is declining, the epidemic in developing countries is still expanding at an alarming rate [2, 3]. In the short time interval of 4 years – from 1994 to 1998 – the incidence of HIV-related admissions due to meningitis has increased from one in six patients to more than one in two patients at the PAH. This obviously has grave implications for the future costs of the health sector.

Together with the increase in HIV seropositivity, the spectrum of adult meningitis has shifted over the past 4 years. A recent study from the Baragwanath Hospital [4], predicted an increase of tuberculous and cryptococcal meningitis due to the HIV epidemic and speculated that the incidence of pneumococcal meningitis might also increase. In the PAH study the most noteworthy increase has been in cryptococcal meningitis (from 6% of all admissions in the 1st year to 26% in the final year), as well as in TBM (from 16% of total admissions to 31% in the last year). While there have been reports of a high risk of pneumococcal bacteremia in HIV-positive patients [5] and predictions of an anticipated overwhelming increase in bacterial meningitis in South Africa, this study does not substantiate this. Only three HIV-positive patients (7%) had bacterial meningitis in this study.

In this study, the overwhelming majority (41/44) of HIV-positive patients was not aware of their HIV status, presenting *de novo* with an AIDS-defining illness in the form of TB or cryptococcal meningitis in 38/41 patients. As expected, the CD4 counts that had been performed, showed very low values – with an interesting tendency towards counts of below  $100 \times 10^6/l$  in the cryptococcal meningitis group. In this group 4/15 patients had CD4 counts below 20.

Worldwide, mortality rates in meningitis remain high despite adequate treatment. For pneumococcal meningitis, mortality rates still range between 19 and 40% [6–8]; the mortality for bacterial meningitis at the PAH was 22% with a specific mortality for pneumococcal meningitis of 23%. This relatively high mortality rate might be a reflection of late presentation of many of the patients, as well as the small number of ICU beds available for medical patients. Studies reporting on the mortality rates in TBM reveal figures between 20 and 30% [9]. A recent study [10] found that HIV status did not affect survival in TBM – our findings seem to support this, since 19% of TBM patients with HIV and 35% of HIV-negative/not tested patients died within 6 to 8 weeks. Contrary to TBM, the mortality of cryptococcal meningitis has been found to be higher in HIV-

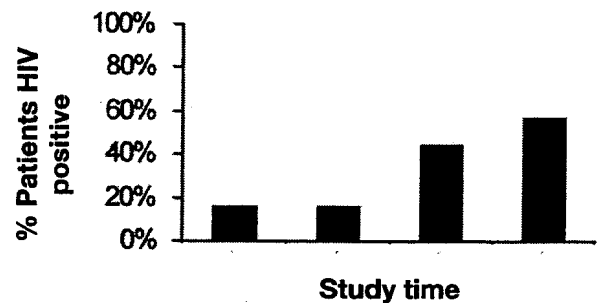


Figure 2  
Increase of HIV-related meningitis over the 4-year period (n = 44; 31% of total).

associated cases as compared to non-HIV-associated cases [11]. Most of our HIV-positive patients who died had cryptococcal meningitis, but no comparison could be made between non-HIV and HIV cases of cryptococcal meningitis as the number of non-HIV-related cases of cryptococcal meningitis was too small. Interestingly, all three patients with bacterial meningitis who were HIV positive, survived without any sequelae.

The male:female ratio in our bacterial meningitis patient population (84% of patients with bacterial meningitis were male; 81% of patients with pneumococcal meningitis were male) remains somewhat puzzling. A slight male predominance for pneumococcal meningitis is reported in the world literature [7, 12], but the marked majority of males in our study is noteworthy. It is remarkable that four of the five females with pneumococcal meningitis were above 55 years of age, while all male patients except one were below 55 years of age. The higher percentage of males with bacterial meningitis has also been commented on in another recent South African study [4]. Complex migration patterns of South African men have been suggested as possible underlying factors, but a higher incidence of head injuries and alcoholism in male South Africans compared to females might also play a role. However, at present, all these arguments remain speculative. In the other forms of meningitis – tuberculous, cryptococcal, as well as HIV-related cases of meningitis – the male:female ratios were approximately 1 : 1.

In conclusion, it can be stated that over a 4-year period the HIV epidemic was responsible for a marked shift in the spectrum of meningitis towards chronic infections such as tuberculous and cryptococcal meningitis as seen at a large urban academic and general hospital in South Africa.

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# Clinical, Cerebrospinal Fluid and Pathological Findings and Outcomes in HIV-Positive and HIV-Negative Patients with Tuberculous Meningitis

C.-M. Schutte

## Abstract

**Background:** The early diagnosis of tuberculous (TB) meningitis remains difficult. In South Africa, the HIV epidemic has shifted the spectrum of meningitis towards chronic infections (mainly tuberculosis [TB] and cryptococcosis). This study aimed to analyze clinical, cerebrospinal fluid (CSF) and pathological findings and outcomes in TB meningitis to evaluate whether HIV infection significantly influences the characteristic findings.

**Patients and Methods:** 40 consecutive patients with TB meningitis presenting at the Pretoria Academic Hospital were evaluated clinically and chest X-rays (CXR), computerized tomography (CT) brain scans, CSF profiles, HIV and routine blood tests were analyzed. Postmortem examinations (PM) were performed in seven patients and outcomes were assessed after treatment.

**Results:** 20 patients were HIV-positive and 17 were negative (three not tested). History and clinical findings were similar in both groups. The mean Glasgow Coma Scale (GCS) value on admission was 13 in both groups, while CXR showed abnormalities consistent with TB in 9/17 with HIV and 7/15 without, with abnormal CT brain scans in 15/19 patients with HIV and 12/16 without. Dilated ventricles and infarcts occurred more commonly in HIV-positive patients. The CSF results showed similar results in both groups. PM in three HIV-positive patients showed weakly formed granulomas and extensive endarteritis and infarcts. Outcomes were similar in the two groups, but a low GCS value on admission was a better prognostic indicator than the CD4-count in HIV-positive patients.

**Conclusion:** HIV infection does not significantly alter clinical and CSF findings in TB meningitis in South Africa, but ventricular dilatation and infarcts are more frequent in HIV-positive patients. The GCS gives a better indicator of prognosis than the CD4-count.

## Key Words

Tuberculous meningitis · HIV infection · Clinical findings · Outcomes

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## Introduction

Tuberculosis remains an endemic disease in South Africa with case notification rates of 194 per 100,000 population [1]. Diagnosing tuberculous (TB) meningitis when the patient first presents is still fraught with difficulties and patients are often treated empirically on clinical suspicion before proof of TB is obtained. Characteristically, TB meningitis develops insidiously, with CSF findings showing lymphocyte predominance, high protein and low glucose values and often elevated adenosine deaminase (ADA) levels. However, exceptions to the characteristic findings are often seen. HIV is a known risk factor for the development of CNS tuberculosis (TB) [2]. It has been shown that the HIV epidemic has shifted the spectrum of meningitis seen in South African hospitals towards chronic infections such as cryptococcosis and TB [3, 4].

The aim of this 5-year study, which is part of an ongoing meningitis study, was to analyze the clinical and CSF findings in adult HIV-positive and HIV-negative patients with TB meningitis and to compare the pathological findings and outcomes in the two groups of patients.

## Patients and Methods

40 consecutive adult patients with proven or clinically probable TB meningitis presenting at the neurology ward of the Pretoria Academic Hospital from March 1994 to June 1999 were included in the study. When either CSF cultures for TB or PCR for TB were positive ( $n = 16$ ), or Ziehl-Neelsen staining showed acid-fast bacilli ( $n = 0$ ) or postmortem (PM) confirmed caseating granulomas with meningeal exudates ( $n = 8$ ), the case was classified as definite TB meningitis. All cultured mycobacteria were *Mycobacterium tuberculosis*. All other patients who had TB at another site ( $n = 9$ ) with characteristic clinical and CSF findings or known previous TB who improved on TB treatment coupled with characteristic clinical and CSF findings ( $n = 4$ ) or showed improvement on TB treatment with characteristic clinical and CSF findings were classified as highly probable TB meningitis cases ( $n = 8$ ). Five of the patients

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on whom a PM was performed also had positive cultures. The patients with only suggestive CSF findings but no other proof of TB nor response to treatment (often because the patient passed away before tests could be done and PM could not be performed) were excluded from the study.

The patients were evaluated clinically and chest X-rays (CXR), CT brain scans, CSF profiles, and HIV and routine blood tests were analyzed. The HIV status was determined by the ELISA test and by Western blotting in all patients where possible. PM was carried out on seven patients.

Statistical analysis was performed using the Chi-square test to evaluate whether significant differences exist for specific tests between the two groups of patients. Since the number of patients is relatively small, OR and CI were then also calculated to further clarify whether HIV infection is a risk factor for specific results or outcomes.

### Results

Of the 40 patients included in the study over the 5-year period, 20 were HIV-positive (50%), 17 were HIV-negative (43%) and in three no HIV test had been done because the patients had passed away soon after admission. The three patients in whom the HIV test had not been performed were excluded from the reported results.

### Clinical Findings

According to the history, most patients had been unwell for almost 2 weeks (range: 2 days to 3 weeks), with an average of 9 days in the HIV-positive group and 11 days in the HIV-negative group. All patients with known history had complained of headache (34/34), and neck stiffness was a universal finding. In both the HIV-positive and HIV-negative groups, 75% of patients were febrile on admission. Two patients had a temperature of  $< 36^{\circ}\text{C}$ , both of whom passed away. On clinical examination, the level of consciousness of the patients was graded according to the Glasgow Coma Scale (GCS) on admission. The values ranged from three to 15 with a mean of 13/15 in both groups.

CXR were abnormal and in keeping with TB (either old or active) in 16/32 patients (50%), of whom nine were HIV-positive and seven were HIV-negative. Thus, HIV-pos-

itive and HIV-negative patients were equally likely to have an abnormal CXR (9/17 or 53% HIV-positive abnormal; 7/15 or 47% HIV-negative abnormal ( $p = 0.72$ , Chi-square; OR 1.29 (0.26–6.53)). The detailed results of the CXR illustrating the different patterns of radiological involvement are shown in table 1.

CT brain scans were abnormal in 27/35 patients (77%); 15/19 (79%) abnormal in the HIV-positive group and 12/16 (75%) abnormal in the HIV-negative group ( $p = 0.78$ , Chi-square; OR 1.25 (0.2–7.8)). The detailed results of the CT brain scans are shown in table 2. Hydrocephalus/enlarged ventricles were the most common findings with 16 patients showing a degree of ventricular dilatation. 50% of HIV-positive and 35% of HIV-negative patients showed ventricular dilatation ( $p = 0.37$ , Chi-square; OR 1.83 (0.4–8.56)). Infarcts also occurred in a much higher proportion of HIV-positive patients (40% infarcts in HIV-positive patients vs 6% in HIV-negative patients ( $p = 0.01$ , uncorrected Chi-square; Fisher's exact 2-tailed test,  $p = 0.02$ ).

The CD4-counts were performed only in HIV-positive patients, ranging from 6.6 to  $473 \times 10^6/\text{l}$  (mean  $180 \times 10^6/\text{l}$ ). Thus, all of the patients showed evidence of immunodeficiency when the lowest value for a normal CD4-count is taken as  $600 \times 10^6/\text{l}$ . 13 patients (76%) had CD4-counts of  $< 200 \times 10^6/\text{l}$ . The serum white cell counts (sWCC) ranged between  $2.2 \times 10^9/\text{l}$  and  $16.4 \times 10^9/\text{l}$  in the HIV-positive group (mean  $6.2 \times 10^9/\text{l}$ ), and 1.6 to 14.4 (mean  $8.2 \times 10^9/\text{l}$ ) in the HIV-negative group. The sWCC was  $< 11 \times 10^9/\text{l}$  in 19/20 (95%) and 14/17 (82%) of HIV-positive and HIV-negative patients, respectively ( $p = 0.21$ , Chi-square; OR 4.07 (0.31–113.7)).

### CSF Findings

The results of the CSF analyses are given in table 3. In comparing CSF parameters among HIV-positive and HIV-negative patients, the two groups were similar with respect to CSF lymphocyte counts, neutrophil counts, protein and glucose levels, and ADA values (unpaired t-test; Welch correction). The HIV-positive group did show a trend towards higher CSF lymphocyte counts (mean 164 in HIV-positive

Table 1  
Results of chest X-ray findings in patients with tuberculous meningitis.

	HIV-positive (N = 17)	HIV-negative (N = 15)
Miliary TB	3	3
Infiltrate	4	1
Effusion	1	1
Bronchopneumonia	1	2
Old TB/pleural thickening	–	2
Normal	8	8

TB: tuberculosis; some patients had more than one abnormality on chest X-ray

Table 2  
Results of CT brain scans in patients with tuberculous meningitis.

	HIV-positive (n = 19)	HIV-negative (n = 16)
Hydrocephalus/ enlarged ventricles	10	6
Meningeal enhancement	3	5
Infarction	8	1
Granuloma	2	3
Edema	1	1
Normal	4	4

Some patients had more than one abnormality on computerized tomography scan



patients vs mean 96 in HIV-negative patients), but this did not reach statistical significance, possibly due to the small numbers. Hypoglycorrhagia was seen in 80% of HIV-negative and in 75% of HIV-positive patients.

### Pathological Findings

PM was performed on 7/9 patients. Of the seven patients, three were HIV-positive and four were HIV-negative. In the HIV-positive cases only the brain was examined. One HIV-positive patient showed necrosis of brain tissue on the base of the brain with involvement of both temporal lobes, the corpora mammilaria and the optic chiasm, together with extensive meningoencephalitis. A dense inflammatory infiltrate of plasma cells and lymphocytes was present with weakly formed granulomas and TB bacilli. The other HIV-positive patients both showed hydrocephalus, one with right-sided uncal and cerebellar tonsillar herniation and communicating hydrocephalus, the other with diffuse slight dilatation of the whole ventricular system. In both patients, infarcts were present; one in the area of the left basal ganglia with TB endarteritis and weakly formed granulomas histologically and one in the areas around the longitudinal fissure with caseating necrosis and TB endarteritis. Chronic inflammatory exudates were also present in both patients in the subarachnoid space.

In the HIV-negative patients, hydrocephalus was found in two patients with uncal herniation in two and tonsillar herniation in one patient. A chronic basal inflammatory exudate was found in all cases subarachnoidally, with well-differentiated TB granulomas and focal cortical involvements but no infarcts. Miliary tuberculosis in other organs was found in all HIV-negative patients, including the lungs, liver, spleen and lymph nodes.

### Outcome

The patients were grouped according to outcome, with a good neurological outcome in patients with no neurological deficit (NND) or only a minor neurological deficit (MND), i.e. they did have evidence of a neurological lesion but could return to former level of functioning, and an adverse outcome in patients who either died or had a severe neurological deficit (SND), i.e. were bedridden/could not return to former level of functioning. In total, 13/20 (65%) HIV-positive patients and 10/17 (59%) HIV-negative patients had a good outcome ( $p = 0.69$ , Chi-square test; OR 0.77 (0.16–3.56)), but interestingly, HIV-positive subjects were more than twice as likely to suffer no neurological deficit on discharge than HIV-negative patients. 12/20 (60%) HIV-positive patients had no neurological

deficit compared to 5/17 (29%) HIV-negative patients ( $p = 0.06$ , Chi-square; OR 0.28 (0.05–1.33)). Although this did not reach statistical significance, it showed a trend towards better outcome in the short term in the HIV-positive group. An adverse outcome (SND or death) was found in 7/17 (41%) HIV-negative and 8/20 (40%) HIV-positive patients, respectively. The two groups were similar regarding adverse outcome ( $p = 0.9$ , Chi-square; OR 0.94 (0.21–4.34)).

The GCS value was a good predictor of outcome in these patients; all patients with a GCS value of eight or less died, while a value of 14–15 was associated with a good outcome in 20/25 patients (80%), of whom nine were HIV-negative and 11 were HIV-positive. The results of the GCS value vs outcome are shown in figure 1.

Ventricular dilatation (occurring more commonly in HIV-positive patients) was associated with an adverse outcome (SND or death) in 9/16 (56%) patients. Of the eight HIV-positive patients with infarcts on CT scan, four died (50%). When comparing the GCS on admission with the CT scans (which were mostly done within 24 h of admission) it can be seen that all patients with normal scans (8/38) had GCS values of 14 or 15. However, when considering all 25 patients with GCS values of 14–15, abnormal scans were still found in 15 (60%), including five patients with granulomas and six with hydrocephalus/dilated ventricles.

In this study, the CD4-counts did not give a good indication of the prognosis of a patient with HIV and TB meningitis. Of the 11 patients with CD4-counts of  $< 150 \times 10^6/l$ , six had a good outcome and five had an adverse outcome (SND or death). However, no patient with a CD4-count of  $> 250 \times 10^6/l$  died (Figure 2).

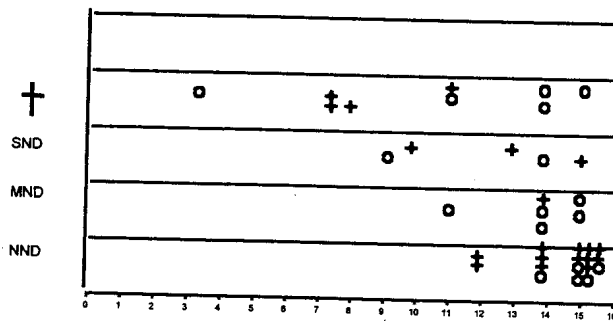
### Discussion

The HIV epidemic in South Africa is still expanding at an alarming rate. Coupled with an endemic disease like tuberculosis, the combination may be devastating. Even in

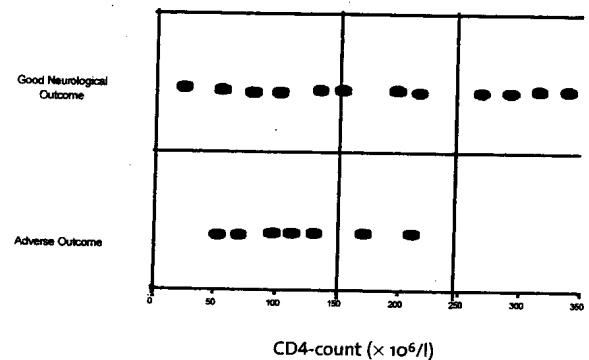
Table 3  
CSF analysis of patients with tuberculous meningitis.

	CSF-L (mean)	CSF-N (mean)	CSF-P (mean)	CSF-G (mean)	CSF-ADA (mean) n = 33
HIV+ve (n = 20)	0–385 (164)	0–293 (69)	1,210–11,522 (2,880)	0.6–6.4 (1.9)	2.5–28.5 (12.6) (n = 18)
HIV-ve (n = 17)	0–275 (96)	0–442 (87)	200–9,220 (3,476)	0.8–5.2 (1.7)	2.2–25.1 (13.5) (n = 15)
P (Welch unpaired t-test)	0.07	0.62	0.51	0.66	0.67

HIV+ve: HIV-positive; HIV-ve: HIV-negative; CSF-L: CSF lymphocyte count/mm<sup>3</sup>; CSF-N: CSF neutrophil count/mm<sup>3</sup>; CSF-P: CSF protein value mg/l; CSF-G: CSF glucose value mmol/l; CSF-ADA: CSF adenosine deaminase level IU/l



**Figure 1.** GCS on admission vs outcome after treatment in patients with TB meningitis. (‡: Death; SND: Severe neurological deficit; MND: Minor neurological deficit; NND: No neurological deficit; GCS: Glasgow Coma Scale; + HIV-positive; o: HIV-negative)



**Figure 2.** CD4 count vs outcome.

HIV-negative patients, TB meningitis is difficult to diagnose. With the decrease in immunity in HIV it was feared that TB meningitis could be missed or that the characteristic findings would be obscured. In the literature no recent prospective study could be found addressing the differences of TB meningitis in HIV-positive and HIV-negative patients. One recent retrospective study spanning 12 years and incorporating 31 patients reported no discernable effects of HIV on the findings in TB meningitis [5]. Other studies have found radiological or CSF differences between HIV-positive and HIV-negative patients [6, 7].

TB meningitis usually develops insidiously [8, 9]. In this study, patients were on average symptomatic for less than 2 weeks, a relatively short time. No patients had reported symptoms for more than 3 weeks and no useful correlation could be made between duration of disease and eventual outcome. The most common presenting symptom was headache and a low-grade temperature occurred in 75% of both the HIV-positive and HIV-negative patients.

Previous studies have reported on CT findings in HIV-positive patients with TB meningitis. One retrospective study reported a higher incidence of mass lesions in HIV-positive patients [6], while another study reported a high incidence of hydrocephalus. In our study, the classic findings of meningeal enhancement on CT scanning of the brain in chronic meningitis occurred in only 8/35 patients, but hydrocephalus/dilated ventricles were present in 16 patients, occurring almost twice as frequently in HIV-positive patients compared to HIV-negative patients. Infarcts were also more commonly found on CT scanning of the brain in HIV-positive patients. 40% of HIV-positive patients had infarcts (half of whom subsequently died), compared to only 6% of HIV-negative patients. A high GCS value on admission did not predict a normal scan; an important finding since radiology departments are sometimes reluctant to perform urgent scans on alert-looking patients. In this study 60% of patients with a GCS value of 14–15 had abnormalities on CT scan, leading to neurosurgical consultations in at least five patients.

All the HIV-positive patients in this study had low CD4-counts and 12/19 (63%) had counts of less than  $200 \times 10^6/l$  indicating a severe degree of immunocompromise. Due to cost restraints, viral load testing could not be carried out in our patients. In most patients the TB meningitis was the presenting feature of their positive HIV status and, at the same time, the AIDS-defining illness. There was no correlation between the CD4 count and clinical outcome after treatment in our study, as almost half of all patients with very low CD4-counts still recovered fully. This contrasts with findings in other studies where a low CD4-count implied an adverse prognosis [7]. The sWCCs were normal in the majority of patients, although there was a propensity to lower counts in the HIV-positive patients (mean  $6.2$  vs  $8.2 \times 10^6/l$  in HIV-negative patients).

The CSF findings were similar in both HIV-positive and HIV-negative patients in this study. A recent report of 31 patients with TB meningitis showed a higher incidence of hypoglycorrhachia in the HIV-positive patients (84% vs 50% in HIV-negative patients) [5]. In this study no such difference was found: 75% of HIV-positive and 80% of HIV-negative patients had CSF glucose values of  $< 2.2$  mmol/l. Interestingly, in this study the HIV-positive patients showed a trend towards higher CSF lymphocyte counts, but this did not reach statistical significance due to the still small number of patients. The mean ADA levels (12.6 IU/l and 13.5 IU/l in the HIV-positive and HIV-negative groups, respectively) were also similar in the two groups with 28/33 (85%) patients having values  $> 6$  IU/l. In previous studies it has been suggested that a higher cutoff point for ADA values might improve the diagnostic yield for TB meningitis; in this study 20/33 (60%) patients had values  $> 10$  IU/l. Definite proof for TB (cultures, Ziehl-Neelsen staining, PM positive) was present to the same extent in both groups, as was also found in the study by Yechoor et al. [5]. In the cases with highly probable TB meningitis, cervical or axillary lymph node biopsies confirmed TB in three patients, as was also previously reported [10]. The newer diagnostic assays are not routinely performed at our hospital. The pathological findings confirmed



that granulomas are not as well formed in HIV-positive patients compared to HIV-negative patients. Evidence of endarteritis causing infarcts was found in two of the three HIV-positive patients in this study and border-zone encephalitis, with necrosis of brain tissue in the basal areas, in one.

In this study a correlation was found between stage of the disease according to the GCS value on admission and ultimate outcome after treatment. This has also been reported previously [11]. The GCS is accurate, it is well known to medical staff and objective to use. A GCS value of  $\leq 8$  was associated with an adverse outcome in all patients, while a GCS of 14–15 predicted a good neurological outcome in 80% of patients. The findings were similar in both HIV-positive and HIV-negative patients, although HIV-positive individuals were twice as likely to be completely neurologically intact on discharge than HIV-negative patients. Similar studies did not find a correlation between stage of disease and outcome [5, 12], but different methods of classification were used with vague terminology. Other studies, however, have confirmed a correlation between stage of disease and outcome [8, 13].

Thus, in summary, this study found similar clinical features in HIV-positive and HIV-negative patients with TB meningitis, but ventricular enlargement and infarcts occurred more commonly in HIV-positive patients. Outcomes were similar in the two groups and the GCS value on admission was a better indicator of prognosis than the CD4 counts in HIV-positive patients.

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## Case report

### Lymph node biopsy as an aid in the diagnosis of intracranial tuberculosis

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**SUMMARY.** This report describes five patients with intracranial tuberculosis (TB): four with tuberculous meningitis and one with intracranial tuberculomas. In all cases the diagnosis was confirmed by excision biopsy of an enlarged cervical or axillary lymph node. The biopsies showed caseating granulomas and acid fast bacilli, confirming the diagnosis of TB within 48 h of admission. Lymphnode biopsies may be an effective and practical aid in diagnosing intracranial TB.

**RÉSUMÉ.** Cette observation décrit cinq patients atteints de tuberculose intracrânienne: quatre atteints d'une méningite tuberculeuse et le cinquième porteur de tuberculomes intracrâniens. Dans tous les cas, le diagnostic de tuberculose a été confirmé par biopsie-excision d'un ganglion cervical ou axillaire hypertrophié. Les biopsies ont montré des granulomes caséifiés et des bacilles acido-résistants confirmant le diagnostic de tuberculose dans les 48 heures après l'admission. Des biopsies ganglionnaires pourraient être un moyen efficace et pratique d'aider au diagnostic de la tuberculose intracrânienne.

**RESUMEN.** Este trabajo describe pacientes con tuberculosis intracranial: cuatro con meningitis tuberculosa y uno con tuberculomas intracraniales. En todos los casos se confirmó el diagnóstico de tuberculosis por excisión biopsica de un ganglio cervical o axilar aumentado de volumen. Las biopsias mostraron granulomas caseosos y bacilos ácido-resistentes, confirmando así el diagnóstico de tuberculosis a las 48 horas después de la hospitalización. La biopsia ganglionar puede ser una ayuda eficaz y práctica para el diagnóstico de la tuberculosis intracranial.

The diagnosis of intracranial tuberculosis (TB), i.e. tuberculous meningitis or tuberculomas, is notoriously difficult. Very often the diagnosis is based on suspicion and response to treatment rather than on microbiological evidence. We report five patients, four with tuberculous meningitis and one with intracranial tuberculomas, whose diagnosis was confirmed within 2 days on lymph node biopsy. To our knowledge this is the first report of lymph node biopsies aiding in the diagnosis of intracranial TB.

#### CASE REPORTS

Patient 1, a 29-year-old female, had a 3-week history of headache, neck stiffness and fever. On admission, she was awake without focal neurological signs. She had neck stiffness, a temperature of 38.5°C and lymphadenopathy in the cervical and axillary regions. Cerebro-

spinal fluid (CSF) showed a protein level of 2060 mg/l, chloride 115 mmol/l, glucose 1.4 mmol/l (serum glucose 6.8 mmol/l), 251 lymphocytes/mm<sup>3</sup> and 10 neutrophils/mm<sup>3</sup>. Gram stain, capsular antigen and cryptococcus antigen tests were negative and culture yielded no growth. Polymerase chain reaction (PCR) for TB in the CSF was negative; adenosine deaminase (ADA) was 8.3 units/l. The patient was human immunodeficiency virus (HIV) positive, with a CD4 count of 110. Chest X-ray (CXR) showed a reticulonodular pattern, possibly in keeping with miliary TB, and the PPD was strongly positive (15 mm). Computed tomography (CT) brain scan showed a small granulomatous lesion in the right parietal area. Biopsy of a mobile, soft, rubbery cervical lymph node 1 cm in diameter showed acid-fast bacilli (AFB) and caseating granulomas, confirming the diagnosis of TB within 48 h of the patient's arrival at the hospital. She received only anti-TB treatment and improved rapidly.

Patient 2, a 20-year-old male, complained of headache, neck stiffness and fever for 10 days. Neurological examination showed only neck stiffness, a temperature of 38°C and cervical lymphadenopathy. In the CSF, the

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protein level was 3270 mg/l, chloride 100 mmol/l, glucose 1.1 mmol/l (serum glucose 6.8 mmol/l), lymphocytes 220/mm<sup>3</sup>, neutrophils 18/mm<sup>3</sup>, ADA 16.4 units/l. Gram stain, capsular antigen tests, cryptococcus antigen and culture were negative. CXR and CT brain scan were normal; PPD was positive (13 mm). Biopsy of a 1.5 cm diameter cervical lymph node showed caseating granulomas, and a diagnosis of tuberculous lymphadenitis was made though AFB were not reported.

Patient 3, a 32-year-old male, had a two-week history of headache, neck stiffness and fever. He presented after a generalized convulsion, was feverish with neck stiffness, and had loose, rubbery, enlarged lymph nodes in the axillary and cervical regions. The rest of his neurological examination was normal. CSF showed a protein level of 1970 mg/l, chloride 116 mmol/l, glucose 3.9 mmol/l (serum glucose 5.2 mmol/l), ADA 10.6 units/l, lymphocytes 12/mm<sup>3</sup> and no neutrophils. Capsular antigen tests, cryptococcus antigen, gram stain and culture were negative. The patient was HIV positive with a CD4 count of 100. CXR showed an interstitial pattern; on CT brain scan, basal meningeal enhancement and a lacunar infarct in the posterior limb of the left internal capsule were seen. An axillary lymph node of 1.5 × 2 cm diameter was biopsied, showing caseating granulomas, and AFB were seen on special staining. The patient improved on anti-TB medication. Eight weeks later, *Mycobacterium tuberculosis* was cultured from CSF.

Patient 4, a 56-year-old male, presented with focal and generalized convulsions and a left hemiparesis. He had no signs of meningeal involvement, but a CT brain scan showed multiple granulomatous lesions. Rubberly, mobile lymph nodes 1–2 cm wide were present in the cervical and axillary regions. CSF had a protein level of 1000 mg/l, chloride 120 mmol/l, glucose 2.9 mmol/l (serum glucose 5.0 mmol/l), ADA 0.7 units/l, one lymphocyte and 10 neutrophils/mm<sup>3</sup>. Capsular antigen tests, cryptococcus antigen, gram stain and culture were negative, as was PCR for TB. A reticulonodular pattern was seen on CXR and a biopsy of two axillary lymph nodes showed caseating granulomas and AFB. The patient improved on anti-TB treatment. *M. tuberculosis* was eventually cultured from the sputum.

Patient 5, a 40-year-old male, had a 3-month history of weight loss and malaise. Two weeks before admission he developed progressive headache and neck pain. Neurological examination was normal, except for terminal neck stiffness, a low grade fever of 37.6°C and cervical and axillary lymphadenopathy. The lymph nodes varied in size from 1–2 cm diameter, and were firm and mobile. CSF showed a protein level of 2190 mg/l, chloride 121 mmol/l, glucose 1.0 mmol/l (serum glucose 3.4), and 385 lymphocytes/mm<sup>3</sup>. Gram stain, capsular antigen and cryptococcus antigen tests were negative and culture did not yield any growth. PCR for TB was negative in the CSF, with an ADA level of 28.5 units/l. The patient was HIV positive with a CD4 count of 149. CXR showed a reticulonodular pattern, and CT brain scan was normal. A right axillary lymph node biopsy was performed within

24 h of admission, showing caseating granulomas typical of tuberculosis. AFB were present on special staining. The patient was started on anti-TB treatment alone and improved rapidly. Eight weeks later, *M. tuberculosis* was cultured from CSF.

## DISCUSSION

This report describes four patients with tuberculous meningitis and one with only intracranial tuberculous granulomas. In all patients the diagnosis of TB was confirmed by excision biopsy of enlarged lymph nodes showing AFB and/or caseating granulomas. In numerous reports in the literature the difficulty in diagnosing TB meningitis is stated.<sup>1,2</sup> Often the diagnosis is based on vague 'clinical and laboratory data compatible with TB' with no bacteriological histological confirmation. Newer tests, i.e. TB-antigen and PCR, are often unreliable,<sup>3,4</sup> as was also found in the three patients where CSF-PCR for TB was performed and found to be negative. CXR was suggestive of TB in four of the five patients, but sputum was difficult to obtain in all cases and can be negative even in miliary TB.

Whereas lymph node biopsies have been performed to diagnose pulmonary TB,<sup>5</sup> no reports in the literature could be found where they aided in the diagnosis of intracranial TB. In this report lymph node biopsies rapidly (within 2 days) confirmed the diagnosis of mycobacterial infection, leading to earlier and specific treatment. In all patients other causes of chronic meningitis (e.g. cryptococcus) were excluded, and it is important to note that every patient received only anti-TB treatment and improved rapidly.

In four patients AFB were detected in the histological specimens and *M. tuberculosis* bacilli were eventually cultured from the sputum or CSF in three. Unfortunately, no cultures were then taken from the lymph nodes; all lymph node specimens have since been sent for microscopy, culture and sensitivity, as susceptibility testing is of increasing importance in the era of multi-drug resistance and HIV infection.

Three patients were HIV positive. It is possible that tuberculous lymphadenopathy is more common in patients with HIV and intracranial TB than in non-HIV patients; further studies are needed to clarify this issue.

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# Discrimination Between Viral and Nonviral Meningitis by Visually Analyzed and Quantitative Electroencephalography

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## Key Words

Electroencephalography  
Glasgow Coma Scale  
Meningitis, Classification  
Quantitative EEG

## INTRODUCTION

The landmark studies of the EEG in meningitis revealed nonexistent or only mild abnormalities in viral (aseptic) meningitis<sup>1</sup> but more pronounced abnormalities in bacterial meningitis.<sup>2</sup> These reports appeared more than 35 years ago, and relatively few studies have been published in the past 2 decades.

The clinical value of the visually-analyzed EEG (VEEG) in meningitis seems limited. While certain VEEG signs may be of prognostic value,<sup>3</sup> a more recent study reported minimal VEEG contributions to information derived solely from clinical assessments.<sup>4</sup> In practice emphasis is placed on the evaluation of the level of consciousness. A comparison of findings on the Glasgow Coma Scale (GCS) and the VEEG in meningitis has not been previously reported.

Our literature survey failed to identify any studies using quantitative EEG (QEEG) techniques in meningitis. Further gaps in this sphere relate to the paucity of studies involving adults, perhaps due to the consistent finding of less marked abnormalities than in children.<sup>1,2</sup> Renewed interest in older patients with meningitis has been fueled by the HIV epidemic.<sup>5</sup>

The aims of the present study were to compare the extent to which the VEEG and QEEG discriminated between two broad categories of mostly adult meningitis patients, namely those requiring minimal treatment (a viral meningitis group) versus those patients requiring urgent intravenous antibiotics or antituberculous/antifungal treatment (a nonviral meningitis group). The EEG was also compared with the GCS.

## SUBJECTS

This was a prospective study of 55 patients with meningitis. Approval was obtained from an accountable ethics committee. Assessments took place within 48 hours of admission to hospital.

Inclusion criteria were: presence of headache,

meningismus, active CSF and an age of more than 13 years. The subjects ranged in age from 14-75 years (median, 30 years). There were 20 females and 35 males. The patients were assigned to one of four categories: viral (n = 12), bacterial (n = 19), tuberculous (TB) (n = 16) or cryptococcal (n = 8) meningitis. Viral meningitis was diagnosed when the patient's clinical and CSF findings were compatible with aseptic meningitis. Acute bacterial meningitis was confirmed when the CSF cultures were positive for *S.pneumoniae*, *N.meningitides* or any other bacteria. TB meningitis was diagnosed when the CSF and clinical findings were typical of chronic meningitis and the patient improved on antituberculous treatment, when CSF cultures were positive for *M.tuberculosis* or when the CSF and clinical findings were compatible with TB meningitis and evidence of tuberculosis was found in another site. Cryptococcal meningitis was confirmed when *C.neoformans* was cultured from the CSF. An additional 30 patients in whom the diagnosis was uncertain were excluded from analysis. Patients who could not be transported to the EEG laboratory by virtue of severity of disease were excluded from the study.

## METHODS

### VEEG

Electrodes, applied according to the International 10-20 System, were secured by adhesive paste. Impedances were < 5 kOhm. Either Nihon-Kohden models 4221, 4418 or 7310 were used for recordings. Bipolar and common reference montages were included. Eye movements were recorded from outer canthus electrodes referred to M2. The appearance of slow eye movements was used to assist in the identification of periods of drowsiness. Furthermore, normal slow wave variants such as posterior slow waves of youth and temporal theta and delta of the elderly were considered where appropriate.

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**Table 1**

	"Gold Standard"		Total
	Nonviral	Viral	
VEEG grade 3-4 (nonviral)	30	0	30
VEEG grade 0-2 (viral)	13	12	25
Total	43	12	55

VEEG: visually analyzed EEG

Analysis was performed by an experienced electroencephalographer (PB) blind to clinical data. A 5-point grading system was used as follows: grade 0, normal; grade 1, 6-7 Hz theta; grade 2, 4-5 Hz theta and/or delta occupying < 20% of the recording; grade 3, intermittent rhythmic delta activity (IRDA) and/or delta occupying > 20% of the recording; grade 4, persistent polymorphic, nonreactive delta activity (PDA). Epileptiform paroxysms were classified as either focal or generalized.

#### QEEG

Recordings were performed on Nihon-Kohden EEG systems, either model 4418 or 7310. The high pass filter setting was 0.2 Hz and the low pass setting was 35 Hz. Bipolar recording derivations were as follows: F4-C4, F3-C3, P4-O2, P3-O1, T4-T6, T3-T5. Recordings took place with the patient supine on a bed with eyes closed.

Stellate Systems Rhythm® version 3.0 programs were used. The digitizing rate was 128 Hz. Power was determined in 0.25 Hz steps by applying the Fast Fourier Transform to 45 epochs of 4 sec each, after the off-line editing of eye movement and muscle artifacts. Epochs containing EEG or eye movement signs of drowsiness were excluded. Recordings from obtunded patients were devoid of signs of drowsiness and specific EEG sleep features. The results of spectral analysis were summed into four frequency bands: delta (0.75-3.75 Hz), theta (4-7.75 Hz), alpha (8-13.0 Hz), and beta (13.25-31.0 Hz). Results were expressed on an amplitude ( $\mu$ V) scale. Absolute and relative values were obtained. The variables chosen for statistical analysis were the ratio of alpha amplitude to combined delta/theta amplitude from the six derivations recorded.

#### RESULTS

For purposes of analysis VEEG results were dichotomized by grouping grades 0-2 (normal to moderately abnormal) as opposed to grades 3-4 (markedly to severely abnormal). The VEEG grade of abnormality relative to the category of meningitis is shown in Table 1. The "gold standard" refers to diagnosis on clinical grounds or on the basis of microbiological findings.

The sensitivity of the VEEG for the prediction of nonviral

**Table 2**

	"Gold Standard"		Total
	Nonviral	Viral	
QEEG > 2.1 (nonviral)	32	2	34
QEEG $\leq$ 2.1 (viral)	8	9	17
Total	40	11	51

meningitis was 70% (30/43) and the specificity was 100% (12/12). The positive predictive value was 100% (30/30) while the negative predictive value was 48% (12/25).

Right-left comparisons were made of the respective QEEG variables using paired *t*-tests. There were no statistically significant ( $p > 0.05$ ) interhemispheric differences, and hence the mean ratios for left and right were calculated for each of the frontocentral, parieto-occipital and mid-post-temporal derivations. A two-way analysis of variance with main effects subjects and derivations revealed significant differences ( $p = 0.035$ ) between the derivations. The parieto-occipital mean ratio was significantly lower than both the frontocentral and temporal ratios. The parieto-occipital results were used for further analysis. The mean parieto-occipital ratio was significantly higher in nonviral (mean  $\pm$  SD = 4.22  $\pm$  2.62) than in the viral (mean  $\pm$  SD = 1.67  $\pm$  0.75) meningitis groups (two-sample *t*-test:  $t = 5.4$ ,  $p < 0.001$ ).

The optimal cut-off point to differentiate viral from nonviral meningitis was sought using the QEEG ratio of alpha/theta plus delta recorded from the parieto-occipital derivation. This operation was based on the sensitivity and specificity but with emphasis on minimizing false positives. Subjects with a ratio value  $\leq 2.1$  were classified as viral while  $> 2.1$  led to a classification as nonviral meningitis (Table 2).

The sensitivity of this QEEG variable for the prediction of nonviral meningitis was 80% (32/40), while the specificity was 82% (9/11). The positive predictive value was 94% (32/34) and the negative predictive value 53% (9/17).

GCS scores were dichotomized by grouping scores 13-15 (relatively intact) versus scores 3-12 (markedly to severely abnormal). The GCS scores relative to the category of meningitis are shown in Table 3.

The GCS achieved a sensitivity of 38% for the prediction of nonviral meningitis (16/42) and the specificity was 100% (12/12). The positive predictive value was 100% (16/16) and the negative predictive value 32% (12/38).

The Z-test was used to determine the degree of agreement between the VEEG grade of abnormality and the



**Table 3**

	"Gold Standard"		
	Nonviral	Viral	Total
GCS score 3-12 (nonviral)	16	0	16
GCS score 13-15 (viral)	26	12	38
<b>Total</b>	<b>42</b>	<b>12</b>	<b>54</b>

GCS: Glasgow Coma Scale

**Table 4**

	Cross-tabulation of subjects on the basis of VEEG gradings and GCS results	
	VEEG 0-2	VEEG 3-4
GCS 13-15	22	14
GCS 3-12	2	14

GCS (Table 4). The test result of 3.16 was statistically significant ( $p = 0.0007$ ). However, the Kappa statistic (0.394) was interpreted as indicating a poor degree of agreement (for moderate agreement the value is 0.4-0.75).

The occurrence of particular VEEG findings in relation to the category of meningitis is shown in Table 5.

#### DISCUSSION

The main thrust of this study was to assess the accuracy of the classification of meningitis patients into two broad categories, viral and nonviral on the basis of the VEEG and the QEEG, and to compare the EEG with the GCS. We are unaware of previous reports using this approach. The nonviral meningitis group in this study was heterogenous, consisting of acute bacterial meningitis patients as well as those with subacute or chronic forms of the disease (tuberculous or cryptococcal meningitis). Nevertheless, the rudimentary two-way classification attempted has potential clinical relevance.

The sensitivity of the VEEG and QEEG for the prediction of true positives, in this context patients with nonviral meningitis, attained the reasonably high values of 70% and 80%, respectively. In contrast, the sensitivity of the GCS was only 38%. Therefore, the proportion of nonviral meningitis patients having relatively abnormal test results, a highly desirable situation, was substantially higher for both EEG assessments than for the GCS. Each of the three tests had high positive predictive values of 94% or better. Therefore, the probability of a patient with one or more abnormal test results actually having nonviral meningitis was very high.

High specificities were attained by each of the three tests, 100% for the VEEG and GCS and 82% for the

**Table 5**

VEEG	The occurrence of particular VEEG findings in relation to the category of meningitis		
	N	Meningitis	
		Viral	Nonviral
Normal	6	6	0
Theta	12	5	7
Delta < 20%	7	1	6
Delta > 20%	4	0	4
IRDA	19	0	19
PDA	7	0	7

IRDA: intermittent rhythmic delta activity

PDA: polymorphic delta activity

QEEG. Adjustment of the QEEG criterion could have improved this value but only at the expense of lowering the sensitivity. The consistency with which true negatives were identified in this study, namely those patients with viral meningitis, was poor due to negative predictive values of only 53% in the case of the QEEG, 48% for the VEEG and 32% for the GCS. This was due to the marked overlap of relatively normal test results in both viral and nonviral meningitis categories with the GCS faring worst in this regard.

Taking account of particular VEEG abnormalities provided a way of increasing sensitivity. All but one patient with some form of abnormal delta activity had nonviral meningitis. The exception was a patient with the lowest grade of delta abnormality, namely delta occupying < 20% of the recording. All patients with the other categories of delta abnormalities, including IRDA and PDA had nonviral meningitis. At the other end of the spectrum, all normal VEEGs occurred in viral meningitis. Theta activity, on the other hand, had no discriminating implications with almost equal proportions falling in either category of meningitis.

This suggests an overall advantage for the VEEG over the QEEG. It should be borne in mind that our QEEG analysis was relatively basic in terms of the number of channels and type of signal processing used. Other QEEG strategies may fare better.

In conditions with impaired cerebral responsiveness there is generally a correlation between the EEG and measures of the impairment of consciousness.<sup>6</sup> Our findings of a statistically significant concordance between the VEEG grading of abnormality and the GCS concurs with this statement in respect of patients with meningitis. However, the degree of agreement between the VEEG and the GCS was poor. This was mainly due to a substantial proportion of patients with relatively high GCS scores but with markedly or severely abnormal EEG findings.

The EEG is likely to be of value in the acute phase of meningitis even though CSF findings may often be con-



fusing in patients in the early stage of the disease.<sup>7,8</sup> While it is widely believed that acute bacterial meningitis can be distinguished from acute viral meningitis by a predominance of neutrophils in the CSF, several studies have shown that polymorphs may predominate in the CSF of up to 40% of cases in the first spinal fluid analysis.<sup>9</sup> In bacterial meningitis, 15% of patients may show a lymphocytic predominance on the first lumbar puncture. Chronic meningitis usually shows a lymphocytic predominance in the CSF, but exceptions to this rule are well described particularly when spinal taps are performed early in the course of the disease.<sup>10</sup> Any investigation that could thus help to distinguish viral from nonviral infections at an early stage would be invaluable.

#### SUMMARY

A prospective study was conducted to assess the ability of the visually analyzed electroencephalogram (VEEG), the quantitative EEG (QEEG) and the Glasgow Coma Scale (GCS) to discriminate between patients with viral and nonviral meningitis. The 55 subjects, aged 14-75 years, fell into one of the following categories: viral (n = 12), bacterial (n = 19), tuberculous (n = 16) or cryptococcal (n = 8) meningitis. EEG recordings and Glasgow Coma Scale (GCS) scores were obtained within 48 hours of admission to hospital.

The sensitivity of the VEEG and QEEG for the prediction of patients with nonviral meningitis (true positives in

this context) attained reasonably high values of 70% and 80%, respectively. In contrast, the sensitivity of the GCS was only 38%. Each of the three tests achieved high degrees of consistency in this regard with positive predictive values of 94% or better. The specificity for each of the three tests was high, 100% for the VEEG and the GCS and 82% for the QEEG indicating a high probability for the correct prediction of viral meningitis (true negatives). The consistency of this prediction was, however, poor due to negative predictive values of only 53% for the QEEG, 48% for the VEEG and 32% for the GCS.

The QEEG results did not reveal any obvious advantages over the VEEG. Rather the assessment of the occurrence of particular VEEG abnormalities showed that patients with delta abnormalities had a very high probability of nonviral meningitis. At the other end of the spectrum, all normal VEEGs occurred in viral meningitis.

In important respects the predictive ability of the EEG was superior to that of the GCS. While there was statistically significant agreement between the VEEG and GCS, the degree of agreement was poor. This study indicates that the EEG is a valuable and probably underestimated test in the acute phase of meningitis and provides complementary information to the GCS.

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## Significance of Cerebrospinal Fluid Adenosine Deaminase Isoenzymes in Tuberculous (TB) Meningitis

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Adenosine deaminase (ADA) exists as two isoenzymes, ADA<sub>1</sub> and ADA<sub>2</sub>. It appears that the ADA<sub>2</sub> isoenzyme originates mainly from monocytes and macrophages. In tuberculous pleural effusions most of the ADA activity consists of ADA<sub>2</sub>. The aim of this prospective study was to analyse ADA isoenzymes in the CSF of patients with meningitis to investigate whether the expected rise of the ADA<sub>2</sub> isoenzyme would occur in tuberculous meningitis. ADA isoenzyme analysis was performed on the CSF of 15 patients with tuberculous and

11 patients with bacterial meningitis by an automated kinetic enzyme coupled assay in the presence and absence of a specific ADA inhibitor. The ratio of ADA<sub>2</sub>/ADA<sub>Total</sub> was >0.8 in 14/15 patients with tuberculous meningitis. In bacterial meningitis the ratio was ≤0.8 in 10/11 patients. The ADA<sub>2</sub> isoenzyme is the major contributor to increased ADA activity in the CSF of patients with tuberculous meningitis, probably reflecting the monocyte–macrophage origin of the ADA. *J. Clin. Lab. Anal.* 15:236–238, 2001. © 2001 Wiley-Liss, Inc.

**Key words:** chronic meningitis; tuberculosis; diagnosis

Adenosine deaminase (ADA) is the catalysing enzyme for the deamination of adenosine (or deoxyadenosine) to inosine (or deoxyinosine) and ammonia. There are two isoenzymes of ADA namely, ADA<sub>1</sub> and ADA<sub>2</sub> (1), each encoded by different gene loci. While the ADA<sub>1</sub> isoenzymes can be found in all cells with highest activity in lymphocytes and monocytes, ADA<sub>2</sub> is mainly present in monocytes (2). It is well known that total ADA activity is increased in pleural fluid of patients with tuberculous (TB) effusions, as well as in cerebrospinal fluid (CSF) of patients with TB meningitis. However, high ADA activity is also often found in the CSF in bacterial meningitis, limiting the diagnostic utility of ADA determination in CSF (3).

It has been shown previously that ADA<sub>1</sub> and ADA<sub>2</sub> isoenzymes contribute independently to ADA increase in tuberculous pleural effusions. In TB effusions most of the measured ADA activity is due to the ADA<sub>2</sub> isoenzyme, probably reflecting monocyte–macrophage origin (4).

In this prospective study the composition of ADA enzymes in the CSF of patients with TB and bacterial meningitis was investigated to determine whether the trend found in tuberculous effusions was also present in CSF of patients with TB meningitis.

### MATERIALS AND METHODS

#### Patients

The CSF of 15 consecutive patients with TB meningitis and 11 consecutive patients with bacterial meningitis present-

ing at the Pretoria Academic Hospital was investigated. The laboratory performing the ADA determination was unaware of the clinical diagnosis of the patients. Of the patients with TB meningitis, 7 were male and 8 female; the ages ranged from 15 to 45 years. All patients were Black. The time elapsed since beginning of symptoms (headache, neck pain, fever) and first ADA analysis at admission ranged from 5 days (one patient) to more than 2 weeks (5 patients).

Of the patients with bacterial meningitis, 9 were male and 2 were female; the ages ranged from 18 to 65 years, and all patients were Black. The time elapsed from beginning of symptoms to ADA analysis ranged from 2 days (6 patients) to 5 days (1 patient).

The activity of ADA and its isoenzymes was determined by an automated kinetic enzyme-coupled assay in the presence and absence of a specific ADA<sub>1</sub> inhibitor, erythro-9-(2-hydroxy-3-nonyl)adenine (5). The Mann–Whitney *U*-test was used to determine whether the two groups of CSF differed significantly. Linear association tests (Pearson) were performed to establish whether correlations between ADA<sub>1</sub> and ADA<sub>2</sub> and lymphocyte/neutrophil counts in the CSF, respectively, were present.

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**RESULTS**

The diagnosis of TB was made according to standard criteria including typical CSF findings, clinical findings, histology, and positive cultures of *Mycobacterium tuberculosis*. The criteria for the diagnosis of tuberculous meningitis were as follows: presence of *M. tuberculosis* on CSF examination; positive culture and/or PCR of *M. tuberculosis* from CSF; post mortem examination confirming tuberculosis; CSF findings of a predominantly lymphocytic pleocytosis with CSF-protein > 0.5 g/l and CSF-serum-glucose ratio of <50% together with typical clinical findings and/or presence of tuberculosis in other organs and response to anti-tuberculous treatment. The laboratory evaluation of the CSF findings is shown in Table 1. In 4 patients the diagnosis of TB was confirmed at post mortem; in 3 patients histologic evidence for TB was found on lymph node biopsies as previously described (6); in one patient CSF cultures were positive; and in 7 patients the diagnosis was made by typical clinical and CSF findings with clinical response to anti-tuberculous treatment.

In the patients with bacterial meningitis *Streptococcus pneumoniae* was cultured from the CSF in 8, while 2 patients had meningococcal meningitis, and one had streptococcal Group B infection. The laboratory evaluation of the CSF findings is shown in Table 2.

The results of the ADA activity studies are also shown in Tables 1 and 2. The ratio of ADA<sub>2</sub>/ADA<sub>Total</sub> was >0.8 in 14/15 patients with TB meningitis and ≤0.8 in 10/11 patients with bacterial meningitis. Statistical analysis shows a significant difference between the two groups (P = 0.0001). The one patient with TB meningitis with an ADA<sub>2</sub>/ADA<sub>Total</sub> ratio of <0.8 had marked hydrocephalus, and CSF was obtained from the ventricles when an external drain was placed. Two pa-

**TABLE 1. CSF findings in TB meningitis<sup>a</sup>**

N	L	CSF Glu-S Glu	P	ADA <sub>T</sub>	ADA <sub>2</sub>	ADA <sub>2</sub> /ADA <sub>Total</sub>
270	42	0.9-6.2	3,400	3.5	3.2	0.91
55	128	0.7-5.5	2,960	7.5	6.1	0.81
77	108	0.8-5.7	1,850	10.5	9.9	0.94
12	470	1.5-5.2	2,300	10.5	9.7	0.92
0	244	6.4-1.6	3,000	16.5	14.3	0.87
0	385	1.0-3.43	2,190	22.2	20.6	0.93
24 <sup>b</sup>	134	1.9-7.8	200	6.4	4.4	0.7
385	275	0.8-12.1	2,300	15.5	13.1	0.85
0	647	2.2-7.9	1,400	10.4	10.2	0.98
36	18	1.1-4.5	3,645	14.8	14.0	0.94
10	251	1.4-6.8	2,060	17.7	17.6	0.99
61	97	1.0-?	3,649	38.67	37.0	0.95
85	12	2.5-4.6	6,415	14.9	13.7	0.92
323	293	2.6-6.3	4,177	27.2	23.9	0.88
48	256	2.1-6.8	2,434	22.0	21.9	0.99

<sup>a</sup>N, neutrophils (/mm<sup>3</sup>); L, lymphocytes (/mm<sup>3</sup>); CSF Glu-S Glu, CSF glucose-serum glucose (mmol/l); P, protein (mg/l); ADA<sub>Total</sub>, ADA total (U/l); ADA<sub>2</sub>, ADA<sub>2</sub> isoenzyme (U/l).

<sup>b</sup>CSF is ventricular fluid collected when external drain was inserted; diagnosis of TB confirmed at postmortem.

**TABLE 2. CSF findings in bacterial meningitis<sup>a</sup>**

N	L	CSF Glu-S Glu	P	ADA <sub>Total</sub>	ADA <sub>2</sub>	ADA <sub>2</sub> /ADA <sub>Total</sub>
672	250	0.1-8.9	4,298	10	5.2	0.52
684	24	2.1-7.1	4,991	6.7	2.2	0.33
138	0	0.1-13.5	17,200	9.8	8.6	0.88
1,311	30	0.3-16.4	17,700	9.4	7.5	0.79
600	75	1.6-8.3	1,310	56.4	25.4	0.45
5,894	507	1.3-5.1	5,720	4.6	2.1	0.45
2,200	110	0.1-17.2	5,870	3.8	1.5	0.39
2,536	208	1.9-5.5	2,370	27.5	7.3	0.26
6,313	12	0.1-6.3	3,910	5.1	3.9	0.76
12,100	22	0.2-9.5	5,810	6.3	2.5	0.39
4,620	110	1.3-4.8	2,120	15.8	9.9	0.63

<sup>a</sup>N, neutrophils (/mm<sup>3</sup>); L, lymphocytes (/mm<sup>3</sup>); CSF Glu-S Glu, CSF glucose-serum glucose (mmol/l); P, protein (mg/l); ADA<sub>Total</sub>, ADA total (U/l); ADA<sub>2</sub>, ADA<sub>2</sub> isoenzyme (U/l).

tients with bacterial meningitis had relatively high ratios of ADA<sub>2</sub>/ADA<sub>Total</sub> (0.88 and 0.79)—in both patients the CSF protein values were exceptionally high (17,200 and 17,700 mg/l, respectively), which possibly could have affected measurement of ADA. On statistical analysis no significant correlations, i.e., linear associations were present either between ADA<sub>1</sub> (or transformation of ADA<sub>1</sub>) and CSF lymphocytes and neutrophils, respectively, or between ADA<sub>2</sub> (or transformations of ADA<sub>2</sub>) and CSF lymphocytes and neutrophils, respectively. Biplots of ADA<sub>1</sub> and ADA<sub>2</sub> versus both neutrophils and lymphocytes also reflected no correlations.

**DISCUSSION**

The ADA<sub>2</sub> isoenzyme was found to be the major contributor to total ADA activity in the CSF of patients with TB meningitis, with a median contribution of 90%. In bacterial meningitis, the median ADA<sub>2</sub> isoenzyme contribution was 51%.

The origin of ADA activity in the CSF of patients with TB meningitis is uncertain, but studies based on isoenzyme occurrence in body fluids suggest a monocyte-macrophage origin (7). In another recent study it was found that the ADA<sub>1</sub> isoenzyme was responsible for all the ADA activity in lymphocytes while ADA<sub>2</sub> was present only in monocytes (2). The increased ADA activity in CSF in TB meningitis therefore is probably due to monocyte-macrophage activation. In the bacterial meningitis group the ADA activity probably originates from neutrophils—the most abundant cell present in the CSF in bacterial meningitis—and lymphocytes. Total CSF ADA activity is often also increased in bacterial meningitis, decreasing the specificity of ADA determination in the diagnosis of TB. However, as this study shows, measurement of the ADA isoenzymes could help to distinguish between bacterial and TB infections in the CSF.

In conclusion, the ADA<sub>2</sub> isoenzyme is the major contributor to increased ADA activity in the CSF of patients with TB meningitis, probably reflecting monocyte-macrophage origin of the ADA. Thus, the same trend found in studies of



tuberculous pleural effusions where the ADA<sub>2</sub> isoenzyme is the major contributor to increased ADA activity is also found in cerebrospinal fluid of patients with TB meningitis.

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