TB Meningitis in an HIV-endemic Setting

Tommy Du, MD 2016, UT Southwestern

Introduction

Tuberculous meningitis (TBM) is a rare but deadly form of tuberculosis. Although it represents only about 1% of TB cases, it leads to mortality or severe disability in about 50% of patients. Early treatment has been recognized as the single most important factor determining outcome: left untreated, TBM patients quickly progress to coma and death. However, treatment is often missed because early symptoms of the disease are non-specific and can overlap considerably with those of bacterial or viral meningitis. Advanced symptoms may become more specific but often only after the window for successful treatment has closed. Current laboratory tests- including smear microscopy, culture, and PCR- all lack sensitivity. CSF values, on the other hand, cannot reliably distinguish between TBM and other types of meningitis and therefore lack specificity.

Furthermore, tuberculosis is often associated with HIV co-infection, and little is currently understood about how HIV seropositivity affects clinicians' ability to diagnose TBM.

This prospective cohort study aims to explore the effect of HIV status on the diagnosis and presentation of TBM, with three particular questions in mind:

1. How do existing diagnostic algorithms[1] perform in an HIV-endemic setting?
2. Which variables are predictive of TBM, and does HIV infection alter this?
3. How does HIV status influence the clinical presentation of TBM?

Methods

- Prospective, observational cohort of 96 patients from Tygerberg Hospital in Stellenbosch, South Africa
- Criteria for entry: age > 15 years, clinical features of meningitis, and an abnormal lumbar puncture (high CSF protein or CSF pleocytosis)
- Collected routine clinical and laboratory data on admission: age, gender, duration of symptoms, neurological exam findings, CSF values, blood, microscopy, culture, imaging, etc.
- Applied two diagnostic algorithms for TBM and calculated sensitivity and specificity of these algorithms
- In HIV-positive patients, and then HIV-negative patients, compared statistical distributions of clinical and laboratory values between two groups: Definite TBM (those with confirmed TBM) and Not TBM (those with confirmed meningitis due to other causes)
- In patients with confirmed TBM, compared statistical distributions of clinical and laboratory values between HIV-positive and HIV-negative groups

Table 1.
Comparing variables between patients with and without TBM, in *HIV-negative patients*

	p
CSF total WCC	.013*
CSF % lymphocytes	.048
CSF protein	.394
CSF glucose	.164
WBC count	.001*
Blood sodium	.001*
Age	.002*
Duration of symptoms	.034*
Lymphadenopathy	.157
Hemiplegia	.423
Cranial nerve palsies	1
Decreased LOC	1
Systemic symptoms	.009*
Positive chest x-ray	.179

*Reject the null hypothesis

Table 2.
Comparing variables between patients with and without TBM, in *HIV-positive patients*

	p
CSF total WCC	.046
CSF % lymphocytes	.354
CSF protein	.076
CSF glucose	.002*
WBC count	.374
Blood sodium	.097
Age	.253
Duration of symptoms	.672
Lymphadenopathy	1
Hemiplegia	.357
Cranial nerve palsies	.692
Decreased LOC	.097
Systemic symptoms	.638
Positive chest x-ray	.023*

*Reject the null hypothesis

Results

- Current diagnostic algorithms do not perform well in this cohort, especially in HIV-positive patients
- In patients without HIV, several variables are predictive of TBM: CSF white cell count, WBC count, blood sodium, age, duration of symptoms, and presence of systemic symptoms (fever, night sweats, chills)
- In HIV-positive patients, we see a much different picture: the only significant variables are CSF glucose and positive chest x-ray
- Clinical presentation of TBM was generally similar, regardless of HIV status- only age and WBC count were significant
- However, HIV-infection is associated with higher mortality in this cohort

Table 4. Performance of existing diagnostic algorithms

	Sensitivity (95% CI)	Specificity (95% CI)
Performance in HIV-negative patients		
Logistic regression	11/11 = **100%**	6/16 = **38% (.14 to .61)**
Classification tree	10/11 = **91% (.74 to 1)**	8/16 = **50% (.26 to .75)**
Performance in HIV-positive patients		
Logistic regression	17/17 = **100%**	1/8 = **13% (0 to .35)**
Classification tree	16/17 = **94% (.83 to 1)**	1/8 = **13% (0 to .35)**

Table 3.
Comparing variables between HIV-negative and HIV-positive patients, *with TBM*

	p
CSF total WCC	.317
CSF % lymphocytes	.121
CSF protein	.842
CSF glucose	.438
WBC count	.029*
Blood sodium	.963
Age	.001*
Duration of symptoms	.111
Lymphadenopathy	1
Hemiplegia	.191
Cranial nerve palsies	.717
Decreased LOC	1
Systemic symptoms	.438
Positive chest x-ray	.621

*Reject the null hypothesis

Table 5.
Survival of TBM patients, comparing HIV-negative vs. HIV-positive

	Percent alive at time of second assessment
HIV-negative	10/11 = **91%**
HIV-positive	9/19 = **47%**

Conclusion

The findings suggest that HIV is a complicating factor that affects both diagnosis and prognosis of TBM. The presence of HIV infection makes it harder to distinguish between TBM and other causes of meningitis, when relying on current diagnostic approaches. HIV was also associated with increased mortality in this cohort. Considering the high prevalence of TB and HIV co-infection in regions like Southern Africa, it will be critical for clinicians to develop improved methods for detecting TBM, a disease with dire consequences if not diagnosed and treated promptly.

References

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