



Brief Communication



Validation of the Uniform Case Definition Criteria for Differentiating Tuberculous Meningitis, Viral Meningitis, and Bacterial Meningitis in Adults

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ABSTRACT

We validated the uniform case definition for differentiating tuberculous meningitis (TBM) from both viral meningitis (VM) and bacterial meningitis (BM) in adults from South Korea, a country with an intermediate TB-burden. ‘Probable’ TBM differentiated ‘definite’ TBM with a sensitivity of 81% and specificity of 98%. ‘Possible TBM’ criteria identified ‘definite’ TBM with a sensitivity of 100% and specificity of 60%. Despite the usefulness of the uniform case definition criteria, there was substantial overlaps among VM, BM, and ‘possible’ TBM, especially in severe cases of VM and indolent cases of BM.

Keywords: Tuberculous meningitis; The uniform tuberculous meningitis case definition; Differentiation; Viral meningitis; Bacterial meningitis

Solomons et al. have evaluated the utility of the uniform tuberculous meningitis (TBM) case definition [1] for differentiating TBM from bacterial meningitis (BM) [2, 3] and viral meningitis (VM) [3] in children. They reported that ‘probable TBM’ criteria identified culture-confirmed TBM with a sensitivity of 74% and specificity of 95% [3]. When ‘possible TBM’ criteria were used, sensitivity increased (97%) but specificity declined (48%) [3]. However, utility of the uniform case definition needs to be validated more precisely for discriminating TBM from both VM and BM especially in adults from TB endemic area.

We prospectively enrolled adult patients aged ≥ 16 years who were suspected of having TBM in Asan Medical Center, a 2,700-bed tertiary hospital in Seoul, Korea, a country with an intermediate TB-burden, from April 2008 through March 2014 [4, 5]. Using this prospective cohort, we evaluated the utility of the uniform case definition for differentiating between definite TBM, VM and BM. Patients with TBM were categorized as definite TBM (acid-fast bacilli seen on cerebrospinal fluid (CSF) microscopy, positive culture of *Mycobacterium*

Conflict of Interest

No conflicts of interest.

Author Contributions

Conceptualization: SHK. Data curation: MCK, KHP. Formal analysis: MCK, KHP. Funding acquisition: SHK. Investigation: SAL, SHK. Methodology: SHK. Project administration: SHK. Resources: SAL, SHK. Software: MCK, KHP. Supervision: SHK. Validation: MCK. Visualization: MCK. Writing - original draft: MCK. Writing - review & editing: SHK.

tuberculosis in CSF, or positive polymerase chain reaction (PCR) of *M. tuberculosis* in CSF), probable TBM (diagnostic score ≥ 12), and possible TBM (diagnostic score 6 - 11) according to the uniform case definition [1]. A diagnosis of definite VM was established if viral pathogens were identified by positive PCR in the CSF. Definite BM was confirmed by positive culture of bacteria in CSF or blood. The study protocol was approved by the Institutional Review Board of Asan Medical Center.

During the study period, 93 adult patients were treated for TBM; 27 (29%) were classified as definite TBM, 25 (27%) as probable TBM, and 41 (44%) as possible TBM. We also identified 23 PCR-confirmed VM and 20 culture-confirmed BM (Table 1). One patient with probable TBM had HIV infection. Most of enrolled patients with TBM, VM and BM underwent cerebral imaging except 2 patients with BM. Among the 27 patients with definite TBM, 22 (81%) were scored as probable TBM and 5 (19%) as possible TBM. Among the 23 patients with definite VM, 13 (57%) were scored as unlikely TBM and 10 (43%) as possible TBM. Of the 10 patients scored as possible TBM, 9 received scores of ≥ 4 on the clinical criteria (maximum 6) and 8 had scores of ≥ 3 on the CSF criteria (maximum 4). There was a trend for meningitis caused by varicella-zoster virus to be scored as possible TBM more often than other VM (60% [6/10] vs. 31% [4/13]; $P = 0.22$). Out of the 20 patients diagnosed with definite BM, 13 (65%) were scored as unlikely TBM, 1 (5%) as probable TBM and 6 (30%) as possible TBM. Of the 7 patients scored as probable or possible TBM, 3 received scores of ≥ 4 on the clinical criteria (maximum 6) and

Table 1. Scoring according to the uniform research case definition in adult patients with tuberculous meningitis, viral meningitis, and bacterial meningitis

Clinical Criterion (diagnostic score)	Definite TBM (n = 27)	Probable TBM (n = 25)	Possible TBM (n = 41)	Definite VM (n = 23 ^a)	Definite BM (n = 20 ^b)
Total score, median (interquartile range)	15 (12-17)	12 (12-14)	9 (8-10)	7 (4-8)	4 (2-6)
Clinical criteria (maximal category score = 6)					
Symptom duration >5 days (4)	25 (93)	24 (96)	36 (88)	9 (39)	3 (15)
Systemic symptoms suggestive of TB (2)	14 (52)	14 (56)	11 (27)	1 (4)	0
Focal neurological deficit (1)	9 (33)	15 (60)	13 (32)	3 (13)	5 (25)
Cranial nerve palsy (1)	5 (19)	7 (28)	2 (5)	1 (4)	4 (20)
Altered consciousness (1)	17 (63)	13 (52)	21 (51)	4 (17)	9 (45)
CSF criteria (maximal category score = 4)					
Clear appearance (1)	27 (100)	25 (100)	39 (95)	22 (96)	12 (60)
Cells: 10-500/mm ³ (1)	26 (96)	20 (80)	30 (73)	19 (83)	8 (40)
Lymphocyte predominance (>50%) (1)	18 (67)	22 (88)	37 (90)	18 (78)	3 (15)
Protein concentration >1 g/L (1)	1 (4)	1 (4)	0	0	14 (70)
CSF to plasma glucose ratio <50% and/or CSF glucose concentration <2.2 mmol/L (1)	22 (82)	22 (88)	33 (81)	14 (61)	13 (65)
Cerebral imaging criteria (maximal category score = 6)					
Hydrocephalus (CT and/or MRI) (1)	5 (19)	3 (12)	1 (2)	0	2/18 (11)
Basal meningeal enhancement (CT and/or MRI) (2)	14 (52)	19 (76)	3 (7)	3 (13)	2/18 (11)
Tuberculoma (CT and/or MRI) (2)	15 (56)	6 (24)	3 (7)	1 (4)	1/18 (11)
Infarct (CT and/or MRI) (1)	4 (15)	6 (24)	1 (2)	1 (4)	4/18 (22)
Pre-contrast basal hyperdensity (CT) (2)	1/19 (5)	2/17 (12)	1/26 (4)	0/13 (0)	1/13 (8)
Evidence of TB elsewhere (maximal category score = 4)					
Chest radiograph suggestive of active TB (2)	13 (48)	4 (16)	0	0	0
Chest radiograph suggestive of miliary TB (4)	10 (37)	2 (8)	0	0	0
Radiological evidence of TB outside the CNS (2)	15 (56)	7 (28)	1 (2)	0	0
Extraneural <i>Mycobacterium tuberculosis</i> confirmation ^c (4)	11 (41)	6 (24)	0	0	0

Data are number (%) of patients, unless otherwise indicated.

BM, bacterial meningitis; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance image; TB, tuberculosis; TBM, tuberculous meningitis; VM, viral meningitis.

^aTen cases were caused by varicella-zoster virus, 8 by herpes simplex virus type 2 (HSV-2), 2 by enterovirus, 2 by mumps virus, and 1 by HSV-1.

^bFour cases with *Listeria monocytogenes*, 3 with Gram-negative enterobacteriaceae (*Escherichia coli*, *Klebsiella oxytoca*), 2 with neurobrucellosis, 1 with neurosyphilis, and 10 cases with other bacteria (*Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Prevotella copris*, *Enterococcus faecalis* and *Orientia tsutsugamushi*).

^cAcid-fast bacilli seen on CSF microscopy, positive CSF *Mycobacterium tuberculosis* culture, or positive CSF *M. tuberculosis* PCR.

6 had scores of ≥ 3 on the CSF criteria (maximum 4). The diagnosis of the 1 patient with BM having probable TBM score was neurosyphilis. Patients with neurobrucellosis and scrub typhus were included in BM patients received possible TBM score.

These findings indicate that some cases of VM and BM could masquerade as TBM despite the usefulness of the uniform case definition criteria, especially in severe cases of VM and indolent cases of BM. Overall, 'probable TBM' criteria differentiated definite TBM from both VM and BM and with a sensitivity of 81% (22/27) and specificity of 98% (42/43), while the 'possible TBM' criteria identified definite TBM with a sensitivity of 100% (27/27) and specificity of 60% (26/43). In detail, specificities of 'probable TBM' criteria for differentiating TBM from VM and BM, respectively, were 100% (23/23) and 95% (19/20). Specificities of 'possible TBM' criteria for differentiating TBM from VM and BM, respectively, were 57% (13/23) and 65% (13/20).

As the findings of Solomons et al. [2, 3], our data suggest that the uniform case definition may be useful for differentiating TBM from VM and BM, but there was substantial overlap in clinical and laboratory features among them. Since the definition criteria were developed for research purposes that facilitating standardization of study cases [1, 6], the scoring system should be interpreted cautiously in diagnosing TBM [7]. To avoid fatalities caused by delayed treatment and morbidity due to unnecessary exposure to anti-TB drug, a rapid and accurate tool for diagnosing TBM is urgently required.

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