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ORIGINAL ARTICLE

Comparison of clinical and CSF profiles in children with tuberculous and pyogenic meningitis; role of CSF protein: glucose ratio as diagnostic marker of tuberculous meningitis

Farah Naz Qamar, Arshalooz Jamila Rahman, Sania Iqbal, Khadija Humayun

Abstract

Objectives: To compare the clinical and laboratory features of tuberculous meningitis with bacterial meningitis and to determine if protein glucose ratio in the cerebrospinal fluid can be predictive of the condition.

Methods: It was a retrospective descriptive study at the Paediatric Ward of Aga Khan University Hospital, Karachi, for which records of 46 patients with tuberculous meningitis and 33 with bacterial meningitis were reviewed. All records related to the study period that was from January 2005 to October 2010. The records were retrieved in December 2010. Tuberculous meningitis was defined as illness $\geq$14 days, basal enhancement or tuberculoma on computerised tomography scan and response to anti-tuberculous therapy. Pyogenic meningitis was defined by the presence of a pathogenic isolate in the cerebrospinal fluid (bacterial culture) or by positive latex particle agglutination or a pathogen on cerebrospinal fluid gram stain and clinical improvement with antibiotics. Logistic regression was used to model the probability of having tuberculous meningitis. To define the optimal protein-glucose ratio, cutoff point for the diagnosis of tuberculous meningitis, a receiver operating characteristic curve was applied. All analysis were done using SPSS 16.

Results: Features predictive of a diagnosis of tuberculous meningitis were protein:glucose ratio of $\geq$2 (OR 21 95% CI 4.7-93); cerebrospinal fluid total leukocyte count <800 (OR 58, 95% CI 5-649); and the presence of hydrocephalus (OR 19, 95% CI 3.3-109).

Conclusion: A set of simple clinical, laboratory and radiological criteria can help in predicting tuberculous meningitis. The value of cerebrospinal fluid protein:glucose ratio needs to be validated in larger studies with bacteriologically-confirmed cases of tuberculous meningitis.

Keywords: Protein glucose ratio, Tuberculous meningitis, Independent predictors, Pakistan. (JPMA 63: 206; 2013)

Introduction

Tuberculosis (TB) is the most common cause of death from a single infectious agent among children. Almost one-third of the world population is infected with Mycobacterium tuberculosis, with 75% of the burden in developing countries.[1] Of the 9-10 million new cases occurring annually across the globe, 50% are extra-pulmonary.[1] The risk of progression of primary TB to tuberculous meningitis (TBM) is higher in children than adults and complicates 0.3% of untreated primary infections in children.[2]

If not treated, TBM is universally fatal, and even when it is treated, high morbidity and mortality is associated with late recognition and delay in the initiation of appropriate therapy.The diagnosis of TBM is complicated, as there are no specific signs and symptoms, and the clinical presentation overlaps with many other acute and chronic diseases of the central nervous system (CNS).[3] The evaluation of cerebrospinal fluid (CSF) is an important laboratory parametre in the diagnosis of meningitis, but CSF abnormalities produced by bacterial pathogens, especially partially-treated cases and fungal meningitis, may at times be difficult to differentiate from TBM. This is particularly true for the early phases of TBM when the protein may not be greatly elevated and the predominant cells may be neutrophils.[4] A study reported an initial neutrophil predominance in CSF as high as 36% of the subjects with TBM.[5] A preliminary diagnosis of TBM in children is usually made on the basis of a suggestive history, clinical examination, CSF and radiological findings. In the absence of isolation of mycobacteria from clinical samples, (either sputum or CSF), there is a diagnostic uncertainty, leading to delay in starting appropriate therapy.[6] The isolation of TB bacilli from CSF requires large volumes of fluid, with sensitivity of CSF culture still remaining low at 40%.[7] The more sophisticated tests such as Mycobacterium tuberculosis (MTB)

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Polymerase Chain Reaction (PCR) have low sensitivity in the paediatric age group (40-60%) are expensive, and are not routinely available in developing countries where the real burden of disease lies.[8,9] In the absence of bacteriological confirmation, the diagnosis of childhood TB is based on a history of close contact with an infectious patient, a positive tuberculin skin test (TST) and presence of suggestive abnormalities on a chest radiograph.[9,10] There are limitations to these criteria as well. Contact tracing is difficult, except in cases where the contact is an immediate family member. Furthermore, latent infection acquired in childhood coupled with routine childhood vaccination with Bacillus Calmatte-Guerin (BCG) and prevalent malnutrition in countries with the highest TB burden, make the interpretation of TST difficult.[11,12] The availability, cost and diagnostic yield of computerised tomography (CT) or Magnetic resonance imaging (MRI) of brain, limits its use in high-burden developing countries at secondary and tertiary hospital care levels. Therefore, simplified diagnostic criteria are needed to strengthen clinical suspicion in such cases.

Regarding biochemical analysis of the cerebrospinal fluid, CSF protein in cases of TBM is higher and glucose is not as low as in bacterial meningitis. It is possible that a protein-glucose ratio in CSF in cases of TBM may have more value as a biochemical marker than either of the values alone. The concept of biochemical ratios being used as diagnostic markers in non-infectious diseases (such as protein-creatinine ratio in urine in nephrotic syndrome) is not new.[13] The current study attempted to evaluate a set of clinical and laboratory parametres that may play a role in predicting TBM in immunocompetent paediatric patients in the absence of bacteriological confirmation. Supportive evidence behind presumptive diagnosis of TBM may lead to earlier initiation of treatment and may be instrumental in preventing a fatal outcome.

Materials and Methods

The retrospective review was done at the Paediatric Ward of Aga Khan University Hospital (AKUH), Karachi, Pakistan. It is a 532-bed tertiary care referral centre which receives patients from all over the country. The paediatric ward is an 82-bed unit with a 15-bed high-dependency section.

After approval from the AKU ethical review committee, patient files were retrieved in December 2010 using ICD codes — bacterial meningitis, acute meningitis, tuberculous meningitis — from the medical records (MR) unit at AKU. Data regarding clinical presentation, physical exam and laboratory profile was extracted from the files of patients fulfilling the inclusion criteria: age <14 years admission in the paediatric ward at AKU during the study period (Jan 2005-October 2010)with the primary diagnosis of TBM or bacterial meningitis.

All patients admitted with a suspicion of meningitis had undergone a complete physical examination and a lumbar puncture on admission. CSF was analysed for glucose and total protein concentration, as well as total and differential leukocyte counts, gram staining, culture and sensitivity. All CSF culture samples were processed at the AKU Clinical Microbiology Laboratory as per Clinical and Laboratory Standards Institute (CLSI) guidelines.[14] Microbiology tests included Gram stain, Ziehl-Neelsen stain, and bacterial cultures (blood and chocolate agar, and Lowenstein-Jensen media). As per institutional policy, a CT scan was performed as early as possible after admission in all cases with focal neurological findings, altered consciousness or cases strongly suspected of having TBM. For the purpose of this study, the subjects were categorised as having tuberculous or bacterial meningitis based on criteria modified from available literature.[5]

Tuberculous meningitis was defined as duration of illness >14 days, presence of basal enhancement or tuberculoma on CT scan and response to empiric anti-tuberculous therapy with or without antibiotics.[15]

Pyogenic meningitis was defined as isolation of a pathogen in the CSF by either a positive bacterial culture or a positive lysophosphatidic acid (LPA) or a pathogen on gram stain (CSF) and a clinical improvement with antibiotics.

Children with bacterial meningitis were treated with a 10-14 days' course of intravenous ceftriaxone. Cases diagnosed as having TBM were treated with a four-drug regimen along with steroids according to the WHO guidelines.[1]

Children with proven viral meningitis (having herpes PCR positive) and children with no organism isolated in the CSF by culture, LPA or gram stain were excluded.

For statistical analysis, the clinical and laboratory features of those fulfilling the diagnostic criteria for TBM and bacterial meningitis were compared by univariate analysis. Multiple logistic regression was used to model the probability of having TBM. A stepwise forward variable selection procedure was used to find independent predictors of TBM.

To define the optimal protein-glucose ratio cutoff point

for the diagnosis of TBM, we applied a receiver operating characteristic (ROC) curve. Using the cutoff point, determined through the ROC, sensitivity and specificity of the index was calculated using clinical criteria for TBM as the gold standard. All analysis was done using SPSS 16.

Results

Headache and irritability at presentation were more common in children diagnosed with pyogenic meningitis. Children diagnosed as TBM presented more frequently with prolonged history (>14days), seizures, focal neurological signs and had a higher protein and a lower glucose in CSF compared to children with pyogenic meningitis (Table-1).

Table-1: Univariate Analysis of Clinical and Laboratory Parameters of Tuberculous and Pyogenic Meningitis.

Clinical and lab parameters	TBM (n=46)	Pyogenic (n=33)	Crude OR
Gender (Male)	27	23	
Mean age (Months)	67±56	63.5 54	1.0 (0.9-1.0)
Mean weight (Kg)	17±10	18.5 13	1.0 (0.9-1.0)
BCG	33	32	0.8(0.01-0.6)
Hib	7	4	1.3(0.35- 5.0)
Fever (documented)	45	31	0.3 (0.03-4)
H/o wt loss	11	0	
H/o vomiting	20	21	0.4 (0.2-1.1)
H/o loss of appetite	15	7	1.8 (0.6-5)
Headache	18	20	0.4(0.2-1.0)
Irritability	7	15	0.2 (0.08-0.6)
Drowsiness	15	11	0.97 (0.3-2.5)
Seizures	21	7	3 (1.1-9)
Cough	5	3	1.2(0.3-5.5)
Photophobia	2	1	1.5 (0.1-16)
Focal neurological signs	11	2	5 (1-24)
Signs of meningeal irritation	16	15	0.6 (0.3-1.6)
Duration of illness (>14days)	42	3	105 (22-103)
Mean ESR (mm 1st hr)	19.5 (±16.5)	31 (± 21)	0.9 (0.9-1.0)
Mean CRP	4 (± 8.5)	5.5 (± 8)	0.9 (0.9-1)
Mean TLC (10^9)	29 (±96)	18 (± 8)	1.0 (0.9-1.0)
MT (mm)	5/12	0/1	
CSF analysis			
Mean TLC (10^9)	268 (±757)	1064 (±2513)	0.9 (0.9 -1.0)
Mean Protein (mg/dl)	340 (±606)	99 (± 80)	1.0(1.0- 1.04)
Mean Glucose (mg/dl)	45 (± 21)	58 (± 23)	0.97 (0.9-1.0)
Protein : glucose			
<2	7	23	13.0 (4.3-38)
≥2	39	10	
CT scan findings	**TBM (n=44)**	**Pyogenic (n=24)**	
Basal meningeal enhancement	18	3	5.0 (1.3-18)
Hydrocephalus	29	4	9.6 (3-33)
Cerebral edema	9	3	2.0 (0.5-8)
Tuberculoma	9	0	6.2(0.7-52)
Infarction	**8**	**2**	**2.5(0.5-13)**

BCG: Bacillus Calmatte-Guerin. Hib: Haemophilus influenza Type B. ESR: Erythrocyte sedimentation rate. CRP: C-reactive protein. TLC: Total leukocyte count. MT: Mantoux test. CSF: Cerebrospinal fluid.

Table-2: Multiple Logistic Regression Analysis.*

Clinical and lab parameters	β- coefficient	Adjusted OR	95.0% C.I for Adjusted OR
Protein: glucose ratio (≥2)	3.0	21	4.7-93
CSF TLC <800	4.0	58	5-649
Hydrocephalus on CT scan	3.0	19	3.3-109

*Nagelkerke R2 of final model is 68%.

OR: Odds ratio. CI: Confidence internal. CSF: Cerebrospinal fluid. TLC: Total leukocyte count. CT: Computerised tomography.

Factors found to be significant at the univariate level were: history of >14 days prior to presentation (this was part of case definition and therefore not included in multiple regression models), headache, irritability, seizures and focal neurological signs. The values of individual parametres of CSF were not significantly different at the univariate level, but the ratio of protein to glucose in CSF (cutoff value of 2) was found to be significant. CT scan of the head was performed in 44 cases diagnosed with TBM and in two-thirds (n=22; 66.6%) of patients with pyogenic meningitis. The CT scan was not performed in 2 (4.3%) patients with TBM due to cost constraints, and in 7 (21.2%) patients with pyogenic meningitis as they had no focal neurological signs or alteration in conscious level, and the attending physician did not feel the need of CT scan in these cases.

Most (n=25; 75.75%) cases of bacterial meningitis had an organism identified on CSF culture; the rest (n=8; 24.24%) were LPA confirmed as per case definition. Overall, most of the cases were due to H influenza (n=11; 14%). The detail of prior antibiotic use was not available in the records of most patients and could not be analysed.

On multiple logistic regression, three features were found to be predictive of a diagnosis of TBM: Protein-glucose ratio of ≥2 (OR 21 95% CI 4.7-93); CSF TLC <800 (OR 58, 95% CI 5-649)) and presence of hydrocephalus on CT scan ((OR 19, 95% CI 3.3-109) (Table-2).

The area under ROC was found to be maximum (0.90) for a protein-glucose ratio of ≥2; the sensitivity and specificity were 80% and 88% respectively.

Discussion

The number of new TB cases reported for the year 2009 was 139/100,000 with 20 deaths/100000 population.[1] With the increasing number of TB cases worldwide, there is a growing need for early case detection, diagnosis and management. The delay in diagnosing childhood TB (pulmonary and extra-pulmonary), due to poor access to laboratory diagnostics and poor yield of available diagnostics, leads to delay in initiating appropriate therapy.[10] The high mortality associated with TBM has led to reports in literature on the role of various combinations of clinical and lab criteria that could be used to reach a 'probable' diagnosis of TB and initiate early therapy.[5,16]

The value of CSF protein and glucose, although well-known to be different from bacterial meningitis, has rarely been reported to be significant in cases of TBM cases.[3,15] In this retrospective analysis, we analysed the ratio of protein to glucose in CSF. A ratio of $\geq$2 was found to be significant because of very high protein and moderately low glucose levels found in cases of TBM, in contrast to very low glucose and moderately high protein in cases of bacterial meningitis. If this criterion is rigorously evaluated and is found to be significant in large-scale studies, it can be a part of a simplified scoring system used for TBM in the absence of isolation of Mycobacterium Tuberculosis on CSF culture (CSF biochemical evaluation is routine in most cases of paediatric meningitis at secondary and tertiary care health facility level).

History of seizures and focal neurological signs on presentation were common in most of the cases in our TBM group. This is similar to prior reports.[17] We did not find any difference in inflammatory markers such as erythrocyte sedimeutation rate (ESR), C-reactive protein (CRP) and total leukocyte count (TLC) between the two groups. The tuberculin skin test (TST) was applied on only 30% of the subjects and was positive in 5/12 subjects who got the test. The poor yield of the Mantoux test, particularly in cases of TBM, has been mentioned earlier in literature.[18] Similarly, the use of CT scan in cases of TBM has been associated with a non-specific diagnostic yield.[19] However, some authors have reported the significance of basal enhancement, hydrocephalus, infarction and high density within the basal cisterns on non-contrast CT, and their value as a clue to the diagnosis of TBM.[20] In our study, 66% of the patients with TBM had hydrocephalus on CT scan at the time of presentation. This is consistent with the findings reported by other authors.[21]

TBM is a chronic disease, and, hence, the CSF usually appears clear and has moderate numbers of leukocytes, with the predominance of lymphocytes. The cutoff value of CSF cell counts in the diagnosis of TBM is documented as < 1000 in most studies.[3,5,22] We also found a CSF cell count of < 800 as a predictor of TBM.

The most common scoring system that has been widely used in the sub-continent is the Kenneth Jones Scoring Criteria (KJSC), which was designed in the late 1960s.[23] Some of the factors in the KJSC may need revision. For instance, the TST, with its inherent low sensitivity, and malnutrition, which may be multi-factorial in resource-constrained settings. Furthermore, with the emergence of human immunodeficiency virus (HIV), these criteria may have even lower sensitivity in HIV-infected patients.[24]

The limitation of this study was its retrospective nature and the absence of any comparison group with positive CSF, Acid-fast bacillus (AFB) cultures to validate the findings. Furthermore, the sample size was small, leading to wide confidence intervals.

Conclusion

If the clinical and laboratory parametres found significant in this study are further validated on a larger scale, they may prove useful in an empiric diagnosis of TBM and could be used in settings with limited microbiological support and early initiation of appropriate therapy.

Disclosure/Support

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