RESEARCH ARTICLE

A mathematical approach in the management of hydrocephalus from tuberculous meningitis

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ABSTRACT

Background: The unavailability of standardized treatment algorithms to properly select tuberculous meningitis (TBM) patients for surgery delays optimal management. **Aim and Objective:** This study developed a mathematical model as an objective guide in deciding whether to perform surgical intervention or not among patients with hydrocephalus from TBM. **Materials and Methods:** Using 13 different clinical and cerebrospinal fluid parameters, a saturated logistic regression model was developed and tried retrospectively on 37 previously managed cases of hydrocephalus from TBM. **Results:** The model is statistically significant ($P = 0.0170$) with 93.2% concordance index in predicting physician's decision on admission whether the patient will undergo surgical intervention or not. Patients are recommended for surgical intervention if *g*-score >0.04 with 90.48% sensitivity. **Conclusion:** With its significant *P*-value and high concordance index, the model is a good representative of the actual decision making of physicians in the management of hydrocephalus from TBM.

KEY WORDS: Hydrocephalus; Tuberculous Meningitis; Shunt; Surgery; Mathematical Model; Logistic Regression

INTRODUCTION

Central nervous system (CNS) infections are still prevalent in developing countries like the Philippines. About 250 cases of CNS infections are admitted each year in the Philippine General Hospital, and almost 75-90% of these is due to tuberculous meningitis (TBM), the most lethal form of extrapulmonary tuberculosis.[1] Hydrocephalus often develops in TBM when the inflammatory exudates cause cerebrospinal fluid (CSF) outflow obstruction in the ventricular system.[2] It is the most common complication of TBM, which occurs in about 70% of patients, becoming more common as the disease progresses. The mortality is high and a considerable number of patients are left with severe neurologic deficits.

Medical management in TBM works because treatment with anti-Koch's medications lessen the inflammatory response preventing further formation of basal exudates. However, for some patients, medical management alone is not sufficient especially when hydrocephalus develops. Surgical intervention in the form of repeated tapping through burr holes, suboccipital decompression, lateral and third ventriculostomy (open or endoscopic), ventriculo-subarachnoid and ventriculoperitoneal shunts (VPS) may sometimes be needed[3] since performing shunt surgery

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showed beneficial effects.[4] However, despite the clinical improvement that has been shown with surgical intervention, not all patients who underwent surgery showed improvement postoperatively.[5] In fact, some even died despite the added surgical intervention. In addition, shunt surgery is not without complications, and shunt malfunctions and infections are not uncommon.[6]

Several algorithms have been proposed across different institutions to properly select the patients for surgery.[3,5,7] The most commonly used criteria in the treatment pathways include the severity of signs and symptoms of increased intracranial pressure (ICP), the radiologic evidence of the type and severity of hydrocephalus, CSF indicators of disease burden, the presurgical condition of the patient using the Vellore and Glasgow Coma Scale (GCS) scores, and sometimes, the response of the patient to trial with an external ventricular drainage (EVD).

However, several problems are encountered with these treatment algorithms. First, standardization of these algorithms remains to be done until now. This is because of the paucity of solid evidence and the lack of prospective, multidisciplinary, multicenter controlled trials to validate these treatment pathways.[3] These algorithms are based only on observational studies done in the institution where they were made. Furthermore, while huge cost savings can be obtained by obviating the need for surgery, especially in developing countries where resources are scarce, medical management entails prolonged hospitalization for close monitoring. In addition, these algorithms are difficult to follow as some of the treatment strategies included are not readily available or are not commonly done in the third world countries where TBM is prevalent. For example, doing an air encephalogram to differentiate between a communicating and noncommunicating type of hydrocephalus and trial with an EVD for TBM Vellore Grade 4 patients are not commonly done in our institution. The selection of patients for surgery becomes tedious, causing unnecessary delays in the implementation of the optimal treatment for these patients. Finally, an abrupt increase in ICP can still be missed out in the intervening period, and the physician ends up losing the patient due to their rapid deterioration.[3]

In our institution, there is still no treatment pathway nor is there an objective guide in selecting the patients for surgery. There is also no consensus as to when the surgery should be best done. The authors hypothesize that a mathematical model can be developed to predict whether a patient will need surgery or not using various clinical and CSF parameters which have previously been shown to be significant indicators for surgery. Hence, this endeavor aimed to develop a mathematical model which will serve as an objective guide in helping the clinicians decide whether to perform surgery or not among patients with hydrocephalus from TBM.

MATERIALS AND METHODS

Development of the Mathematical Model

Since the outcome variable in this study is dichotomous in nature, that is, either to perform surgery or not, a logistic regression model was employed. If we have independent observations, with the i^{th} observation treated as a representation of a binomially distributed random variable y_i with probability g and the logit of the underlying probability g is a linear function of the predictors x, the systematic structure of the model can be defined as:

$$\operatorname{logit}(y_i) = \ln\left(\frac{g}{1-g}\right) = \sum\nolimits_{j=1}^{n} \beta_j x_{ji} + \varepsilon_i,$$

where β_j represents the change in the logit of the probability associated with a unit change in the j^{th} predictor holding all other predictors constant,[8] ε_i is the random error term for the i^{th} observation. To obtain a multiplicative model for the odds, exponentiating the previous equation and solving for the probability g in the logit model will give rise to the final formula:

$$g = \frac{e^{\beta_0 + \sum_{j=1}^{n} \beta_j x_j}}{1 + e^{\beta_0 + \sum_{j=1}^{n} \beta_j x_j}}$$

The probability g is the score that will be calculated for each patient and this ranges from 0 to 1. After determining the β-coefficients for each variable, the formula can easily be entered in a spreadsheet file to facilitate the calculation of the g-scores. Table 1 summarizes the variables which were considered as regressors in the construction of the logistic regression model in this study.

Symptoms consistent with hydrocephalus (persistent headache [PH] and vomiting, blurring of vision [BOV], decreased level of consciousness) are significant factors for surgery.[2,9] A depressed level of consciousness on admission is an indication for surgery.[10] Furthermore, the GCS score, a component of the Vellore scoring system, is being used as an indicator for surgery. Patients with a Vellore score of 1-3 should be offered immediate surgery while Grade 4 may have a trial with an external ventricular drainage (EVD) first before having a shunt surgery to see if they would respond to it since these patients are already deemed to respond poorly to surgery.[3,5,10-13] Moreover, CSF characteristics on lumbar tap were also chosen in the construction of the mathematical model since they are also found to be significant factors by other studies, especially the polymorphonuclear cell count, protein count, as well, the opening pressure (OP).[2,7,12]

The other two commonly used parameters - radiographic evidence of the severity of hydrocephalus and the response to trial with an EVD - were not used in the development

Table 1: The 13 clinical and CSF parameters used in the model construction

Variable	Values
x_1: AS	1 - if AS is present; 0 - if absent
x_2: PH	1 - if PH is present; 0 - if absent
x_3: PV	1 - if PV is present; 0 - if absent
x_4: BOV	1 - if BOV and/or diplopia is present; 0 - if absent
x_5: Eye-opening component of the GCS score	1 - none; 2 - to pain; 3 - to speech; 4 - spontaneous
x_6: Verbal output component of the GCS score	1 - none; 2 - incomprehensible sounds; 3 - inappropriate words; 4 - confused/disoriented; 5 - oriented
x_7: Motor response component of the GCS score	1 - none; 2 - decerebrate posturing; 3 - decorticate posturing; 4 - withdraws to pain; 5 - localizes to pain; 6 - follows commands
x_8: CSF OP	CSF OP in cm H_2O
x_9: CSF protein count	CSF protein count in mg/dL
x_{10}: CSF WBC count	CSF WBC count ($\times 10^6$/L)
x_{11}: CSF % neutrophil count	% Neutrophil count of the total WBC count
x_{12}: CSF % lymphocyte count	% Lymphocyte count of the total WBC count
x_{13}: Modified Vellore score	1 - GCS 15 but with headache, vomiting, fever±neck stiffness and with no neurological deficit; 2 - GCS 15 but with neurological deficit present; 3 - GCS 9-14 and neurological deficit may or may not be present; 4 - GCS 3-8 and neurological deficit may or may not be present

AS: Altered sensorium, PH: Persistent headache, PV: Persistent vomiting, BOV: Blurring of vision, GCS: Glasgow coma scale, CSF: Cerebrospinal fluid, OP: Opening pressure, WBC: White blood cell

of our model since these are not commonly done in our institution. In addition, the degree of ventriculomegaly is not an accurate reflection of the degree of increased ICP.[3,14] Furthermore, trial with EVD is not advocated as it only incurs additional costs, is invasive, and has not yet been statistically proven.[15]

Premises of the Model

The mathematical model developed in this study is only applicable to patients suffering from hydrocephalus from TBM, with an assumption that surgical intervention in addition to medical management could prevent deterioration from hydrocephalus. Early surgical intervention had better neurologic outcomes, lesser morbidity and mortality, and when VPS is done within 2 days after they are diagnosed with hydrocephalus.[15] Furthermore, a decision made on admission lessens hospital stay for monitoring since the best possible treatments, both medical and surgical interventions, were already given, and obviating the need for serial lumbar punctures and repeated neuroimaging, which can still miss out abrupt increases in ICP in the intervening period. Finally, since clinical deterioration is avoided by offering immediate surgical intervention to those who will likely benefit from it, the pre-operative clinical condition of the patient is optimized, especially that this is the single most important predictor of good outcome postoperatively.[12]

Patients and Trial of the Mathematical Model

The mathematical model was tried retrospectively on previously admitted patients, both at the charity wards and at the pay floors, managed as cases of TBM with a radiographic evidence of hydrocephalus. The diagnosis of TBM was based only on the clinical presentation, CSF and neuroimaging findings consistent with TBM. Growth on culture studies and polymerase chain reaction studies were not considered necessary to arrive at the diagnosis since these are not routinely done on all patients admitted in our institution. All patients were managed medically (giving of anti-Koch's medications, steroids, and/or medical decompression). Patients who ended up going home, for any reason, before the set observation period of at least 2 weeks were excluded,[16,17] which was the minimum observation period to determine whether medical management alone will suffice for patients with hydrocephalus from TBM. Patients who deteriorated during the 2-week observation period for reasons other than worsening of the hydrocephalus such as the development of arteritis and other medical comorbidities (e.g., hospital-acquired pneumonia, encephalopathy from septic, and metabolic causes) were also excluded from the study.

Records of patients managed as cases of TBM from 2009 to 2014 were retrieved with only 93 charts available during the data collection period. Only 43 cases were included in the study after considering the inclusion and exclusion criteria, but 6 were excluded from the statistical analyses due to incomplete information. Thus, only 37 patients were included in this study.

Outcome Analyses

The model obtained was compared to the physician's decision on admission to determine if it is a good representation of the actual clinical practice and was assessed by obtaining the *P*-values and the concordance index of the computed *g*-scores and the physician's decision on admission for each patient. All calculations were done using the Statistical Analysis System (SAS©) software.

A cutoff value (c) was then determined such that above this value, surgery will be recommended. The *post-hoc* analysis was performed also dichotomous in nature: 1 for surgical intervention and 0 for medical management alone. A score of 1 was given for the following patients: (i) patients deemed for surgery on admission who did not deteriorate clinically up to the day of the surgery, (ii) patients who were managed medically initially but ended up having clinical deterioration (drop in GCS score ≥2, increase in the Vellore score) within the observation period of at least 2 weeks, and (iii) patients who were managed medically initially but ended up having surgery due to persistence of increased ICP symptoms and had resolution of the symptoms postoperatively. On one hand, a score of 0 was given for the following: (i) patients deemed for medical management alone on admission who did not deteriorate clinically during the observation period of at least 2 weeks and (ii) patients whose surgery did not push through due to technical (neurosurgical) difficulties but did not have any clinical deterioration during the observation period.

Ethical Considerations

This study was approved by our institution's research ethics board panel. There was no direct patient interaction during the conduct of the study nor was the patient's management affected since both the patients, and their physicians were not made aware of the study. Furthermore, the investigators had no competing financial interests, organizational tiers, or other relationships that could reasonably be viewed as a conflict of interest in this study. All results obtained in this study were handled with confidentiality.

RESULTS

The *β*-coefficients, *P*-values, and 95% confidence limits of the 13 variables were computed (Table 2). At 5% level of statistical significance, none of the variables included in the study can solely influence the decision to perform surgery on admission. Six variables included in the study have positive parameter estimates. These are persistent vomiting (PV), BOV, motor component of the GCS score, CSF protein level, CSF white blood cell (WBC) count, and the modified Vellore score. An increase in the values of these variables renders a multiplicative increase in the probability of considering surgical intervention. On the other hand, an increase in the scores of altered sensorium (AS), PH, eye-opening and verbal output components of the GCS score, and the CSF OP, neutrophil, and lymphocyte counts favor a multiplicative decrease in the probability of considering surgical intervention. The Vellore score has the highest odds ratio (OR) value reflecting a 10-fold increase in the probability of considering surgery for every unit increase in the Vellore score. In addition to the Vellore score, the presence of PV, BOV, and an increase in the motor component of the GCS score also have OR value estimates >1.

With the *β*-coefficients available, predicted probabilities *g*-scores were calculated for each of the 37 patients. The model was found to be statistically significant ($P = 0.0170$), with a strong 93.2% concordance index, in predicting the physician's decision whether medical management alone or a surgical intervention will be done on admission.

The sensitivity and specificity of the mathematical model was assessed (Table 3). A sensitivity of 90.48% is identified when the minimum cutoff value (*c*) for the probability to perform surgery is set at 0.04, with a specificity of 31.25%. An additional set of criteria was also considered in the selection of the minimum cutoff value (*c*), and this includes the positive predictive value (PPV), negative predictive value (NPV), and the overall accuracy. A 0.04 probability cutoff gives a 63.33% PPV with 71.43% NPV, and a 64.86% level of overall accuracy. A 0.04 probability cutoff is preferred because of its high sensitivity and NPVs with a comparable specificity, PPV, and percent overall accuracy. Thus, when the computed *g*-score of a patient is above 0.04, surgery is recommended based on this study.

DISCUSSION

When correlated clinically, there is congruence in the finding that an increase in the scores of PV, BOV, CSF protein level, CSF WBC count, and Vellore score render a multiplicative increase in the predicted probability *g*-scores toward surgery. PV and BOV imply increased ICP, whereas high CSF protein and WBC count signify an on-going inflammatory process. These variables may signify a more severe degree of hydrocephalus, which could be better addressed by the addition of surgical intervention to medical management. In addition, an increase in the Vellore score, with positive *β*-coefficient is also in accordance with actual clinical practice of advocating surgical interventions among patients with a Vellore score of 2 and 3. Although some studies do not advocate surgical intervention among patients with a Vellore score of 4, there are also some studies showing benefit among these patients.[3,5,10-13] Moreover, this study has also shown that an increase in the scores of eye-opening (E) and verbal output (V) components of the GCS score confers a multiplicative decrease in the probability of considering surgery. Higher E and V scores signify a better sensorium as seen in patients with a Vellore score

Table 2: Summary of the analysis of maximum likelihood estimates (*β*-coefficients) and the ORs of the variables included in the model

Variables	*β*-coefficient	95% confidence limits		*P*-values	OR	95% confidence limits	
AS	−1.9486	−7.727	0.049	0.5087	0.142	<0.001	46.061
PH	−3.0223	−7.691	3.817	0.2045	0.049	<0.001	5.189
PV	1.3395	−2.317	2.791	0.4728	3.817	0.099	147.874
BOV	1.0264	−1.562	0.700	0.4370	2.791	0.210	37.131
E	−0.3560	−2.653	0.232	0.7613	0.700	0.070	6.967
V	−1.4615	−3.319	4.265	0.1231	0.232	0.036	1.486
M	1.4504	−2.140	0.971	0.4285	4.265	0.118	154.53
OP	−0.0294	−0.117	1.000	0.5079	0.971	0.890	1.059
PROT	0.0004	−0.002	1.004	0.4854	1.000	0.999	1.002
WBC	0.0043	−0.004	0.575	0.3180	1.004	0.996	1.013
NEUT	−0.5535	−2.012	0.574	0.4570	0.575	0.134	2.472
LYMP	−0.5555	−1.987	10.357	0.4468	0.574	0.137	2.400
VELLORE	2.3377	−1.468	6.143	0.2286	10.357	0.230	465.446

AS: Altered sensorium, PH: Persistent headache, PV: Persistent vomiting, BOV: Blurring of vision, E: Eye component of GCS score, V: Verbal output component of GCS score, M: Motor component of GCS score, OP: Opening pressure, PROT: CSF protein, WBC: CSF WBC count, NEUT: % Neutrophil count, LYMP: % Lymphocyte count, VELLORE: Vellore score, GCS: Glasgow coma scale, CSF: Cerebrospinal fluid, WBC: White blood cell, OR: Odds ratio

Table 3: Sensitivity, specificity, PPV NPV, and overall accuracy values of the model over the specified probability cutoff

Probability cut-off (*c*)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0.02	90.48	18.75	59.38	60.00
0.04	90.48	31.25	63.33	71.43
0.06	85.71	37.50	64.29	66.67
0.08	71.43	43.75	62.50	53.85
0.10	66.67	43.75	60.87	50.00
0.12	66.67	43.75	60.87	50.00
0.14	66.67	50.00	63.64	53.33
0.16	66.67	50.00	63.64	53.33
0.18	61.90	50.00	61.90	50.00

PPV: Positive predictive value, NPV: Negative predictive value

of 1, where the majority of patients were given medical management.

The *β*-coefficients of some of the variables, however, were not congruent with what was expected clinically. For example, we would have expected that in the presence of PH, which is one of the hallmark symptoms of increased ICP, surgical intervention would have been more favored. In addition, the neutrophil and lymphocyte counts, which reflect the degree of inflammation in the meninges, should have also given a positive *β*-coefficient favoring surgery. Finally, an increase in the OP, which often signifies increased ICP, should have shown a trend toward surgical management. The seemingly contrasting *β*-coefficient for the OP possibly suggests that the lumbar puncture OP does not always reflect the actual degree of increased ICP especially in the presence of high CSF protein, which makes the CSF more viscous and may thus have a lower OP than expected.[18]

CONCLUSION

Findings of the study provide the clinicians an objective guide in deciding to pursue surgical intervention or not in the management of hydrocephalus from TBM. The most critical finding in this study is the cutoff value (*c*), and the model's sensitivity is given more significance than its specificity. The authors want the model to be more sensitive in looking for patients who will need and benefit from surgical intervention early in the disease process when the subsequent course can still be altered. At the set cutoff value of 0.04, it has a sensitivity of 90.48% but its specificity is only at 31.25%. This may mean that some patients may be subjected to unnecessary surgery. But then again, if the presumption holds true that surgery will prevent further clinical deterioration among patients with hydrocephalus from TBM and following the bioethical principle of beneficence, we want to include more patients who will likely benefit from an early surgical intervention rather than subject them to trial with medical management initially but would end up eventually having emergency surgery.

REFERENCES

1. Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK. Central nervous system tuberculosis: Pathogenesis and clinical aspects. Clin Microbiol Rev. 2008;21(2):243-61.
2. Das G, Hameed B, Siddiqui M, Ahmad J. Management of hydrocephalus in tubercular meningitis. JK Pract. 2004;11(3):161-5.
3. Figaji AA, Fieggen AG. The neurosurgical and acute care management of tuberculous meningitis: Evidence and current practice. Tuberculosis (Edinb). 2010;90(6):393-400.
4. Bhagwati SN. Ventriculoatrial shunt in tuberculous meningitis with hydrocephalus. J Neurosurg. 1971;35(3):309-13.
5. Palur R, Rajshekhar V, Chandy MJ, Joseph T, Abraham J. Shunt surgery for hydrocephalus in tuberculous meningitis: A long-term follow-up study. Neurosurg. 1991;74(1):64-9.
6. Ambekar S, Srinivas D, Pandey P, Somanna S, Chandramouli BA, Devi IB, et al. Factors influencing shunt malfunction in patients with tuberculous meningitis. Indian J Neurosurg. 2013;2(2):175-81.
7. Rajshekhar V. Management of hydrocephalus in patients with tuberculous meningitis. Neurol India. 2009;57(4):368-74.
8. Rodriguez G. Logit Models for Binary Data; 2007. Available from: http://www.data.princeton.edu/wws509/notes/c3.pdf. [Last accessed on 2014 Jun 17].
9. Bullock MR, Van Dellen JR. The role of cerebrospinal fluid shunting in tuberculous meningitis. Surg Neurol. 1982;18(4):274-7.
10. Vadivelu S, Effendi S, Starke JR, Luerssen TG, Jea A. A review of the neurological and neurosurgical implications of tuberculosis in children. Clin Pediatr (Phila). 2013;52(12):1135-43.
11. Singh D, Kumar S. Ventriculoperitoneal shunt in post tubercular hydrocephalus. Indian Pediatr. 1996;33(10):854-5.
12. Mathew JM, Rajshekhar V, Chandy MJ. Shunt surgery in poor grade patients with tuberculous meningitis and hydrocephalus: Effects of response to external ventricular drainage and other variables on long term outcome. J Neurol Neurosurg Psychiatry. 1998;65(1):115-8.
13. Agrawal D, Gupta A, Mehta VS. Role of shunt surgery in pediatric tubercular meningitis with hydrocephalus. Indian Pediatr. 2005;42(3):245-50.
14. Schoeman JF, Laubscher JA, Donald PR. Serial lumbar CSF presure measurements and cranial computed tomographic findings in childhood tuberculous meningitits. Childs Nerv Syst. 2000;16(4):203-8.
15. Kemaloglu S, Ozkan U, Bukte Y, Ceviz A, Ozates M. Timing of shunt surgery in childhood tuberculous meningitis with hydrocephalus. Pediatr Neurosurg. 2002;37(4):194-8.
16. Moreira J, Alarcon F, Bisoffi Z, Rivera J, Salinas R, Menten J, et al. Tuberculous meningitis: Does lowering the treatment threshold result in many more treated patients? Trop Med Int Health. 2008;13(1):68-75.
17. Cherian A, Thomas SV. Central nervous system tuberculosis. Afr Health Sci. 2011;11(1):116-27.
18. Johnston PK, Corbett JJ, Maxner CE. Cerebrospinal fluid protein and opening pressure in idiopathic intracranial hypertension (pseudotumor cerebri). Neurology. 1991;41(7):1040-2.

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