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Diagnostic accuracy of routine blood examinations and CSF lactate level for post-neurosurgical bacterial meningitis

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ABSTRACT

Objective: To evaluate the diagnostic accuracy of routine blood examinations and Cerebrospinal Fluid (CSF) lactate level for Post-neurosurgical Bacterial Meningitis (PBM) at a large sample-size of post-neurosurgical patients.

Methods: The diagnostic accuracies of routine blood examinations and CSF lactate level to distinguish between PAM and PBM were evaluated with the values of the Area Under the Curve of the Receiver Operating Characteristic (AUC_{-ROC}) by retrospectively analyzing the datasets of post-neurosurgical patients in the clinical information databases.

Results: The diagnostic accuracy of routine blood examinations was relatively low ($AUC_{-ROC} < 0.7$). The CSF lactate level achieved rather high diagnostic accuracy ($AUC_{-ROC} = 0.891$; CI 95%, 0.852-0.922). The variables of patient age, operation duration, surgical diagnosis and postoperative days (the interval days between the neurosurgery and examinations) were shown to affect the diagnostic accuracy of these examinations. The variables were integrated with routine blood examinations and CSF lactate level by Fisher discriminant analysis to improve their diagnostic accuracy. As a result, the diagnostic accuracy of blood examinations and CSF lactate level was significantly improved with an AUC_{-ROC} value = 0.760 (CI 95%, 0.737-0.782) and 0.921 (CI 95%, 0.887-0.948) respectively.

Conclusions: The PBM diagnostic accuracy of routine blood examinations was relatively low, whereas the accuracy of CSF lactate level was high. Some variables that are involved in the incidence of PBM can also affect the diagnostic accuracy for PBM. Taking into account the effects of these variables significantly improves the diagnostic accuracies of routine blood examinations and CSF lactate level.

Introduction

PBM is a complication of neurosurgical procedures with an incidence that varies between 1% and 10% (Srinivas et al., 2011; Ragguneau et al., 1983; Korinek, 1997; Korinek et al., 2008; McClelland and Hall, 2007). PBM prolongs the hospital stay, increases the overall cost of hospital care and results in severe disabilities. Importantly, the mortality rate of patients may exceed 20% if PBM is not treated in time (Federico et al., 2001). Therefore, an accurate and rapid diagnosis is critical for the prognosis of PBM patients.

However, the clinical manifestations of this disease (i.e. fever, headache, neck stiffness and mental status changes) are not sufficiently specific or sensitive to diagnose PBM. The value of CSF examinations, such as measurements of the cell counts, protein concentration and glucose levels, is limited, especially in distinguishing PBM from Post-neurosurgical Aseptic Meningitis (PAM) (van de Beek et al., 2010). PAM is triggered by an aseptic inflammatory response to hemolysis products, tumor antigens (Zarrouk et al., 2007), bone dust and implants, which are usually produced during neurosurgery. More importantly, CSF cell counts are still determined by manual counting, which would cause a large inter-observer variability. CSF culture is unreliable partly due to the technique limitations and the extensive prophylactic administration of antibiotics before neurosurgical operations. At our center, the positive detection rate was as low as 6-8% (Li et al., 2015). Moreover, CSF culture is time-consuming and hinders early diagnosis.

Routine blood examinations, such as the WBC counts, neutrophil proportions and platelet counts, are most commonly used to

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diagnose bacterial infections in clinical settings. And a blood examination is safer and more convenient than collecting CSF with a lumbar puncture. Although several studies have reported that the blood WBC counts are significantly higher in PBM than in PAM patients (Sanchez et al., 2008; Ross et al., 1988; Choi, 2013), the actual diagnostic accuracy for PBM of blood WBC counts and other routine blood examinations has not been comprehensively evaluated. In addition, we have observed the clinical phenomenon that hyponatremia is very common among PBM patients. But there was no report regarding postoperative hyponatremia as an indicative of PBM.

CSF lactate originates from anaerobic glycolysis inside bacteria and ischemic brain tissue caused by bacterial infection (Salord et al., 1994; Tureen, 1995). The CSF lactate level reportedly is a good marker to distinguish bacterial meningitis from aseptic meningitis (Sakushima et al., 2011; Huy et al., 2010). A few studies have also shown that CSF lactate was a better marker for the diagnosis of PBM than a routine CSF examination (Li et al., 2015; Tavares et al., 2006; Maskin et al., 2013; Grille et al., 2012; Leib et al., 1999). However, these studies included relatively small sample sizes and variable cut-off diagnostic values.

More importantly, it has been reported that some variables, such as patient gender, operation duration, surgical diagnosis etc., can affect the incidence of PBM (Korinek et al., 2008; Kono et al., 2011; Korinek et al., 2005). Do these variables also affect the accuracies of routine blood examinations or CSF lactate to diagnose PBM? There was no such report, as far as we know.

Therefore, in this study, we first comprehensively evaluated the PBM diagnostic accuracy of routine blood examinations and CSF lactate level among a large sample-size of patients. The variables of patient age, operation duration and surgical diagnosis were shown to affect the incidence of PBM. We then investigated the effect of these variables on the PBM diagnostic accuracy of the examinations. Finally, we built algorithms by integrating the variables with these examinations to improve the diagnostic accuracy for PBM.

Patients and Methods

Patients and data sources

The datasets were extracted from the databases of EMRs, CLI and EMOs of patients who underwent neurosurgery at our hospital between Dec 1, 2012, and Nov 30, 2013. A total of 8524 patients were operated at the period. More than 3 million datasets from the three databases were extracted and matched to exclude redundancy and incompleteness. This study was approved by the institutional review board of our hospital (KY2014-021-01). Because this study did not reveal the individual information of included patients, no specific consent regarding this study was obtained.

Definition of PBM and PAM patients

Supplemental Figure S1 in the online version at DOI:10.1016/j.ijid.2017.03.026(doi:10.1016/j.ijid.2017.03.026) shows the workflow to define PBM and PAM patients. PBM was considered when all the three requirements were met. (1) The patients required a diagnostic lumbar puncture because of fever, headache, neck stiffness or mental status changes after neurosurgeries. (2) CSF bacterial cultures were positive or routine CSF examinations were positive. The routine CSF examination was considered positive when it met all of the following criteria: 1) CSF WBC count $\geq$1000/L and polykaryocyte percentag $\geq$75%, 2) CSF glucose $<$2.5 mmol/L or ratio of CSF glucose to blood glucose $<$0.4 (Li et al., 2015), and (3) The patients received antibiotic treatment after neurosurgeries. PAM was defined when the results of CSF tests did not meet the PBM criteria but the routine CSF tests were still abnormal (over the normal range). The PAM patients also required a diagnostic lumbar puncture, but did not receive postoperative antibiotic treatments (Supplemental Figure S1 in the online version at DOI:10.1016/j.ijid.2017.03.026(doi:10.1016/j.ijid.2017.03.026)).

Statistical analysis

Except the ROC curves analyses, all statistical analyses were performed using SPSS software version 20 (IBM, New York, United States). Continuous data were compared with Student's t-test. The categorical data were compared with a Chi-squared test. The diagnostic accuracy of each examination was evaluated by the ROC curves analyses, which were performed using MedCalc statistical software. The evaluation of AUC_{-ROC} values and comparison of ROC curves was analyzed by the method reported by DeLong ER (DeLong et al., 1988). The diagnostic accuracy was classified as follows: 0.90 to 1.00 AUC_{-ROC} value = excellent, 0.80 to 0.89 = good, 0.70 to 0.79 = fair, 0.60 to 0.69 = poor and 0.50 to 0.59 = failure (Tavares et al., 2006). Fisher discriminant analysis was applied to build algorithms by integrating the variables that affect the incidence of PBM with the results of the routine blood examinations or CSF lactate level. A p value $<$0.05 was considered to be significant.

Results and Discussion

In this study, we evaluated the diagnostic accuracy of routine blood examinations and CSF lactate level for PBM. The best PBM inclusion criteria should be based on the pathogenic examination-CSF bacterial culture. However, CSF bacterial culture represented an unreliable test with a high number of false-negatives (Salord et al., 1995). CSF bacterial culture has been reported to remain negative in up to 70% of suspected clinical cases (Ross et al., 1988; Blomstedt, 1985), and its positive detection rate has been as low as 6-8% in our center (Li et al., 2015). Therefore, the majority of PBM diagnostic studies accept the results of routine CSF examinations, such as cell counts, protein concentration and glucose levels, as inclusion criteria (Li et al., 2015; Maskin et al., 2013; Grille et al., 2012; Leib et al., 1999). Thus, our PBM inclusion criteria also contained routine CSF examination results and followed the standard reported by Li et al. (2015). The PAM group consisted of patients who presented with fever, headache, neck stiffness or mental status changes that were sufficiently severe to require a diagnostic lumbar puncture and have the results of CSF tests entered into the CLI database. In PAM patients (Supplemental Figure S1 in the online version at DOI: 10.1016/j.ijid.2017.03.026 (doi:10.1016/j.ijid.2017.03.026)), the results of CSF examinations did not meet the PBM criteria but routine CSF tests were still abnormal (over the normal range). As recommended by other studies (Forgacs et al., 2001), the inclusion criteria for PAM also required the patients to improve without antibiotic treatment.

A total of 8524 patients underwent neurosurgery at the Beijing Tiantan Hospital between Dec 1, 2012, and Nov 30, 2013. Among these patients, 554 patients developed bacterial meningitis and 868 patients developed aseptic meningitis. As a result, the incidence of PBM and PAM among this group of patients was 6.5% and 10.2%, respectively. As shown in Table 1, the incidence of PBM or PAM was significantly affected by the variables of patient's age, operation duration and surgical diagnosis. The PAM incidence negatively correlated with age and decreased from 12.8% ($\leq$14 years) to 5.7% (>60 years); in contrast, the PBM incidences were similar among the different age groups. The incidences of PBM and PAM significantly positively correlated with the duration of surgery, from 4.2% ($\leq$3 h) to 12.9% (>6 h) in PAM and 3.4% ($\leq$3 h) to 12.3% (>6 h) in PBM. Brain tumor patients seem to be more susceptible to PBM and PAM than patients with other diseases.