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Current diagnosis and potential obstacles for post-neurosurgical bacterial meningitis

M.-Y. BAO[1], H.-T. XIE[2], P. GAO[1], X. MAO[1], Z.-Y. LI[1], W.-H. WANG[1], S. SOPHEAK[1], H.-W. CHENG[1], L. YE[1], X. ZHANG[1]

[1]Department of Neurosurgery, the First Affiliated Hospital of Anhui Medical University, Hefei, China
[2]First Clinical Medical College, Anhui Medical University, Hefei, China

Bao and Xie contributed to the study equally

Abstract. – Despite the guidance of aseptic technology applied, bacterial meningitis seems to be an unavoidable obstacle in the process of neurosurgery, with high rates of disability and mortality. The diagnosis of post-neurosurgical bacterial meningitis (PNBM) mainly depends both on clinical symptoms and laboratory outcomes. Due to the excessive neuro-inflammatory reactions which are evoked by the primary brain disease or the craniotomy operation, the symptoms derived from the infection and aseptic may not be easily distinguished. On the other hand, the low positive rate and time-consuming character restrict the clinical practical values of bacterial culture. Therefore, it is always difficult to make a definite diagnosis of post-neurosurgical bacterial meningitis. Here, we reviewed the established literature about the diagnostic biomarkers for the PNBM and analyzed the potential obstacles in both clinical and scientific studies. Given the obstacle which has negative impacts on further investigation about the biology of PNBM, we only find relatively small numbers of study on PNBM. In this review, we summarize the established diagnostic methods and biomarkers for PNBM. Meanwhile, we also propose some potential investigation prospects. This review may help to better understand the character of PNBM in both clinical diagnosis and scientific investigations.

Key Words:
Meningitis, Neurosurgery, Bacterial infection, Aseptic inflammation, Biomarker.

Introduction

Central nervous system (CNS) infection is a severe infectious disease, leading to about 20.4 million disability-adjusted life year globally[1]. Among that, nosocomial bacterial meningitis, also named post-neurosurgical bacterial meningitis (PNBM), refers to a category of severe complications after the craniotomy, causing inevitable obstacles in the procedures of neurosurgery.

The PNBM types mainly include the meningitis, brain abscess, subdural empyema, and epidural abscess, with a common hallmark event of the blood brain barrier (BBB) breakdown which is attributed to the pathogen derived toxin and the host-related excessive neuro-inflammatory reactions[2-4]. In comparison with the community-acquired bacterial meningitis, the excessive neuro-inflammatory reactions by the triplicity of primary CNS disease, neurosurgical process and bacterial infection in the PNBM conspire to make accurate diagnosis difficult. However, as the occurrence of PNBM increases the overall cost of hospital care, postpones the neurological recoveries after effective treatment for the primary CNS disease and, the most importantly, results in disabilities[5,6], it is still urgently necessary to seek for the optimal management of these often critically ill patients.

The incidence of PNBM varies a lot among studies, ranging from 0.3% to 10%[7,8], and is usually influenced by numerous factors, such as indication for surgery, underlying medical condition, longer operation time, indwelling drainage tube, implantation of artificial materials, cerebrospinal fluid leakage and underlying diseases of the patients[9]. The epidemiological study showed that <45 aged patients had higher risks for infection[10]. In addition, among all the brain tumors, infratentorial and intraventricular tumors have higher risks for infection[10]. Importantly, the application of artificial material significantly increases the incidence rate of PNBM. It has been reported[11] that the patients who used external drainage have a 9.4-fold higher risks than the patient who did not

Corresponding Authors: Xing Zhang, MD; e-mail: zxahmu1h@163.com
Lei Ye, MD; e-mail: yelei8778@sina.cn

use it. Meanwhile, we also noticed that the mortality of PNBM was 20%-50%, if no proper treatments were timely applied[12]. In some specific type of meningitis, such as carbapenem-resistant gram-negative postoperative meningitis (CR-GNPOM), the mortality can reach as high as 60%-70%[13].

Clinically, the etiology of PNBM has a wide spectrum of microorganisms, which are from gram-positive cocci to gram-negative bacilli. Meanwhile, during the last decade, the infectious bacterial spectrum for the PNBM has altered from staphylococcus aureus, coagulase negative staphylococcus, and enterococcus gram-positive bacteria to gram-negative bacilli, especially enterobacteriaceae, probably due to the extensive usage of antibiotics nosocomially or in community[14,15]. Another important epidemiological issue is the ever-increasing situation for drug-resistance bacteria. World Health Organization (WHO) reported in 2017 that the carbapenem-resistant enterobacteriaceae and extended spectrum beta-lactamase (ESBL) producing enterobacteriaceae were the most urgent antibiotic-resistant bacteria worldwide[16]. In China, the Chinese Anti-microbial Surveillance Network reported that the proportion of methicillin-resistant *S. aureus* is almost 100% and the resistance rates for both erythromycin and clindamycin are also 100%[17]. In clinical practice, the clinicians usually use vancomycin as an empiric choice for management of multi-drug resistance (MDR) *S. aureus*, but the low rates for BBB penetration and bioavailability in CNS restrict its application in treating PNBM[17]. As the empirical usage of antibiotics increases the risk for the bacteria spectrum alteration and causes more chances for the MDR bacteria, the timely diagnosis of infection and the accurate recognition of bacteria species are two issues which are urgently to be coped with.

In this review, we mainly focus on the current diagnostic methods and biomarkers of PNBM. Given the limited numbers of the research on PNBM, we meanwhile discuss the existing obstacles in both clinical diagnosis and laboratory investigations, and at the end we are seeking for several potential breakthroughs in the PNBM study. Ultimately, we want the review to provide some clinical or laboratory clues in helping the precision medicine for PNBM.

Diagnostic Methods and Biomarkers

Diagnostic Criteria

The clinical diagnosis of PNBM usually depends on both symptoms and laboratory outcomes, but it is still dubious sometimes regardless of the applied methods. The clinical symptoms include neck stiffness, fever, headache and vomiting. However, since the patients receive a neurosurgery before symptoms' occurrence, the signs of both chemical meningitis and aseptic inflammation, which are attributed to the primary neurosurgical disease and the craniotomy itself, are performed similarly[18]. Thus, clinical symptoms could only provide preliminary clues, rather than a specific indication in the diagnosis.

On the other hand, the clinicians would like to use the laboratory tests to make a definite diagnosis, especially for the outcomes in the cerebrospinal fluid (CSF). Although the PNBM infects the tissues in CNS in a localized manner, systemic immunological reactions also have significant effects against the pathogenic bacteria[19]. In normal conditions, the micro-environment of the CSF keeps steady since the segregation function of BBB. However, BBB dysfunction usually can be found due to the primary neurosurgical disease or the secondary infection before the PNBM onset[20,21]. Subsequently, the CSF biochemical alterations, including the proteins, glucose and chloride ions, are observed in laboratory tests. In another aspect, immunocytes are another indication for the infection. It has been reported that massive peripheral immunocytes infiltrate across the highly permeable BBB into the subarachnoid space at the early stage of PNBM, especially for leukocytes and neutrophils. However, numerous factors could mimic the infection-related CSF alterations, such as blood, surgical operation, artificial materials and bone dust, triggering the inflammation processes, so the index are not specific enough in the differential diagnosis between infection and aseptic inflammations[22]. We summarized potential biomarkers in diagnosis of PNBM in currently established studies (Table I).

Even so, the diagnosis of PNBM still predominantly depends on the biochemical results of CSF. Currently, four criteria are widely used for diagnosing PNBM which are proposed by the Centers for Disease Control and Prevention (CDC)[23], the Massachusetts General Hospital (MGH)[24], the Infectious Diseases Society of America (IDSA)[25] and the Committee of Neurocritical Specialists of China[26].

Neuroimage

In most hospitals, neuroimaging has the characteristic of easy operating to be performed routinely to have a preliminary screening for the suspected PNBM and other neurosurgery-related infections. The neuroimage has outstanding per-

Table I. Clinical indications for the biomarkers for the potential diagnostic of post-neurosurgical bacterial meningitis.

Clinical indication		Sensitivity	Specificity	Potentially influencing factor	Reported cutoff value for diagnosis	Ref.
Bacterial culture		Low	High	Antibiotic application prior to the sampling	-	25
Gram staining		Low	High	Antibiotic application prior to the sampling	-	
CSF lactate		Moderate to high (76.36% - 97.0%)	Moderate to high (78.0% - 91.6%)	Hemolysis	>3.45 mmol/L to >4 mmol/L	8, 22, 69
CSF procalcitonin		Moderate to high (68.0% - 100.0%)	Moderate to high (66.0% - 100.0%)	-	>0.075 ng/L to >2 ng/L	5, 26, 52, 55
CSF cytokines	IL-6	High (100.0%)	High (100.0%)	-		34
	IL-8	Moderate (67.6%)	Low (46.8%)	-	≥85.5 ng/L	35
	IL-12	High (94.6%) High (83.3%)	Moderate (64.6%) High (85.7%)	-	≥3.2 ng/L	34, 35
	IL-13	Moderate (67.6%)	Low (40.0%)	-	≤42.3 ng/L	35
	IL-17	High (100.0%)	High (100.0%)	-	-	34
	IL-23	High (83.3%)	High (100.0%)	-	-	34
	IFN-γ	High (100.0%)	High (99.9%)	-	≤200 ng/L	35

formance in some infection types, such as an abscess, subdural and epidural empyemas, or other surgical site infection[27]. Meanwhile, a high-resolution thin section CT with bone window clearly identifies a port-of-entry of the infection. However, the neuroimage has its inherent defect that cannot distinguish the bacterial species, and therefore, it provides poor information about the precision antibiotics treatments.

Gram Staining and Bacterial Culture

Both gram staining and bacterial culture are commonly used in clinical practice towards the suspected PNBM patients. Gram staining is rapid and highly specific. However, it has poor sensitivity in clinical practice, applying only about 20% positivity. Bacterial culture is considered as a gold standard with a high specificity for distinguish exact bacterial species and drug sensitivity types for the PNBM patients. However, probably due to the influences of antibiotics pre- and post-surgery, the positive rate of CSF culture is extremely low, accounting for ~10% in the clinical test and 10-20% in the majority of investigations[28,29]. Furthermore, the time-consuming character of the bacterial culture, which usually takes more than 24 hours for the results, is always inconducive to the precision antibiotics treatment. The false-positive results which are caused by the contamination also restrict its clinical efficacy in usage. Therefore, according to the standard proposed by the Centers for Disease Control (CDC), patients exhibiting certain symptoms and signs would be categorized as having meningitis even if no organism is detected in the CSF[30].

Peripheral Indications

As PNBM also stimulates systemic immunological reactions, some studies[31,32] attempted to investigate whether biochemical index in the peripheral blood could indicate the occurrence of meningitis. Zhang et al[8] compared the index in the blood routine test between 554 patients with PNBM and 868 patients with aseptic inflammation. Unlike the sensitive index in the patients of sepsis, the diagnostic values of the white blood cell (WBC) proportion and neutrophil proportions were inferior to the platelets counts and the Na concentration. However, the area under the curve (AUC) values of the index, which reflect diagnostic accuracies, in blood routine tests were all lower than 0.7, indicating poor diagnostic accuracies for these peripheral biomarkers in PNBM.

CSF Cytokines

Increasing evidence has found that the cytokines in the CSF have potential diagnostic roles in PNBM. Ye et al[33] has found an association of interleukins (ILs) with the bacterial gram staining types in both sepsis and PNBM. The results indicated the IL-6 and IL-10 levels increased in patients with Gram-negative bacteria infection, while the IL-2 level significantly decreased when patients suffered from Gram-negative bacteria infection. However, the results were controversial. Cuff et al[34] measured proteomics that included 182 immunological and neurological biomarkers in 14 PNBM patients using the Olink platform. The results indicated that although increased IL-6 level could be observed in the inflammatory response, it could not distinguish between bacterial infection and aseptic inflammation. Within the patient cohort with neurological inflammation, a pattern of raised IL-17, IL-12p40/p70 and IL-23 levels delineated nosocomial bacteriological infection from background neuro-inflammation. Furthermore, Kul et al[35] found that the CSF concentrations of IL-8 and IL-12 were upregulated, while IL-13 and IFN-γ were downregulated in the PNBM patients.

Lactate

As a metabolite production, the CSF accumulation of lactate is predominantly derived from the increased productions of anaerobic glucose metabolism, bacterial metabolism and neutrophil glycolysis[36]. Meanwhile, as the penetration speed of lactate from the peripheral circulation is rather slow, it could be considered that CSF lactate is rarely affected by serum lactate at the early stage of PNBM[26,37]. Therefore, CSF lactic acid or lactate could directly reflect the brain metabolism in the presence of bacterial infections. Meanwhile, it has also reported that CSF lactate was used to distinguish bacterial from viral meningitis in children[22,38,39]. Some meta-analyses[40,41] demonstrated that the CSF lactate level is served as a better marker for bacterial meningitis than conventional markers, such as CSF glucose, CSF protein, and CSF cell count. Zhang et al[8] found that the receiver operator characteristic (ROC) curve value of CSF lactate on postoperative days >7 was lower than that on postoperative days <7. However, some reports[42,43] have indicated that the CSF lactate level was influenced by the intrinsic metabolism of CSF red blood cell (RBC). Therefore, the tissue damages in the processes of neurosurgery or lumbar puncture might inevitably release RBC, and

subsequently influence the lactate level, leading to unwittingly mock CSF solutions and false-positive results. So, its diagnostic efficacies should be carefully taken into account in some neurosurgical diseases, especially in the hemorrhagic diseases.

Procalcitonin (PCT)

PCT, the propeptide of calcitonin, is commonly considered as an endogenous nonsteroidal substance without a hormone activity[44,45]. It is reported that PCT is an indicator for the bacterial infection because the bacterial endotoxins and cytokines in the circumstance of infections could blunt the final step of synthesis of calcitonin[46,47], thus causing an abundance of the precursor PCT. However, the originality of PCT has been in a matter of debate among scientists. Some researchers[48,49] believed that the CSF PCT could not be synthesized and released from the brain tissue and was derived from the serum as a result of dysfunction of BBB. Recently, Karzai et al[50] reported that PCT was released by parenchymal cells when stimulator was present, such as bacterial endotoxins, IL-6 and TNF-α. Muller et al[51] also demonstrated that the mRNA of calcitonin was isolated in hamster brain tissues, providing the possibility and rationality of PCT in the bacterial meningitis. Numerous studies[52,53] have found the excellently diagnostic values of PCT in PNMB. Viallon et al[52] and Tomio et al[53] drew the same conclusions, demonstrating that the specificity and sensitivity of CSF PCT in diagnosing PNBM could be as high as 100% and 95%, respectively.

However, there are some disagreements for its diagnostic efficacies. It has been reported that PCT concentration usually remained within the normal range even in the presence of a positive bacterial culture in patients with ventriculitis and ventricular catheters. Wang et al[5] and Laifer et al[54] found that no significant differences in serum PCT levels were found between PNBM patients with the non-infection patients, but Alkholi et al[55] reported that serum PCT with cutoff values higher than 2 ng/mL showed sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 66%, 68%, and 100%, respectively, for the diagnosis of bacterial meningitis. Moreover, there has no uniform cutoff value of CSF PCT concentration for the diagnosis. Current studies[52,55] usually define the positivity of PNBM according to the PCT value are mostly ranging from 0.28 ng/mL to 2 ng/mL. In addition, as Tomio et al[53] suggested that PCT had higher levels in the specific typical meningitis agents (pneumococci and meningococci), we assumed that the PCT value, both in CSF and serum, might probably depend on the bacterial species and virulence.

Polymerase Chain Reaction (PCR) and Next-Generation Sequencing (NGS)

In recent decades, PCR and NGS tests for bacterial infections have been widely applied among investigations. Under the principle of reference of 16S rRNA sequence of bacteria, both PCR and NGS could generally detect the bacterial species and drug resistant types with high positive rate[56,57]. Meanwhile, in comparison with traditional bacterial culture method, PCR and NGS are timesaving which only take several hours to read the consequences. Nonetheless, the technologies have their defects that are still not widely applied in clinical laboratory tests to support a final diagnosis. PCR test has a high false positive rate due to the sample contamination during the lumbar puncture and the interaction between the gene probes and other unrelated germ, resulting in a low specificity of the technique[58,59]. According to another study[60], NGS has a high-throughput characters, allowing thousands of samples tested simultaneously. However, the expensive device and the related reagents, complex and time-consuming operation restrict its application for clinical routine tests. Furthermore, what the clinicians or laboratorians mostly care about is that it could not distinguish the bacterial types which have predominantly infectious property when multiple bacterial infections occur by NGS test.

Key Barriers in Clinical and Scientific Research

We roughly screened the established clinical and mechanical investigations through the PUBMED database using the keyword of "post-neurosurgical bacterial meningitis", but there are just hundreds of related studies. In comparison with other investigations on a certain disease, the numbers of the study on PNBM are extremely limited. Owing to the low diagnostic rate and the indefinite information about the infectious bacterial species, it is difficult to collect enough size of positive samples and also to make a definite research target and strategy. Additionally, due to the prophylactic antibiotic treatments which could uncover the phenotypes of infections, it could hardly eliminate the influences for the bacteria from the antibiotics. Given that these potential obstacles restrain the scientists on per-

forming relative studies on this field, the most important issue on PNBM is to develop an effective method on recognizing the infection occurrence and the bacterial species.

Hypotheses in Scientific Studies Of PNBM

Bacterial Translocation from Gut Causes the Infection

Due to the lack of sufficient studies, the originality of infectious bacteria is unclear. Previous studies[14,61] indicated that the infection might be derived from colonized cutaneous organisms, even though the surgery was free of pathogens. The environment of CNS was considered to be privileged for pathogens and the immunocytes in the peripheral circulations, but current attitudes have changed a lot. BBB prohibits the various materials from the brain[62]. Whereas, in most of CNS diseases, the physiological structures of cerebral vessels are changed, leading to the destruction of BBB. As a consequence, various materials could penetrate from the permeable BBB. Kigerl et al[63] reported that in the animal model of spinal cord injury (SCI), the gut bacteria translocated to multiple abdominal organs through the destructed gastrointestinal mucosa, such as lung, liver, spleen and mesenteric lymph nodes. Therefore, we might hypothesize a probability that gut bacteria can also translocate to the CNS environment through the dysfunctional BBB, leading to the bacterial meningitis. However, the correlation study between the bacterial meningitis and gut bacterial translocation after brain injury or craniotomy are still blank.

In Situ Infection by the Intra-Tumoral Bacteria

In 2020, Nejman et al[64] tested the existence of bacteria in seven cancers, including breast, lung, ovary, pancreas, melanoma, bone, and brain tumors. Interestingly, the results found that the intra-tumoral bacteria existed mostly in intracellular region, and the intra-tumoral bacteria might exert certain effects on influencing the phenotypes of tumors and the response to therapies. Meanwhile, in spite of the pathogen free characters and aseptic technique applied in the neurosurgery, especially for the neurosurgery on the brain tumors, the rate of PNBM on the brain tumor-related neurosurgery is supposed to be lower than the other type of the neurosurgical diseases[8]. However, the epidemiological studies on the PNBM of brain tumors have discovered that the incidence rate of PNBM on brain tumors was generally ranging from 6.8% to 7.9%, in spite of tumor types, indicating a slightly higher rate[8,10]. Based on the situation, we hypothesize a potential relationship between the releases from the tumor-colonized bacteria and the PNBM occurrence. Therefore, studying on the originality of infected bacteria is essential for guidance of surgical methods in clinical practice.

Genetic Susceptibility in PNBM

The bacterial genetic variations for the drug resistance have been widely investigated, indicating that the bacteria have the genetic evolution with drugs, but there is no report investigating the potentially genetic risks for the patients to be affected with bacteria. Previously established evidence[65,66] supported the attitude that the risk of PNBM predominantly influenced by both the bacterial virulence and the immunological status of individuals. It seems that the infectious disease has little relationship with the genetics factors. Interestingly, we found that a study group by Zhang et al[67] has intensively screened the genetic risks for the leprosy infection, a disease caused by mycobacterium leprae. Multiple genes and related gene pathways were discovered to be associated with susceptibility in the infection of *M. leprae*[68]. It provides a clue that all the patients who underwent neurosurgical processes have potential exposure risks to be infected by bacteria. Whether the genetic factors influence the susceptibility of PNBM may be targeted for further investigation.

Prospect

Although the current incidence rate of PNBM is lower than that in the last century because of the advanced technologies applied in the neurosurgical processes, it seems unchanged during the recent decades. The bottleneck on meningitis is still attributed to the low recognition rate of microbe species and related drug-resistance types. Except for the definite results in bacterial culture, most diagnostic methods and biomarkers could only provide suggestive information about the inflammatory or infectious status of patients. We infer that this problem might be of greatest priority in both clinical therapies and laboratory studies. Meanwhile, two prospects in the PNBM can be taken into account, which might open a new insight for the disease. First, we should explore a novel method with high sensitivity and specificity to make a definite recognition of bacterial species and drug-resistance types. Second, given that we

stated in the above context, the originality of microbe should be carefully noticed.

Conclusions

In this review, we summarize the established diagnostic methods and biomarkers for PNBM. Meanwhile we also propose some potential investigation prospects. This review may help to better understand the character of PNBM in both clinical diagnosis and scientific investigations.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

LY and HTX designed the study. PG, XM, ZYL, WHW and BSW collected and interpreted the literature. LY, HTX and SS drafted the manuscript. YQZ and HWC revised the manuscript. All authors read and approved the final manuscript.

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