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Analysis of Cerebrospinal Fluid in Diagnosis of Bacterial Meningitis; Using Nuclear Magnetic Resonance Spectroscopy: A Systematic Review

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- ***NMR spectroscopy of biofluids provides an immensity of information on the endogenous metabolic processes in an organism***
- ***NMR spectroscopy of CSF can be used to diagnosis of bacterial meningitis***

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ABSTRACT

Background: Analysis of biofluids provides a unique window into the biochemical status of a living organism since the composition of a given biofluid will be modulated according to the level of function of the cells that are intimately concerned with its manufacture and secretion. One of the most successful approaches to biofluid analysis has been the application of NMR spectroscopy.

Objectives: The aim of this study was the survey of the role of Nuclear Magnetic Resonance (NMR) Spectroscopy in differential diagnosis of septic bacterial meningitis.

Methods: Using the search strategy from three databases (MEDLINE/PMC, Web of Science, Scopus), list of references of selected articles and gray literature, without time and language limitation, articles up to March 2017 were entered into this review. In this review, 219 articles were acquired at the primary search. Study selection and quality assessment processes were done based on Cochrane library guidelines. After assessing the quality and inclusion and exclusion criteria, 4 articles were selected and entered into the data synthesis.

Results: The results of 4 studies demonstrated relative elevation of lactate value and extracellular acidosis in bacterial meningitis not in aseptic meningitis. Moreover in most of them, decreasing its level by treatment was evident.

Conclusion: Metabolomic analysis with NMR spectroscopy of cerebrospinal fluid can become a powerful helping in differentiation of septic meningitis from aseptic meningitis.

Keywords: Metabolomics; Magnetic Resonance Spectroscopy; Meningitis, Bacterial

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Introduction

Meningitis is characterized as inflammation of the membranes encompassing the brain and spinal cord. Microbiological causes include bacteria, viruses, fungi and parasites (1). The types of bacteria that cause bacterial meningitis vary according to the infected individual's age group. In premature babies and newborns up to three months old, common causes are *group B streptococci* and bacteria that normally inhabit the digestive tract such as *Escherichia coli*. *Listeria monocytogenes* (serotype IVb) is transmitted by the mother before birth and may cause meningitis in the infant (2). Older children are more commonly affected by *Neisseria meningitidis*, (meningococcus) and *Streptococcus pneumonia* (serotypes 6, 9, 14, 18 and 23) and those under five by *Haemophilus influenza* type B (in countries that do not offer vaccination) (3,4). In adults, *Neisseria meningitides* and *Streptococcus pneumonia* together cause 80% of bacterial meningitis cases. Danger of infection with *Listeria monocytogenes* is increased in persons over 50 years old (5,4). The introduction of pneumococcal vaccine has lowered rates of pneumococcal meningitis in both children and adults (6). Viruses that cause meningitis include enteroviruses, herpes simplex virus (generally type 2, which creates most genital wounds; less commonly type 1), varicella zoster virus (known for causing chickenpox and shingles), mumps virus, HIV, and LCMV (7). There are a number of risk factors for fungal meningitis, including the use of immunosuppressant's (such as after organ transplantation), HIV/AIDS (8), and the loss of immunity associated with aging (9). The most common fungal meningitis is cryptococcal meningitis due to *Cryptococcus neoformans* (10). A parasitic cause is often assumed when there is a predominance of eosinophils (a type of white blood cell) in the CSF. The most common parasites involved are *Angiostrongylus cantonensis, Gnathostoma spinigerum, Schistosoma*, as well as the conditions cysticercosis, toxocariasis, baylisascariasis, paragonimiasis, and a number of rarer infections and non-infective conditions (11).

Acute bacterial meningitis (ABM) is a severe, potentially life threatening neurological emergency requiring prompt diagnosis and treatment. The appraised incidence of ABM is 0.4-6 per 100 000 adults per year in developed countries. Worldwide, ABM is one of the top 10 causes of infection related death and 30-50% of survivors have permanent neurological disability (1).

They infect the central nervous system (CNS) via inhalation, haematogenous spread, direct extension from dental and paranasal infections, direct implantation (eg, after surgery) or rarely secondary to infections in the epidural or subdural spaces. Imaging is not essential for the diagnosis or management in many cases of ABM and diagnosis is usually based on clinical examination findings and cerebrospinal fluid (CSF) analysis (1). In the other words, the most important test in identifying or ruling out meningitis is routine analysis of the CSF through lumbar puncture (LP, spinal tap) It is based on the CSF level of Glucose and Protein and cellular counts (12).

Establishing biomarkers for conditions affecting the central nervous system is an important goal which will aid diagnosis and inform therapy. Metabolomics, a reflection of both genetic and environmental factors, has the potential to define accurate disease-specific biomarkers in neurology. Within the

field of neurological disorders, human biofluid NMR metabolic profiles have been characterised in Huntington's disease, multiple sclerosis (MS), schizophrenia and meningitis. The feasibility of CSF metabolite analysis, using NMR spectroscopy, was initially demonstrated over 20 years ago and recognition that CSF metabolites were related to clinical conditions. More recently, studies of CSF metabolite profiles have demonstrated the differentiation of schizophrenia from healthy controls and separation of viral, tubercular and bacterial meningitis (13).

Since proton magnetic resonance (^{1}H-NMR) spectroscopy was applied by gated decoupling or presaturation method with reduction of the H_2O signal to identify the human serum components, such as glucose, lactate, choline, drugs *etc.*, many attempts have been made to apply ^{1}H-NMR spectroscopy in clinical situation, especially for the biochemical examinations of patient samples such as serum, plasma, urine, and blood cells (14). Ex vivo MRS of CSF performed in proven cases of pyogenic meningitis has reported the peaks of cytosolic amino acids (0.9 ppm), lactate (1.33 ppm), alanine (1.47 ppm), acetate (1.92 ppm), and acetoacetate (2.24 ppm) along with reduced levels of glucose. Anaerobic bacterial metabolism is likely to explain increased glucose consumption and consequently lactic acidosis in the CSF (15).

There is a vast range of biochemical, toxicological, and clinical chemical problems that can be addressed using metabolomics based on high resolution ^{1}H-NMR spectroscopy of biomaterials. It should soon be possible to combine genomic, proteomic, and metabolomic data sets into comprehensive ‘‘bionomic’’ systems for the holistic evaluation of perturbed in *in vivo* function (16).

A systematic review was conducted to have a clear answer and deep understanding of the topic of concern. Nuclear Magnetic Resonance (NMR) spectroscopy allows physicians and researchers to obtain biochemical information about the tissues of the human body. This study describes the place of NMR spectroscopy in the diagnosis and management of meningitis.

Materials and Method

Search Strategy:

This review was established using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (17). International databases including MEDLINE/PMC, Scopus, and Web of Science were searched. The databases were thoroughly searched for articles with no time limit, until March 2017. Language limitation and type of documents were not set as inclusion criteria.

Key words:

The search strategy is described in table 1. The search terms with similar meanings were combined using the OR logic, and the search terms were coupled using the AND logic.

Table 1. Search strategy applied in the PubMed, Scopus, and Web of Science databases

#1 Meningitis
#2 Magnetic Resonance Spectroscopy
#3 MR Spectroscopy
#4 MRS
#5 Nuclear Magnetic Resonance Spectroscopy
#6 Nuclear MR Spectroscopy
#7 NMR spectroscopy
#8 NMRS
#9 Proton Magnetic Resonance Spectroscopy
#10 H MR spectroscopy
#11 H MRS
#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)

Criteria for Inclusion and Exclusion:

An article was excluded in our systematic review if it was

1. An article studied on Animal Model
2. An article studied on one of the Paranchymal, Intraparanchymal and Focal lesions such as abscess, encephalitis, cerebritis, endocarditis, cerebral microhaemorrhages (microbleeds)
3. An article studied on immonocompromised host such as HIV+ (Human Immunodeficiency Virus (HIV) is the causative agent for AIDS.) OR VDRL+ (The Venereal Disease Research Laboratory test (VDRL) is a blood test for Syphilis.)
4. An article studied patients only after surgery
5. An article studied on pachymeningitis
6. An article studied on meningoencephalitis
7. An article studied on cerebral malaria (malaria infecting the brain)
8. An article studied on tuberculous meningitis

At first, we evaluated the titles and abstracts of the retrieved articles to determine the initial eligibility; and if necessary, the full articles were studied in detail in order to be selected for the review. Data were extracted by two reviewers. After a detailed study, the remaining articles were included.

Assessment of the Quality of Articles:

The quality assessment of the included articles was also a necessary task. There are many international standards for quality measurement of articles. We used the STARD (Standards for Reporting of Diagnostic Accuracy) which included quality standards for the completeness and transparency of reporting of diagnostic accuracy studies (18).

Methods of Data Extraction:

After screening databases and available resources, the initial articles were selected and their data were extracted uniformly.

Results

After eliminating the duplicate articles and reviewing the titles and abstracts, 129 articles were obtained for this review. After removing 73 unrelated records, 17 full texts were assessed for eligibility. After reading the full text of the articles, according to the inclusion and exclusion criteria mentioned in the methodology, 2 articles were included into the systematic review. In addition, 2 studies identified through bibliographic cross-reference of articles obtained (figure 1). Figure 1 summarizes the article acquisition based on the PRISMA Flow Diagram.

The studies' characteristics are listed in table 2. The selected articles (n=4) consisted of three original studies and one case report study.

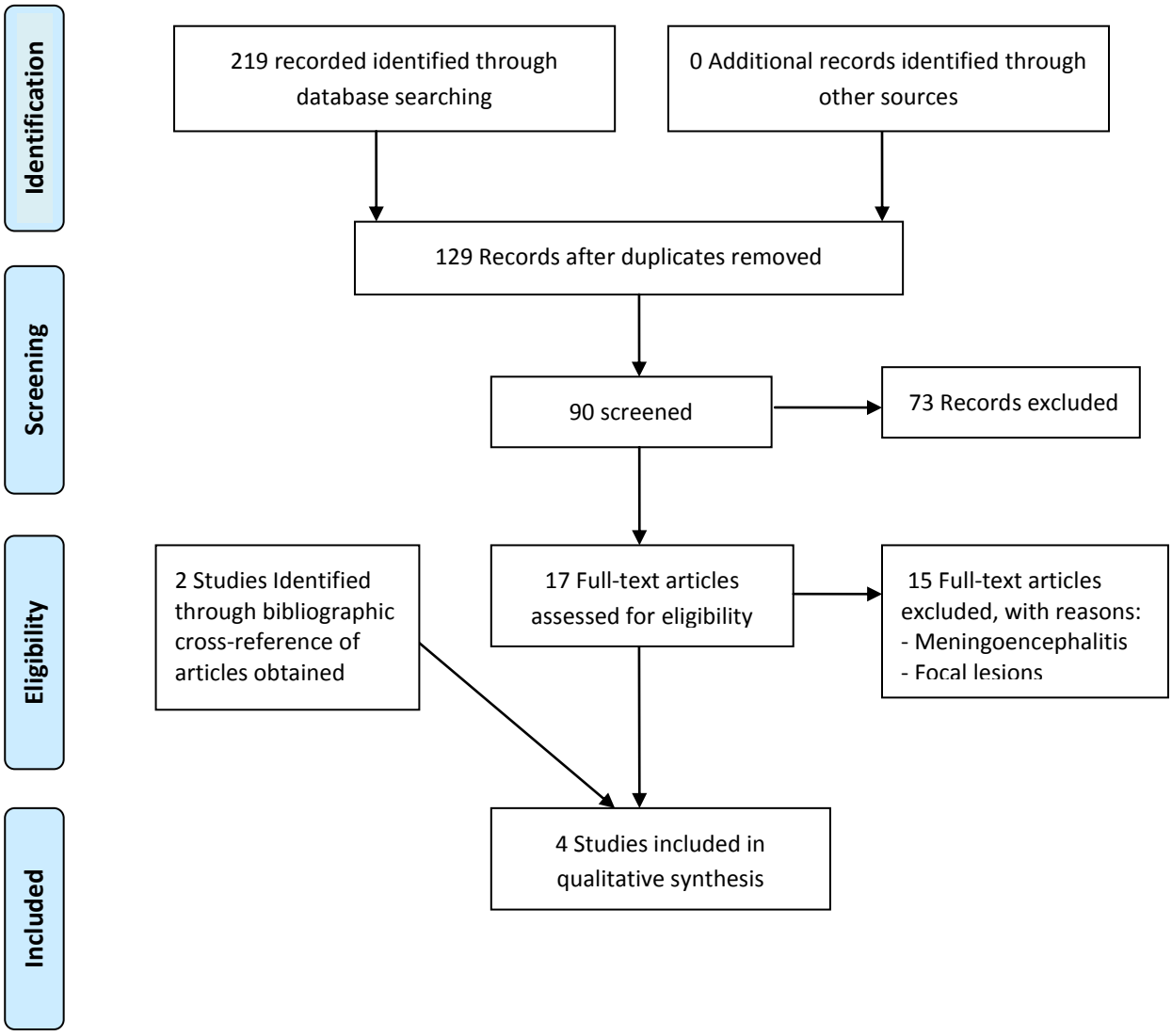

Figure 1. PRISMA 2009 Flowchart for the Included Studies of Diagnosis of Meningitis Caused by Infectious Agents using MRS

Table 2. General features and results of included studies

Author, Year, County	Study type	Number of participants (or Samples)	Age (year)	Case group	Control group	Exclusion criteria	Type of biofluid/ Sampling site	Metabolomic analysis modality	Main Results (Concern Diagnosis of Meningitis)
Coen *et al.*, 2005, Australia	Original	28 patients (19 male, 10 female)	1-79	adults with community-acquired meningitis or external ventericulostomy drainage (EVD) - associated ventriculitis	subjects without neurological disease	Patients who had received therapeutic doses of relevant antibiotic(s) for >18 h (or 1 dose in cases of meningococcal meningitis)	CSF / lumbar	^{1}H-NMR spectroscopy–based metabolomics (using a DRX-400 wide bore spectrometer (Bruker) (400.13 MHz))	- Disproportionately elevated lactate concentrations in bacterial and fungal meningitis. - Elevated CSF concentrations of pyruvate and amino acids— particularly alanine, isoleucine, and leucine—were evident in bacterial and fungal meningitis -Metabonomic analysis clearly distinguished patients with bacterial or fungal meningitis from patients with viral meningitis
Bell JD et al., 1986, England	Original	11 patients (6 male, 5 female)	3-67	patients with diabetes, bacterial meningitis and Liver failure	normal subjects	-	CSF / lumbar	^{1}H-NMR spectroscopy (using a Bruker AM500 and WH400 spectrometers operating in quadrature detection mode at 500 and 400 MHz respectively. All spectra were recorded at a probe temperature of 25°C)	Greatly increase lactate (doublet for lactate at 1.3 ppm present at a concentration of 6.3 mmol/l, but lowered glucose signals, relative to normal adults, with a complete absence of signals from citrate)
Matthews *et al.*, 1989, Canada	Case Report	1 man	29	An encephalopathic patient with pneumococcal meningitis and severe CSF acidosis	Seven young, healthy volunteers were studied while awake and without sensory deprivation.	-	CSF / lateral and third ventricles	Phosphorus magnetic resonance spectroscopy (using a $T_{5,1}$-m bore clinical magnetic resonance imaging and spectroscopy system (Philips, Best, Holland) operating at T15 (25.84 MHz for phosphorus 31)	The results of Phosphorus MR spectroscopy demonstrated the extracellular acidosis. Additionally it proposed that human brain can maintain tight control of intracellular pH even in the presence of marked extracellular metabolic acidosis and the encephalopathy associated with meningitis was not a result of either intracellular acidosis or energy failure
Hiraoka *et al*, 1994, Japan	Original	34 patients (16 male, 18 female)	19-76	patients with CNS diseases (CI, CA, BM, VM, AD, MS, PD, AS, E, P, DN, HE, SCH, DI, NTH and OMND)	none	-	CSF / lumbar	^{1}H-NMR spectroscopy (using a Varian Unity NMR spectroscopy (399.96 MHz) The relative lactate concentration was using a semi-quantitatively determined on the basis of glucose concentration and the ratio of the peak heights (lactate CH 3/ glucose – αCH)	-The relative lactate value was elevated in bacterial meningitis (and decreases with treatment) but not in viral meningitis. 1H-NMR spectroscopy of CSF can become a powerful aid in biochemical diagnosis of CNS disease including bacterial meningitis.

Abbreviations used:
CSF, cerebrospinal fluid;
BM, bacterial meningitis;
LF, Liver failure;
CI, cerebral infarction;
CA, cerebro-arteriosclerosis;
VM, viral meningitis;
AD, Alzheimer 's disease;
PD, Parkinson 's disease;
AS, amyotrophic lateral sclerosis;
E, epilepsy;
P, polyneuritis;
DN, diabetic neuropathy;
HE, hepatic encephalitis;
SCH, schizophrenia;
DI, depressive illness;
NTH, neurosis and tension headache;
OMND, other miscellaneous neurological disorders;

Discussion

Bacterial meningitis is a medical emergency that must be diagnosed quickly from viral and other causes of acute meningitis. Associated mortality is high, with severe neurological sequelae characterized in 25% of cases. Prognosis is directly related to the speed with which the diagnosis is established and treatment initiated. Identification of the causative organism from cultures of CSF is the most sensitive routine test (19).

NMR spectroscopy of biofluids provides an immensity of information on the endogenous metabolic processes in an organism. Details of the various types of biofluid and the types of NMR experiment that are effective are given. The specifications of biofluid NMR spectra are described and practical details of spectral acquisition are also presented. However, the spectra are very complex and many resonances have not been assigned. Therefore, in order to focus on significant differences between a set of spectra from control organisms and from abnormal subjects (e.g., humans with diseases or animals in toxic situations), recourse is made to pattern recognition or chemometric methods. This is exemplified using NMR spectra of a number of different biofluids such as urine, blood plasma, and cerebrospinal fluid. This approach is encapsulated in the concept of metabolomics, a subject which can be regarded as complementary to studies of the genome (genomics) and the proteins in an organism (proteomics). Metabolomics is defined as ‘‘the quantitative measurement of the multi-parametric metabolic response of living systems to pathophysiological stimuli or genetic modification” (16). Establishing biomarkers of the diseases affecting central nervous system is an important goal in diagnosis and inform therapy. Metabolomics is available to define accurate disease-specific biomarkers in neurology (13).

Metabolomic analysis is rapid, requires minimal sample processing, and is not targeted to specific microbial pathogens, making the platform potentially appropriate for use in the diagnostic laboratory. In a pilot study by Coen *et al.* disproportionately elevated lactate concentrations have been reported for patients with bacterial meningitis. This study indicates that metabolomic analysis of cerebrospinal fluid is practical and a potentially more powerful diagnostic tool than conventional rapid laboratory indicators for diagnosing bacterial from viral meningitis and for monitoring treatment. This should have important consequences for early management, reduced experimental use of antibiotics, and treatment duration (19).

The high lactate levels are mainly produced by cerebral glycolysis, with species-dependent, minor contributions from microbial metabolites and little contribution from inflammatory cells (20). Consistent with a minimal contribution from leukocytes, lipids characteristic of inflammatory neutrophils (21,22) were not identified, and NMR spectra for CSF supernatants were similar to those for unspun specimens. Impairment of the citric acid cycle caused by reduced production of acetyl coenzyme A leads to accumulation of pyruvate and production of amino acids from pyruvate via transamination.

Elevated CSF concentrations of pyruvate and amino acids— particularly alanine, isoleucine, and leucine—were evident in bacterial and fungal meningitis. The presence of the ketonebodies 3-hydroxybutyrate,

acetoacetate, and acetone suggests a compensatory response to severe glucose depletion and reduced ATP levels (19).

Within the field of neurological disorders, human biofluid NMR metabolic profiles have been characterised in Huntington's disease, multiple sclerosis (MS), schizophrenia and meningitis. The feasibility of CSF metabolite analysis, using NMR spectroscopy, was initially indicated over 20 years ago, and recognition that CSF metabolites were related to clinical conditions paved the way for further research in this area. More recently, studies of CSF metabolite profiles have demonstrated the differentiation of viral, tubercular and bacterial meningitis (13).

Hiraoka *et al.* suggested that 1H-NMR spectroscopy of CSF can become a powerful help in biochemical diagnosis of CNS disease. Considering CSF lactate concentration as a reflection of anaerobic glycolysis in the CSF samples tested the relative lactate values semi-quantitatively specified in this way were clearly evaluated in cerebral infarction and bacterial meningitis, but not in other disorders including viral meningitis. Also in bacterial meningitis during therapy it decreases accompanied by favorable changes in the clinical response to treatment, as demonstrated by a reduction in the levels of CSF protein and CSF cell count (14).

The study by Bell *et al.* also revealed considerably increased lactate (doublet for lactate at 1.3 ppm present at a concentration of 6.3 mmol/l), but lowered glucose signals (about 1.7 mmol/l which is nearly half that in normal CSF), in spectra of CSF from three infants (3-4 year) with bacterial meningitis relative to normal adults, with a complete absence of signals from citrate in meningitis (23). Of course this study did not discuss about differentiation between bacterial vs. viral meningitis.

The metabolic basis of the encephalopathy associated with acute bacterial meningitis is unknown. Matthews *et al.* assessed the methabolic reason of encephalopathy associated with acute bacterial meningitis using Phosphorus magnetic resonance spectroscopy in conjunction with characterizing the changes of magnetic resonance spectroscopy signals during bacterial meningitis (24). The results of Phosphorus MR spectroscopy indicated the extracellular acidosis that were compatible with results of other studied which are reported in this review (19,23,14).

The presence of cerebrospinal fluid lactic acidosis and hypoglycorrhachia suggests that intracellular acidosis or cellular energy depletion may play a role. Phosphorus magnetic resonance spectroscopy permits for the non-invasive determination of intracellular pH and relative amounts of phosphate containing metabolites in humans. Matthews *et al.* reported a phosphorus magnetic resonance study of brain metabolism in normal volunteers and in an encephalopathic patient with pneumococcal meningitis and severe CSF acidosis. The apparent relative intensities of resonances from adenosine triphosphate, phosphocreatine, phosphodiesters and phosphomonoesters, and inorganic phosphate were evaluated. An encephalopathic patient with pneumococcal meningitis who had severe cerebrospinal fluid lactic acidosis was studied. Brain intracellular pH and relative phosphate metabolite concentrations were normal. Intracellular acidosis and bioenergetic compromise are therefore not causes of encephalopathy in this disease. Intracellular pH is closely regulated in viable

cells, and pH gradients above those normally exposured can be maintained across cell membranes in vitro, this constitutes the first demonstration of the robust potential for control of brain intracellular pH in humans (24).

Conclusion

It can be concluded that the use of metabolomics is helpful to identify differences in metabolite profiles in patients with CNS diseases. Metabolomics offers potential in establishing neurological biomarkers and efforts should concentrate on optimising spectral processing to increase diagnostic accuracy and establishing a national neurological metabolite database assessing a wide range of neurological conditions.

The relative elevation of lactate value and extracellular acidosis in bacterial meningitis not in aseptic meningitis was demonstrated in this study. Moreover in most of them, decreasing its level by treatment was evident. Metabonomic analysis with NMR spectroscopy of CSF can be helpful in differentiation of septic meningitis from aseptic meningitis.

Limitations

1. Most of the articles in the systematic review underlined the role of MRS in diagnosis of CNS disorders, not just exclusively for meningitis.
2. In addition, the modality of used MRS to diagnosis the meningitis are not uniformed and standardized in all studies, and this may lead to differences in data interpretation.

Suggestions

1. In order to better clarity this systematic review, we need a meta-analysis.
2. Since the repeat the previous diagnostic methods may lead to the discovery of new diagnostic methods, we need to more original papers in this subject. Given that number of studies on this subject is very low in recent years.
3. Do basic research by experts in the field of bioinformatics and molecular and cellular concern MRS in metabolomics

Conflict of Interest

The authors have no conflict of interest.

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