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Comparison of lipid-lactate levels between brain abscesses and brain tumors through magnetic resonance spectroscopy examination

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Original Article

ABSTRACT

Background: Intracranial masses are masses found in the intracranial space, such as brain abscesses and brain tumors. Magnetic Resonance Spectroscopy (MRS) examination is a noninvasive examination procedure with magnetic resonance regarding chemical composition or metabolites. One of the metabolites examined in MRS is lipid-lactate which will appear or increase if there are certain abnormalities such as in abscesses and brain tumors.
Objective: This study analyzed the difference in lipid-lactate levels between brain abscess and brain tumor through MRS examination.
Methods: This research adopted an observational analytic approach with a cross-sectional design. Samples in this study were brain abscess and brain tumor patients examined using MRI and MRS at Siloam Jember Hospital from June 2018 to October 2023. The sampling method employed encompassed a total sampling of 45 patients with 15 brain abscesses and 30 brain tumors.
Results: The results of this study showed that the lipid-lactate levels of all brain abscess patients increased by 15 patients (100%), while in brain tumors, lipid-lactate levels increased by 19 patients (63.3%) and decreased by 11 patients (36.7%). The mean rank of lipid-lactate levels in brain abscesses was 14101,93 while in brain tumors was 6220,69. The statistical analysis results using the Mann-Whitney comparison test obtained a p-value of 0.008 (<0.05), meaning there is a significant difference.
Conclusion: There is a significant difference in lipid-lactate levels in brain abscesses and brain tumors.

INTRODUCTION

The incidence of intracranial masses, namely brain abscesses and brain tumors in developing countries is still high. Brain abscess incidence is about 8% of intracranial masses and it is higher than in developed countries. As many as 0.3-0.9 per 100,000 population occur annually in developed countries, and as many as 1,500- 2,500 cases occur annually in the United States.[1] The average brain abscess occurs at 30 to 40 years of age and is more common in males than females, which is as much as 2:1 to 3:1.[2] The morbidity and mortality rates of brain abscess cases were initially very high, but this can be reduced to 24% with the advancements in imaging technology and the utilization of antibiotics. Nowadays, most mortality rates are usually less than 15%.[3] Another study mentioned that before the discovery of Computed Tomography-Scan (CT-scan), the mortality rate of brain abscess reached 40%-60%. However, with the development of methods of diagnosis and assessment of brain abscess evaluation using CT-scan or Magnetic

Resonance Imaging (MRI), the mortality rate is currently around 0-10%.[2] Meanwhile, brain tumors represent one of the most aggressive forms of cancer. They constitute roughly 1.35% of all malignant neoplasms and contribute to 29.5% of cancer-related fatalities.[4] Based on data from the International Agency for Research of Cancer, every year, patients with brain tumors in the world reach a number above 126,000 people, and above 97,000 people die. Brain tumors suffered by 688,000 people or more are found to be 63% benign brain tumors and 37% malignant brain tumors.[5] While, the incidence of brain tumors in Indonesia is 5,323 (1.5%), with a mortality rate of 4,229 (2%).[6]

Intracranial masses are tissue masses found in the brain or other structures in the intracranial space, including brain abscesses and brain tumors. A brain abscess is a concentrated infection within the brain, originating as a restricted region of cerebritis and progressing into an accumulation of pus enclosed by a well-vascularized capsule, usually due to an infectious process or rarely due to a traumatic process.[7] Meanwhile, brain tumors are abnormal cells that grow in brain tissue abnormally and uncontrollably which can interfere with brain function.[6]

One way to diagnose intracranial masses such as brain abscesses and brain tumors is to use MRI as a supporting examination that has higher sensitivity and specificity in diagnosis and can be used to determine the direction of therapy and assess the response to therapy.[3] Magnetic Resonance Spectroscopy is a noninvasive examination procedure with magnetic resonance regarding chemical composition or metabolites.[7] Several metabolites are examined in the MRS examination, but there are metabolites that can overlap between brain abscesses and brain tumors, namely lipid-lactate metabolites. Lipid-lactate will appear or increase if there are certain abnormalities such as in abscesses and brain tumors. Lipids in brain abscesses appear as one of the components of the pus fluid formed due to the decay of the infected fluid. Lactate in brain abscesses is the result of bacterial metabolism.[8] While in tumors, lipids can be found in tumor areas that experience necrosis and membrane damage.[7] Lactate is a biomarker for anaerobic metabolism so it will appear when the tumor starts using anaerobic glycolysis and controls the blood supply so that insufficient blood flow can cause ischemia or also due to necrosis.[9]

Based on research by Irsalina and Sugiyanto (2021), spectroscopic examination of brain abscesses shows that the perilesion lipid-lactate ratio increases.[3] Based on research by Elshafey et al. (2014), the main resonance results in the MRS of brain abscesses were obtained, one of which was lactate (1.3 ppm) and increased lipids (0.9-1.3 ppm). The MRS of the tumor lesion core also showed high lipid-lactate.[8]

Therefore, lipid-lactate is found to be elevated in brain abscesses and brain tumors due to necrosis and anaerobic metabolism. However, no value indicates the limit of lipid-lactate levels in brain abscesses and brain tumors. The MRS is also a non-invasive test that does not require a biopsy for brain metabolite analysis. This study aims to analyze the difference in lipid-lactate levels between brain abscesses and brain tumors through MRS examination. It is hoped that continued research on MRS examination in brain abscesses and brain tumors will help improve diagnosis and therapy in brain abscesses and tumors especially in rural regions in Indonesia.

METHODS

Study subject

This research adopted an observational analytic approach with a cross-sectional research design, conducted at Siloam Jember Hospital in 2023.

Population and sample

This study used a total population of 123 patients who met the inclusion criteria of patients. The total population of this study were patients who had MRI and MRS performed at Siloam Hospital Jember in June 2018-October 2023 with a diagnosis of brain abscess and brain tumor. Inclusion criteria encompassed brain abscess and brain tumor patients examined using MRI and MRS examinations that were confirmed during surgery. Exclusion criteria in this study were insufficient patient medical record data, and poor image quality due to motion and metal artifacts. The sample of this study after exclusion is 45 patients with 15 brain abscess patients (6 females and 9 males; majority aged 45-65 years old) and 30 brain tumor patients (17 females and 13 males; majority aged 45-65 years old). The independent variable used in this study is lipid-lactate levels in patients with brain abscess and brain tumor. The dependent variable used in this study is brain abscess and brain tumor. This study uses secondary data from medical records and the results of MRI and MRS.

Study procedure

This study used 1.5T MRI with a standardized protocol. Evaluation of brain abscesses and brain tumors were identified through durante surgery by neurosurgeons and imaging studies by radiologists. The lipid-lactate metabolite component that can be detected through MRS examination. The results on MRS obtained different graphs in the brain field of view, namely in the part where there is a mass, around the mass, and normal brain parts. So that lipid-lactate levels will be assessed by evaluating the MRS of the lipid-lactate peak, which is compared from the spectroscopy of the massed part with the healthy part so that the results are decreased or increased.[8]

The intralesional and perilesional multivoxel placement was performed on T1WI sequencing with contrast. Voxel points were placed in the most homogeneous area within the lesion and around the lesion, and lactate lipid metabolite values were recorded. The metabolite value increases when it is above the baseline as seen in the graph.

Statistical methods

Data analysis will be conducted using IBM SPSS statistics software. The analysis of data normality was carried out by Saphiro-Wilk analysis. In addition, this study used Mann Whitney to determine the difference between the two groups (p-value <0.05).

Ethics

Approval of the Research Ethics Committee was published by the Health Research Ethics Commission of the Faculty of Dentistry, University of Jember, with Ref. No.2339/UN25.8/KEPK/DL/2023.

RESULTS

Documentation of variable measurements, namely lipid-lactate levels in brain abscess and brain tumor patients, can be seen in Figures 1 and 2.

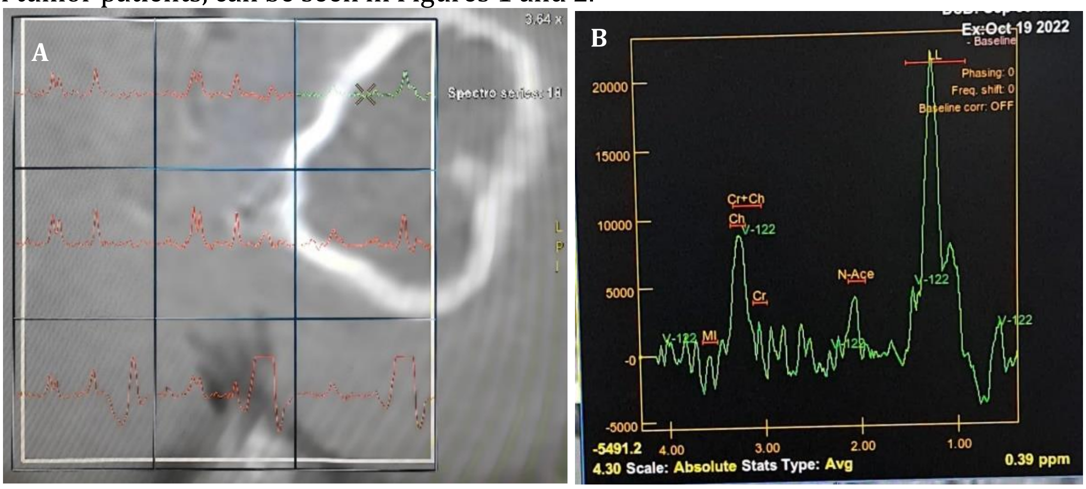

Figure 1. In a brain abscess patient, the brain field image on MRS examination is divided into several sections to see the metabolite levels in each section. The X mark and green color are the selected sections to display the metabolite levels (Figure 1a). Magnetic Resonance Spectroscopy examination results show metabolite levels in the selected section (Figure 1b). The MRS results of brain abscess patients in the mass section with x-marked and green (Figure 1a) show several metabolites, one of which is an increase in lipid-lactate (LL) levels (Figure 1b)

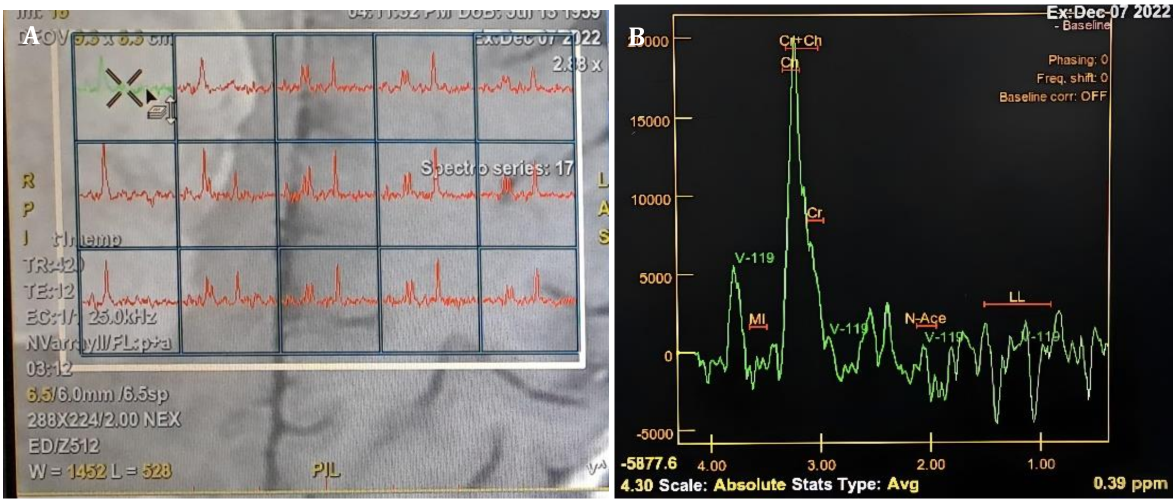

Figure 2. In a brain tumor patient, the brain field image on MRS examination is divided into several sections to see the metabolite levels in each section. The X mark and green color are the selected sections to display the metabolite levels (Figure 2a). Magnetic Resonance Spectroscopy examination results show metabolite levels in the selected section (Figure 2b). The MRS results of brain tumor patients in the mass section with x-marked and green (Figure 2a) show several metabolites, one of which is depressed N-Ace peak and there is no increase in lipid-lactate (LL) levels (Figure 2b)

The results of this study based on age characteristics of brain abscesses and brain tumors were found to occur mostly in those aged 45-65 years with 9 samples (60%) of brain abscesses and 18 samples (60.0%) of brain tumors. Brain abscess patients were found mostly at the age 45-65 years 9 patients (60%), while brain tumor patients were found mostly at the same by 18 patients (60%). The results of this study based on gender characteristics in brain abscesses were found mostly in males (60.0%) while brain tumors were found more in the females (56.7%). This study showed that lipid-lactate levels in brain abscesses increased in all 15 samples (100%). While lipid-lactate levels in brain tumors were found to increase by 19 samples (63.3%) and decreased by 11 samples (36.7%). Overall lipid-lactate levels in brain abscesses and brain tumors were found to increase by 34 samples (75.6%) and decreased by 11 samples (24.4%) (Table 1).

Table 1 Patient characteristics of brain abscess and brain tumor

Patient characteristics	**Brain abscess**		**Brain tumor**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**
Age						
<20 years	0	0.0	2	6.7	2	4.4
20-44 years	3	20.0	9	30.0	12	26.7
45-65 years	9	60.0	18	60.0	27	60.0
>65 years	3	20.0	1	3.3	4	8.9
Gender						
Female	6	40.0	17	56.7	23	51.1
Male	9	60.0	13	43.3	22	48.9
Lipid-lactate levels						
Decreased	0	0.0	11	36.7	11	24.4
Increased	15	100.0	19	63.3	34	75.6

This study used a normality test that was carried out to see the normality of the data distribution. The results of the test normally show that the significance of Shapiro-Wilk is <0.05, which means the data are not normally distributed. Therefore, the analysis used in this study is the Mann-Whitney test. The results of the Mann-Whitney Test showed that the mean rank of lipid-lactate levels in brain abscesses was 14,101.93 while in brain tumors was 6,220.69. In the statistical analysis of the comparison of lipid-lactate levels between brain abscess and brain tumor, the p-value of the Mann-Whitney test was 0.008 (<0.05), which means there is a significant difference (Table 2).

Table 2 Mann-Whitney test result

Lipid-lactate levels	Brain abscess		Brain tumor		p-value
	n	Mean Rank	n	Mean Rank	
	15	14,101.93	30	6,220.69	0.008*

*Mann Whitney test

DISCUSSION

The results of this study found that the characteristics of patients with brain abscesses and brain tumors based on age mostly occurred at the age of 45-65 years. This is in line with the research of Elshafey et al. and Onyambu et al. who found that the average age of patients with brain abscesses and brain tumors was 45.3 years.[8,10] Research by Amila et al., Ardhini et al., and Sensusiati respectively found that the majority of brain tumor patients were 46-65 years old (53.3%), 41-50 years old (31.4%), and 51-60 years old (25.4%), and the average age of brain tumor patients was 48 years old.[11–13] However, this contradicts Valentino and Angraini who stated that the average age of brain abscess patients is 30 to 40 years old.[2]

The age difference that occurs in brain abscesses can be following the source of infection, the main source originating from ear infections is usually 20-40 years old and the risk of incidence will increase if the infection is followed by head trauma and post-surgical procedures.[2] Whereas brain tumors increase with age due to changes in body cells and tissues, exposure to years of risk factors such as radiation and chemicals, genetics, unhealthy lifestyles, environmental factors, and a decreased immune system. However, brain tumors can also occur at a young age due to factors that may influence such as genetics, environment, active or passive smoking, alcohol, obesity, lack of exercise, exposure to pesticides, radiation, nutrition, and so on.[14]

The results of this study based on gender characteristics in brain abscesses and brain tumors found more males than females. This contradicts research by Elshafey et al. and Onyambu et al. who found that patients with brain abscesses and brain tumors were more likely to be males than females, as many as 50.8% of males and 49.2% of females with similar results.[8,10] However, this is per a study by Alshammari et al. indicating that the prevalence of brain lesions among females surpassed that of males, with a ratio of 1.14:1.[15] Research by Valentino and Angraini found that brain abscesses occur more in males than females with a ratio of 2:1 to 3:1.[2] Research by Amila et al., Sensusiati, Ardhini et al., and Aninditha et al. found that females were more affected by brain tumors than males.[11–13,16]

The high prevalence of brain tumors in females may be due to the high prevalence of meningioma in females, which is thought to be due to the role of sex hormones in females and passive or active smoking in females.[16] In females, there can be an increase in the hormone estrogen which can affect the formation of meningioma tumors due to cell proliferation.[17] Meanwhile, the high prevalence of brain abscesses in male can occur due to susceptibility to infection. Several risk factors for brain abscesses, namely infections adjacent to the brain or sources of infection elsewhere that spread hematogenously, procedural neurosurgery, sharp head trauma, pulmonary abnormalities such as infections, arteriovenous fistulas, chronic sinusits or otitis media, and immunocompromising diseases such as HIV/AIDS.[2]

This study assessed lipid-lactate levels through MRS examination in patients with brain abscesses and brain tumors. The MRS can complement MRI in characterizing brain lesions, assessing lesion type, and assisting in grading lesions.[9] One of the metabolites examined in MRS is lipid-lactate which will appear or increase if there are certain abnormalities such as in abscesses and brain tumors. Lipids and substances between them are important components of brain structure and function. The brain possesses the second greatest amount of lipids following adipose tissue, constituting 50% of its dry weight. Lipids in the brain function to produce phospholipids used by cell membranes.[18] Lipid metabolic processes in the brain have the potential to influence neuronal function on a regular basis, as these processes are strongly associated with brain energy regulation, oxidative stress, neuroinflammation, and disturbances in lipid metabolism within neuroglial cells.[19] Meanwhile, lactate is the result of glycolysis, which is one of the metabolic pathways of glucose that can produce energy. Under normal oxygen levels, the primary source of adenosine triphosphate (ATP) production occurs via the mitochondrial electron transport chain. Glucose undergoes conversion into pyruvate through the enzyme pyruvate dehydrogenase (PDH), contributing carbon atoms to the tricarboxylic acid (TCA) cycle. The products of the TCA cycle, such as nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2), fuel the electron transport chain, resulting in the generation of 32-36 ATP molecules. Conversely, in hypoxic or anoxic conditions, ATP is generated through anaerobic glycolysis, where each glucose molecule produces only 2 ATP molecules. In such circumstances, pyruvate is converted into lactate, and the enzyme lactate dehydrogenase (LDH) transforms NADH into NAD^+.[20]

The results of this study showed that lipid-lactate levels in brain abscesses all increased in as many as 15 samples (100%). This is in accordance with research by Mejia et al. found in brain abscess patients there is an increase in lipid-lactate levels.[21] Research by Bluml et al. found that in acute and chronic infections there is an increase in metabolic peaks, one of which is lipid-lactate. In addition, in abscesses that were given antibiotics after 20 days, only lipid-lactate was detected. The brain abscess stage of acute cerebelitis showed an increase in lipid-lactate.[22] A brain abscess is caused by a bacterial or fungal infection in the brain tissue that can come from an infection in the brain, head injury, or infection through the bloodstream. Brain abscess develops in several stages, the first is early cerebritis where there are necrotic centers containing bacteria and diffusely distributed inflammatory cells, while the advanced cerebritis stage has necrotic centers and inflammatory cells that are larger and more numerous. Furthermore, the early capsule stage has decreased inflammatory cells and increased fibroblasts, while the advanced capsule stage has fewer inflammatory cells.[21] Lipids can appear in brain abscesses due to the process of necrosis of infected tissue so that pus fluid is formed containing white blood cells, bacteria, and other materials derived from infected tissues. This pus may contain lipids that are the result of the breakdown of the infected tissue cells. In addition, lactate is a biomarker for anaerobic metabolism. In various pathological conditions characterized by increased metabolism, such as abscesses, lactate concentrations may increase significantly.[23] The increase in lactate can come from increased glycolysis and fermentation of the infecting microorganisms in the brain abscess. Pyogenic bacteria possess the ability to metabolize glucose through the glycolytic pathway, resulting in the significant generation of lactate pools.[8] Therefore, lactate arises due to bacterial fermentation while lipid-lactate may arise due to necrosis in the brain abscess.[21]

In this study, brain tumors were not differentiated based on tumor grading and it was found that not all brain tumor patients had increased lipid-lactate levels in the MRS examination, namely 63.3% increased and 36.7% decreased. This is under research by Weinberg et al. which states that low-grade gliomas usually do not have an increase in lipid-lactate. Increased lipid-lactate is usually found in grade IV tumors and areas of necrosis.[24] Research by Nakamura et al. found that an increase in lipid-lactate was found in grade III (8.3%) and grade IV (44%) brain tumors, while grades I and II were not found, and the p-value <0.05, which means that the peak frequency is significantly different between tumor grades.[25] Lipids in brain tumors are generated from areas undergoing necrosis and escalate in diseases characterized by rapid cell turnover, such as high-grade gliomas.[24,25] As brain tissue undergoes damage or disruption, as seen in the growth of brain tumors, lipid macromolecules are transformed into mobile lipids. In addition, lactate is generated from anaerobic glycolysis conditions associated with hypoxia and hyperglycemia. The buildup of lactate in brain tumors results from heightened glycolytic activity and is linked to ischemic alterations in inadequately supplied tumor tissue or a higher occurrence of necrotic regions.[25] In general, proliferating cancer cells, regardless of oxygen availability (whether hypoxia or normoxia), generate significant quantities of lactate due to the substantial metabolic transition from oxidative phosphorylation to glycolysis. Increased lactate levels can foster immune evasion by tumor cells and increase vascular endothelial growth factor synthesis, thereby facilitating increased cell migration through lactate-induced angiogenesis.[26] Therefore, in brain tumors, increased lipid-lactate tends to be more prevalent in malignant or high-grade tumors due to increased areas of necrosis resulting from the aggressive nature of the tumor tissue.[25] In addition, decreased lipid-lactate levels may be due to structural changes in brain tumor tissue that have lower lipid levels, further oxidation with a metabolic shift to oxidative pathways resulting in lower lactate levels, avoidance of oxidative stress by reducing lactate production that can be a source of free radicals to reduce cell damage, or possible weakness of metabolic mapping in the tumor.[26,27]

In this study, an increase in lipid-lactate levels was found more in brain abscess cases compared to brain tumors. The results of this study also showed that the mean rank of lipid-lactate levels in brain abscesses was 14,101.93 while in brain tumors was 6,220.69. This is per research by Elshafey et al. which obtained different lipid-lactate peaks in brain abscesses and brain tumors. The study contained 45 samples and the results of an increase in lipid-lactate were identified in 14 samples of 15 brain abscess samples and 13 brain tumor samples of 30 necrotic brain tumor samples, which means that an increase in lipid-lactate is more common in brain abscess cases.[8] Research by Alshammari et al. found a peak increase in lipid-lactate in malignancy or high-grade glioma (3.3%), meningioma (3.3%), and abscess (16.6%). Abscesses showed increased lactate on MRS compared to neoplastic lesions.[15] Research by Elsadway and Ali found an increase in lipid-lactate in infection and glioma. Not all tumors have an increase in lipid-lactate.[28] Research by Onyambu et al. found $p<0.001$ MRS results to distinguish tuberculoma from multiform glioblastoma. In these two diseases, an increase in lipid-lactate was found. Research by Gupta et al. demonstrated that tuberculosis showed a marked increase in lipid levels within the lesions. In addition, it was also found that there was an increase in lipid-lactate in low- and high-grade tumors.[29] Therefore, the examination of metabolic profiles has the potential to enhance diagnostic precision and refine disease stage evaluation for various brain conditions such as brain tumors, hypoxic-ischemic injury, inborn errors of metabolism, and infections.[22]

The limitations of this study are number of brain abscess and tumor patients who performed MRI and MRS examinations, data related to other risk factors that can affect both variables were not studied, the components detected in spectroscopy are not only lipid-lactate, but in this study only took the value of lipid-lactate levels, the scale of the study only decreases and increases in lipid-lactate levels, and brain tumors are not divided based on tumor grading so it is possible to affect the results obtained. Future researchers are expected to continue to improve research on other metabolites detected in MRS, not only lipid-lactate but also include other risk factors that can affect variables to avoid bias. Future researchers are expected to split the grading of brain tumors that may affect the results of the study and are expected to increase the number of larger samples.

CONCLUSION

Based on the findings from data analysis and discussion conducted in the study comparison of lipid-lactate levels between brain abscess and brain tumor through MRS examination, it can be inferred that there is a significant difference between lipid-lactate levels between brain abscess and brain tumor with MRS examination. In brain abscesses, the lipid-lactate levels were found to increase, while in brain tumors, most lipid-lactate levels increased and there were also lipid-lactate levels that decreased. Therefore, lipid-lactate levels on MRS examination may help improve diagnosis and screening for brain abscesses and brain tumors. Some suggestions are given for the future are for health facilities to be able to conduct MRI and MRS examinations as a form of screening and can help diagnose patients.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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AUTHOR CONTRIBUTION

NAS and HF performed data collection, assessment, writing, and finalization; KYWP, H, and NKA helped provide advice during the research and draft of the manuscript.

LIST OF ABBREVIATIONS

MRI: Magnetic Resonance Imaging; MRS: Magnetic Resonance Spectroscopy; ATP: Adenosine Triphosphate; PDH: Pyruvate Dehydrogenase; TCA: Tricarboxylic Acid; NADH: Nicotinamide Adenine Dinucleotide; FADH2: Flavin Adenine Dinucleotide; LDH: Lactate Dehydrogenase; VEGF: Vascular Endothelial Growth Factor.

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