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Prognostic Value of Magnetic Resonance Spectroscopy in Patients With Diffuse Axonal Injury: Systematic Review Of The Literature

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ABSTRACT

Introduction: Magnetic resonance spectroscopy (MRS) is an imaging technique that provides spectroscopic information on the changes in biological markers. Studies suggest that MRS can be valuable in the prognosis of patients with diffuse axonal injury (DAI).

Methods: PubMed and Scopus, two major databases, were systematically searched in June 2015 using the following search strategy: ((((Magnetic resonance spectroscopy OR MRS OR MR spectroscopy)) AND (Diffuse axonal injury OR DAI)) AND Prognosis). Relevant articles were selected, and the prognostic value of MRS in patients with traumatic DAI was investigated. All necessary information was extracted for data synthesis based on the primary objective of this study.

Results: Out of 19 articles found in PubMed and 151 in Scopus, eight documents were selected for data extraction following inclusion/exclusion criteria. The total number of patients included in the selected studies was 197. All selected articles demonstrated that MRS can be used to quantitatively analyze metabolite changes in patients with DAI.

Conclusion: Based on the results of the included studies, MRS is a sensitive tool that can help predict the prognosis of patients with DAI.

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Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide and represents a significant global health issue. Diffuse axonal injury (DAI) is one of the most common causes of deterioration in patients with TBI, affecting approximately half of those with head injuries. Traffic accidents are the most common cause of DAI (1). DAI is a brain pathology that can result in prolonged traumatic coma. It typically occurs following TBI, with extensive axonal damage caused by disorganization of cellular structures and axonal edema in various areas of the brain (2-5). In conventional imaging, there is often a weak correlation between the prognosis of patients and the primary lesion. This may be due to DAI affecting surrounding areas or regions beyond the original injury, as well as microscopic axonal damage (6, 7). DAI is a significant cause of long-term disability. Although the exact prevalence of brain injuries varies by region, the incidence of mild TBI is estimated to be between 100 and 600 cases per 100,000 people (8).

The prognosis of a disease can vary depending on the severity, location of the lesion, and access to medical care. However, severe axonal damage often leads to coma and is associated with an unfavorable outcome (8-10). Since CT scans and other macroscopic imaging techniques cannot effectively visualize these microscopic processes, diagnosing diffuse axonal injury (DAI) can be challenging. To date, no diagnostic method has been able to accurately predict the prognosis of patients with diffuse axonal brain lesions. According to the results of various studies, the levels of brain metabolites are directly correlated with the severity and prognosis of patients. Clinical findings suggest that measuring brain metabolites using magnetic resonance spectroscopy (MRS) may help predict the prognosis of the disease.

Nuclear magnetic resonance (NMR) spectroscopy, commonly known as magnetic resonance spectroscopy (MRS), is a sensitive, accurate, and non-invasive method that allows for the evaluation

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of brain metabolite changes following trauma (11). It is an imaging technique that provides spectroscopic information about changes in biological biomarkers and other metabolites during organ activation. Studies suggest that neurobiochemical findings can aid in evaluating the prognosis of patients with diffuse axonal injury (DAI) (12)This study aimed to systematically review the prognostic value of MRS imaging in diffuse brain lesions.

Methods

Search methods

We systematically searched PubMed and Scopus, two major databases, using the key terms "Magnetic resonance spectroscopy" and "Diffuse axonal injury" in the title, keywords, and abstract of papers where the prognostic value of MRS as a practical and non-invasive imaging technique had been evaluated in traumatic diffuse axonal injury. The following search strategy was used: ((((Magnetic resonance spectroscopy OR MRS OR MR spectroscopy)) AND (Diffuse axonal injury OR DAI)) AND Prognosis) to find relevant documents in PubMed and Scopus. Additionally, a customized search strategy was employed for Scopus: "magnetic resonance spectroscopy" was first searched, followed by "diffuse axonal injury" within the results. The results from both databases were then limited to documents published in English and conducted on human subjects. The database search was performed in June 2015. To further minimize the possibility of data loss, after systematically searching the databases, Google Scholar and the Google search engine were also used to search for the relevant key terms. The reference lists of the collected articles were manually screened to identify other potentially relevant studies.

Study selection and inclusion/exclusion criteria

No time range was defined in the customized search strategy for selecting appropriate documents. However, only articles published in English were included in this study to minimize data loss, reduce the risk of errors, and prevent possible misinterpretation of data in the subsequent data synthesis process. The customized search method allowed the inclusion of articles with various types of clinical designs, including case-control studies, cross-sectional studies, clinical trials, comparative studies, and prospective cohort studies for further data processing. However, conference papers, abstracts, editorials, review articles, and meta-analyses were excluded from further evaluation. In the first step of article selection, publications with duplicated data and articles with irrelevant subjects or languages were excluded based on a review of the title, keywords, and abstract. Articles with unavailable full text were also excluded from the data synthesis process. Additionally, studies conducted in vitro or on animals were excluded. Similarly, articles in which MRS was used for the clinical evaluation of metabolites in pathological conditions other than DAI were also excluded. Therefore, the inclusion criteria for article selection in this review were all English-language articles in which the prognostic value of MRS had been investigated in patients with DAI.

Data synthesis

General information was extracted and recorded, including the first author's name, country of origin, date of publication, study design, and the number of participants. Additional data, including demographic information, assessment methods, and main findings, were collected under the primary objective of this study. Data were extracted and analyzed based on studies reporting the efficacy and prognostic value of MRS in DAI. Two reviewers independently performed all data processing, including article selection and data extraction, following the recommended standard protocol outlined in the PRISMA 2009 checklist (13). Any discrepancies during the data extraction process were resolved between the authors before proceeding with further data synthesis.

Results

Study search results

A total of 19 relevant articles were found in the PubMed database and 151 in Scopus. After thoroughly reviewing the abstracts, 93 irrelevant articles were excluded in the first step. Additionally, 23 documents were excluded due to language irrelevancy. Twenty-five documents with duplicated data were then excluded during the article selection process. Eighteen articles in which MRS imaging had been used to diagnose hepatic diseases or other pathological conditions were also excluded from further assessment. Furthermore, nine studies conducted on animals were excluded. Five additional relevant documents were identified through manual reference list screening of the previously selected articles. One more paper was found and included through a Google Scholar search. Four of these papers were excluded due to the unavailability of the full text. Finally, after a rigorous article selection and comprehensive review, only eight relevant articles that met all the defined inclusion/exclusion criteria were included for data analysis. The step-by-step process of literature search and study selection is shown in Figure 1.

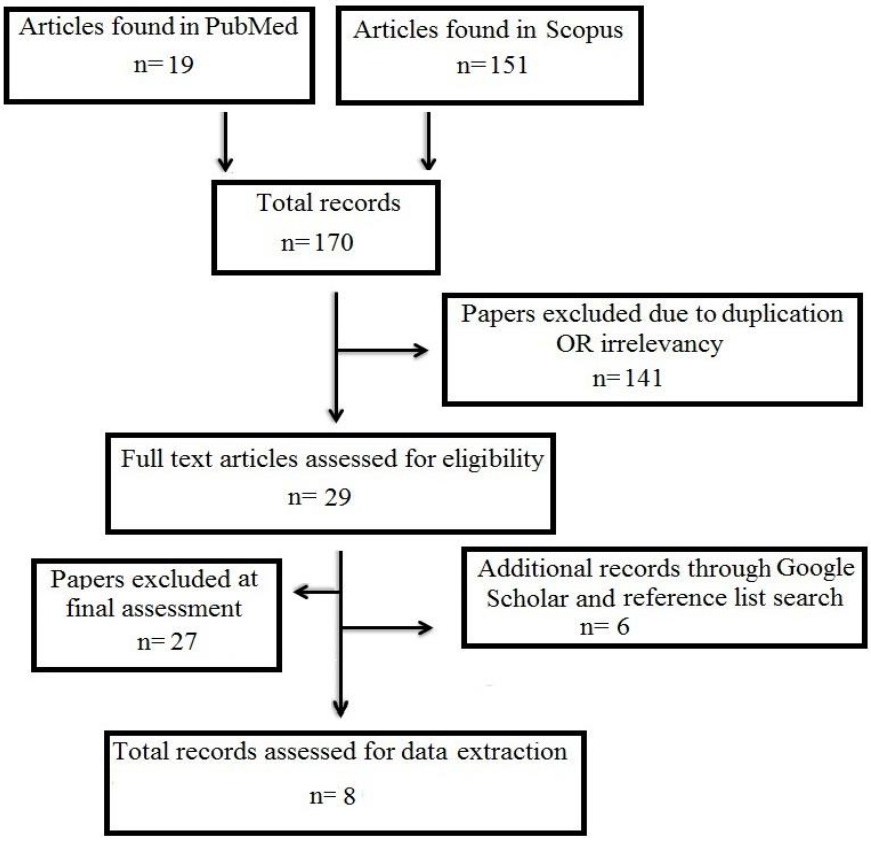

Figure 1. The literature search strategy for the selection of relevant documents.

General characteristics of the included articles

A total of 197 participants were enrolled in the selected studies, in which the prognostic value of MRS as an accurate and non-invasive imaging technique was evaluated in patients with DAI. In some studies, 55 healthy participants were included as a control group. The number of patients enrolled in the selected studies ranged from 8 to 60. According to the extracted data, participants of both genders were included in the selected studies. However, the sex ratio was not reported in 2 studies, preventing gender-based analysis. In those articles with fully described demographic data, 86 participants were male and 63 were female. The ages of patients in the selected studies ranged from 1-year-old children to 65 years. Among the included studies in this literature review, one was a prospective cohort study, two were cross-sectional studies, and one was a comparative study. Additionally, there was one retrospective study and three evaluation studies. The most recent study included in this review was published in 2013, while the oldest was published in 2002. The general characteristics of the included studies are presented in Table 1 in chronological order of publication.

Table 1. General information about the included articles.

No	First author	Year	Country	Study design*	Study population®	Sex ratio (M/F)	Patients number
1	Kirov II (14)	2013	USA	PSC	mTBI	21/5	26
2	Babikian T (15)	2010	USA	CSS	TBI	8/2	10
3	Govind V (16)	2010	USA	ES	TBI	25/4	29
4	Gasparovic C (17)	2009	USA	RS	mTBI	4/6	10
5	Holshouser BA (12)	2005	USA	ES	TBI	-	40
6	Yoon SJ (18)	2005	Korea	CS	TBI	-	8
7	Uzan M (19)	2003	Turkey	ES	VS	9/5	14
8	De Stefano N (20)	2002	Italy	CSS	MS	19/41	60

* PCS: Prospective cohort study, RS: Retrospective study, CSS: Cross-sectional study, CS: Comparative study, ES: Evaluation study,

® Mild traumatic brain injury (mTBI), VS: Vegetative state, MS: Multiple sclerosis

Study results

The results of this review indicate that MRS is a suitable imaging technique capable of accurately detecting even small variations in metabolite levels in clinical practice, particularly for brain pathological assessments. All of the articles

included in this study demonstrated that MRS can quantitatively detect changes in primary brain metabolites, such as N-acetyl aspartate (NAA), total choline (Cho), total creatine (Cre), myo-inositol (mI), glutamine, glutamate, and cerebrospinal fluid fractions in patients with DAI. Therefore, the findings of this study suggest that MRS can be considered a reliable imaging method for assessing axonal injuries. The primary clinical outcomes and methods of assessment are summarized in Table 2.

Table 2. Detailed information on the included documents.

No	First author	Assessment ®	Variables *	Main findings
1	Kirov II	MRI, multivoxel proton MRS, pathological analysis	NAA, Cho, Cr, mI	DAI is quantifiable with Proton MRS imaging
2	Babikian T	MRI, proton MRS, NST	NAA, Cr	MRS provides non-invasive, quantifiable metabolite measures
3	Govind V	MRI, MRS, NST	NAA, Cho, Cr, GCS	MRS provides valuable quantitative information in the diagnosis of mTBI
4	Gasparovic C	Single-voxel MRS, MRS, NST	NAA, Cr, Glu, Gln	H-MRS is more sensitive than other methods in predicting metabolite alterations.
5	Holshouser BA	MRS, SWI, HL	NAA, Cr, Cho, Lac, GCS	Proton MRSI more accurately detected metabolite changes of DAI in brain tissue that appeared normal on imaging.
6	Yoon SJ	MRS, FIM	NAA, Cho, Cr, mI	MRS has the potential to be used for detecting DAI
7	Uzan M	MRI and MRS	NAA, Cr	MRS determines the degree of severity in neuronal and axonal injury
8	De Stefano N	MRS, SWI, MTr	NAA, Cr	MRS is suitable for metabolite detection in MS patients with neuronal injury

*** NAA: N-acetylaspartate, Cho: Choline, Cr: Creatine, mI: myo-inositol, Gln: Glutamine, Glu: Glutamate. GCS: Glasgow coma scale**

® MRI: Magnetic resonance imaging, MRS: Magnetic resonance spectroscopy, NST: neuropsychological test, HL: Hemorrhagic lesions, SWI: Susceptibility-weighted imaging, MTr: Magnetization transfer ratio, FIM: Functional independence measure.

The research limitations in this study were unreported data, particularly demographic information, including the sex ratio.

Discussion

Diffuse axonal injury, which is histopathologically characterized by the observation of axonal edema, is a subset of brain damage caused by trauma (21, 22). This injury occurs in nearly half of the cases of brain damage resulting from severe trauma and is a significant cause of the vegetative state in these patients (23). Conventional imaging methods like CT scans and MRI have limited diagnostic capabilities. Magnetic resonance spectroscopy (MRS) is a non-invasive and sensitive method by which post-traumatic brain metabolite changes can be evaluated. It appears that MRS may help evaluate the prognosis of patients with diffuse axonal injury by measuring brain metabolites such as creatine and choline, which serve as markers of metabolic energy and cell membrane health, respectively (12). Numerous studies have assessed the prognostic value of MRS in acute brain injury and coma, evaluating metabolite levels in different brain regions (24). The results indicate significant changes in brain metabolites following neuronal damage (3, 25, 26). Evaluation of brain metabolite levels, such as the NAA/Chol, Lip/Cr, and Lac/Cr ratios in the normal brain, internal capsule, and cerebral peduncle using MRS in patients with mild TBI, showed that these metabolite ratios significantly change in patients with DAI (5, 27, 28). Studies indicate that MRS imaging can be an effective tool for determining the prognosis of patients with DAI. Additionally, the findings showed that metabolite indices, such as the NAA/Chol ratio, can accurately assess the severity of DAI. The results also demonstrated that NAA levels are directly associated with both the severity of the injury and the prognosis of patients, with lower levels of this metabolite suggesting more severe injury and a poorer prognosis.

Conclusion

The findings show that MRS imaging can accurately assess the levels of brain metabolites such as NAA, choline (Chol), and creatine (Cr), which may reflect the severity of DAI. According to the results of the studies included in this literature review, MRS is a sensitive, accurate, and noninvasive imaging method that holds prognostic value for patients with severe TBI and DAI.

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