ORIGINAL PAPER

Intelligent Computer Systems for Multiple Sclerosis Diagnosis: a Systematic Review of Reasoning Techniques and Methods

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ABSTRACT

Objective: Intelligent computer systems are used in diagnosing Multiple Sclerosis and help physicians in the accurate and timely diagnosis of the disease. This study focuses on a review of different reasoning techniques and methods used in intelligent systems to diagnose MS and analyze the application and efficiency of different reasoning methods in order to find the most efficient and applicable methods and techniques for MS diagnosis. **Methods**: A complete research was carried out on articles in various electronic databases based on Mesh vocabulary. 85 articles out of 614 articles published in English between 2000 to 2018 were analyzed, 30 of which have been selected based on inclusion criteria such as system scope and domain, full description of reasoning method and system evaluation. **Results**: Results indicate that different reasoning methods are used unintelligent systems of MS diagnosis. In 27% of the studies, the rule-based method was used, in 20% the fuzzy logic method, in 18%the artificial neural network method, and in 35% other reasoning methods were used. The average sensitivity, specificity and accuracy of reasoning methods were0.91, 0.77, and 0.86, respectively. **Conclusions**: Rule-based, fuzzy-logic and artificial neural network methods have had more applications in intelligent systems for the diagnosis of MS, respectively. The highest rate of sensitivity and accuracy indexes is associated to the neural network reasoning method at 0.97 and 0.99, respectively .In the fuzzy logic method, the Kappa rate has been reported as one, which shows full conformity between software diagnosis and the physician's decision .In some articles, in order to remove the limitations of the methods and enhance their efficiency, combinations of different methods are used.

Keywords: Decision Support Systems, Clinical Decision Support Techniques, Artificial Intelligence, Diagnosis, Computer-Assisted, Multiple Sclerosis.

1. INTRODUCTION

Multiple Sclerosis (MS) is a kind of chronic and progressive disorder in the central nervous system. This disorder creates a progressive disability, mostly afflicting young people (1-3). The diagnosis of this disorder is based on neurological background and physical examinations and there is no single diagnostic experimental method to prove it (4-9). MS diagnosis is complex because its signs and symptoms are widespread, having a similarity with the symptoms of other neurological and demyelinating disorders, infectious diseases, vascular diseases, inflammatory diseases, and metabolic genetic disorders (10-14).

Decision support systems and expert systems in the realm of medicine can help in diagnosing the disease by using data mining methods and artificial intelligence and also aid the diagnosis process based on parametric and non-parametric decision-making models (15-18).

The advantages of clinical decision support systems in diagnosing central nervous system disorders such as MS include: increasing reliability, increasing diagnosis accuracy, decreasing time loss, decreasing expenses, increasing access to expert neurologists, training inexperienced physicians and clinicians, helping researchers in studies associated with disorders of the nervous system, and eventually noticeable improvement in the quality of the care system and patient life quality (19-24).

Various studies carried out worldwide indicate that many researchers use different software techniques to solve the problems associated with diseases and nervous system disorders (19, 25).

Review studies on "Data mining in

Developer	Year	Task	Reasoning methods	Algorithm/technique/model
Knowledge Based Methods				
1. I. Galea (53)	2015	Prediction and diagnosis	Evidence-Based	—-
2. Ahmad A. Al-Hajji (20)	2012	Diagnosis	Rule- based	Backward chaining
3.Ayangbekun (21)	2015	Diagnosis and treatment	Rule- based	Backward chaining
4.RajdeepBorgohain (22)	2016	Diagnosis	Rule- base	RETE algorithm
5.AtulKrishan Sharma (19)	2014	Diagnosis	Rule-based	Backward chaining
6.YC Cohen (32)	2000	Diagnosis and assess-ment of disability	Rule–based	Ambulation-based EDSS algorithm
7.V.Kurbalija (33)	2007	Diagnosis	Case-based	Case Retrieval Net
8.YelizKaraca (35)	2014	Diagnosis and prognosis of course disease	Model- based	Linear mathematical model
9.M Daumer (34)	2007	Diagnosis and prognosis of course disease	Model- based	Matching Algorithm and OLAP-tool
Non-knowledge based methods				
10.Mary F Davis (43)	2013	Diagnosis and prognosis of course disease	Natural language processing	Perl algorithm
11.Richard E. Nelson1(44)	2016	Diagnosis and prognosis of course disease	Natural language processing	Perl algorithm
12.Herbert S. Chase (42)	2017	Diagnosis and prognosis of course disease	Natural language processing	Definitive type 1, Definitive type 2,possible type 1, possible type 2al-gorithms
13.V. Wottschel (30)	2015	Prediction and diagnosis	Support vector machine (SVM)	—-
14.JM Nielsen (54)	2007	Diagnosis	Statistical analysis	Systematic approach
15.Adrian Ion M_argineanu (51)	2017	Diagnosis	(1) Statistical analysis2) Support Vector Machines (SVM)	(1)Linear Discriminant Analysis (LDA)
16.R. Linder (49)	2009	Diagnosis	(1)Artificial neural network(2) Sta-tistical analysis	(1) Neural net clamping technique(2) Multiple logistic regression(MLR2 , MLR5)
17.Yeliz Karaca (46)	2015	Diagnosis and prognosis of course disease	Artificial neural network	(1)Radial Basis Function (RBF) (2)Learning Vector Quantization (LVQ)3) Feed Forward Back Propaga-tion(FFBP)
18.YasharSarbaz (47)	2017	Diagnosis	Artificial neural network	multilayer perceptron (MLP) with Feed Forward Back Propaga-tion(FFBP)
19.Imianvan Anthony (41)	2012	Diagnosis	Fuzzy logic	Fuzzy cluster means(FCM)
20.Ayangbekun (37)	2015	Diagnosis	Fuzzy logic	Mamedani inference model
21..Ali Amooji (38)	2015	Diagnosis	Fuzzy logic	Mamedani inference model
22.M.ArabzadehGhahazi (39)	2014	Diagnosis	Fuzzy logic	Mamedani inference model
23.Massimo Esposito (40)	2011	Diagnosis	Fuzzy logic	Sugeno inference model
24.G. Panagi (55)	2012	Diagnosis	(1)Genetic programming(2)Induc-tive machine learning approach	(1)Genetic algorithm(2)Decision tree
Compound methods				
25.Bikram L.Shrestha (23)	2008	Diagnosis	Case-based and Rule-based	Backward chaining
26. Shiny Mathew (24)	2015	Diagnosis	Case-based and Rule-based	Backward chaining and(1)Euclidean Distance2)Manhattan Distance(3)Ma-halanobis distance
27.Yijun Zhao (52)	2017	Diagnosis	Support vector machines (SVM)and Statistical analysis	Logistic regression (LR)
28.Gabriel Kocevar (48)	2016	Diagnosis and prognosis of course disease	Artificial neural network andSup-port vector machine (SVM)	Radial Basis Function(RBF)
29.Bartolome Bejarano (45)	2011	Prediction and diagnosis	Statistical analysis andInductive machine learning approach and Ar-tificial Neural Network	Naïve Bayes AndRandom deci-sion-tree meta-classifier and multi-layer perceptron (MLP) with Feed For-ward Back Propagation(FFBP)
30.Fanis G. Kalatzis (31)	2009	Diagnosis and prognosis	Fuzzy logic AndRule-based	Fuzzy cluster means(FCM) AndFor-ward chaining

Table 1. List of Characteristics reviewed in selected articles

multiple sclerosis: computational classifiers. Introduction and methods", "soft computing techniques survey in neuroscience" and "Knowledge and intelligent computing system in medicine" have analyzed different reasoning methods such

Reasoning Methods	Algorithm/ technique/ model	Indicator Evaluation result								
		sensitivity	specificity	accuracy	AUC	Positive predictive value	Negative predictive value	Kappa	Precision	comments
Fuzzy logic	Sugeno model (40)	0.87	0.7562	--	0.85					
	FCM (41)							1		
	Mamedani model (38)									increasing efficiency,
	Mamedani model (37)									accuracy is very good
	Mamedani model (39)									high performance
Inductive Machine Learning (ML) Approach	Decision tree (55)	0.93	0.97							
Genetic programming	Genetic algorithms (55)	0.93	0.75	0.9						
natural language processing	Perl algorithm (43)	0.94	0.81			0.9			0.88	
	Perl algorithm (44)	0.94	0.91			0.93	0.82			
	Definitive type 1, Definitive type 2, possible type 1, possible type 2 algorithms (42)	0.95	0.89		0.94	0.89				
Artificial Neural Network	MLP (46) LVQ (46) RBF (46)			0.96 0.91 0.99						
	MLP (47)	0.97	0.82	0.92						
	neural net clamping technique (49)	0.92	0.63	0.84						
Support vector machine	---(51)									BAR=0.85
	---(50)	0. 77	0.66	0.71		0.7	0.74			
Statistical analysis	MLR2 MLR5 (49)	0.94 0.95	0.54 0.54	0.84 0.86						
	Linear Discriminant Analysis (LDA) (51)									BAR=0.87
	Systematic approach (54)	-	-	-						High sensitivity and specificity
Evidence-Based	--- (53)							1		
Rule-based	Ambulation-based EDSS algorithm (32)							0.69		
	Backward chaining (19)							.		Diagnosis of system near possible as a human expert
	Backward chaining (21)									Accurate result
	Backward chaining (20)			0.8						
	RETE Algorithm (22)									Accurate result
Case-based	Case Retrieval Net (33)									Successful diagnosis
Model-based	Matching algorithm and OLAP-tool (34)							0.95		
	Linear mathematical model (35)							1		
				Compound methods						
Case-based and rule-based	Backward chaining and (1) Euclidean Distance (2) Manhattan Distance (3) Mahalanobis distance (24)	0.93	0.866	0.87 0.82 0.84						Mean Error Rate=13.23 Mean Error Rate=17071Mean Error Rate=13.23
	Backward chaining (23)	--	--	--	--	--				High performance
Support vector machine and Statistical analysis	---- LR (52)	0.86								
Support vector machine and Artificial neural network	--- RFB (48)	--	--						0.91	efficiency=0.69
Statistical analysis and Inductive machine learning approach and Artificial neural network	Naïve Bayes and Random decision and FFBP (45)	0.93	0.86	0.8	0.9					
Fuzzy logic and rule-based	Fuzzy cluster means (FCM) and Forward chaining (31)									highly accurate results

Table 2. Efficiency Evaluation of intelligent systems for MS diagnosis

as statistical methods, different algorithms of the artificial neural networks, rule-based, case-based and a combination of different methods (26-28). A review study on "Fuzzy logic: A simple solution for complexities in neurosciences" has examined advantages and disadvantages of the fuzzy logic method in diagnosis, management and prediction of neurological disorders (29). Ina review study on "Neural Networks for Computer-Aided Diagnosis in Medicine…",learning algorithms and different neural networks and their accuracy in diagnosing different diseases have been reported (30).

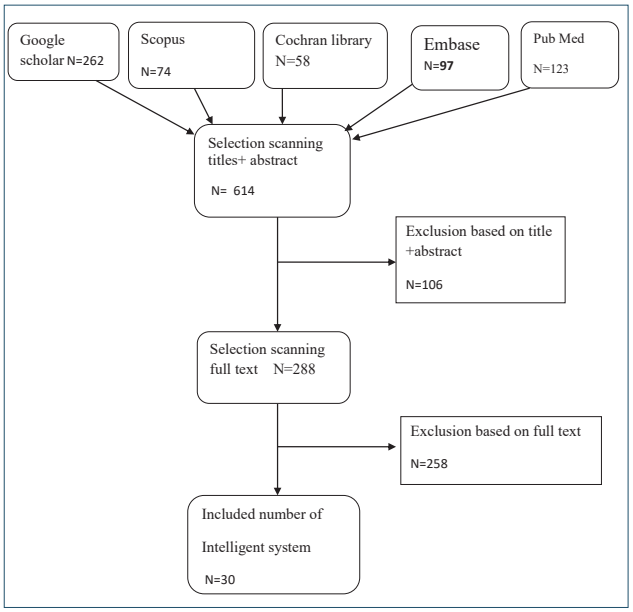

Figure 1. Flowchart of search strategy for selecting articles

The aim of this study is to analyze applied reasoning methods and techniques in intelligent computer systems to help MS diagnosis. Findings of this research answer the following question: "Which reasoning methods and techniques are used nowadays to diagnose MS and how efficient and applicable is each method?", in order to find the most applicable and efficient methods and techniques to diagnose MS.

2. METHODS

In order to carry out a systematic review study, the PRISMA protocol was used. The questions that have been answered in this study are: a) which methods of reasoning are used to diagnose MS in intelligent computer systems? b) To what extent is each reasoning method used to diagnose MS? and c) How efficient is each method in diagnosing MS?

A search was carried out among articles in electronic databases of Pubmed, Embase, Cochrane library, Scopus and Google Scholar during January and February 2018. The search strategy was based on Mesh vocabulary and the combination of these words was done with logical operators, "AND" and "OR" in search phrases. 25 search phrases were used and 614 articles were selected that have been published in English between 2000 and 2018. First, the articles were screened based on title, abstract and objective of the study and their texts were retrieved. Then the whole text was analyzed and investigated and finally 30 articles were selected based on the inclusion criteria.

In this review study, articles having the following inclusion criteria have been selected: a) the intelligent system described in the article should being the domain of MS diagnosis and classifying its clinical types, b) The reasoning method of the system for the diagnosis of MS should be completely described, c) Those articles in which picture processing methods and DNA frequency processing have not been used, and d) The intelligent computer system of disease diagnosis has been evaluated and its results have been reported numerically or descriptively. Data extraction has been done based on research questions of the selected papers. These data include the author, publication year, system application, applied reasoning method used in the intelligent system along with the algorithm used, most evaluation parameters including sensitivity, specificity, accuracy, area under the Receiver Operating Characteristics curve, efficiency and the amount of Kappa conformity that has been recorded in Tables 1 and 2. The calculation formulas for some of the evaluation parameters are as follows:

Specificity = TN / [TN + FP]. (2).

Negative predictive value [NPV]=TN/[TN + FN]. (4, 5).

3. RESULTS

Total amount of 614 articles were retrieved by using the applied search strategy in electronic databases (Figure 1), their titles and abstracts were analyzed, and 288 articles were selected. Their texts were completely analyzed, among which 30 articles with high quality were selected based on the inclusion criteria, with a complete description and explanation of the method design, software development and evaluation.

According to Table 1, different decision making methods have been used in reasoning motors of intelligent systems for MS diagnosis. These methods were divided in to two overall groups of knowledge-based and non-knowledge based. In some articles, integrated methods have been applied, such as integration of rule-based and case-based methods. Each reasoning method included different models and techniques.

According to Table 1, in 5 articles, the rule-based method with backward chaining techniques (19-21, 23, 24), forward chaining techniques (31), and RETE (22) and ambulation based algorithms (32) were used. According to Table 2, in article (32), the Kappa conformity rate between clinical decision support system diagnosis and physician diagnosis was equal to 0.69 and in article (24) the system diagnosis accuracy was 0.8. In three articles (19, 21-22), the evaluation results of the system were described by general phrases such as "accurate result" and the evaluation results of the efficiency of different techniques of this method were not comparable with each other.

In case-based reasoning, for solving new problems, previous solutions are adapted to solve similar problems, which is similar to the human intelligence process that uses his experiences for new problems. In article (9), the case-based method with "case retrieval net technique" was used and its evaluation results were described by the phrase "successful diagnosis". In articles (34, 35), the model-based method was used. The Kappa parameter in this method is equal to 0.95 and 1, and according to the Landis and Coach interpretation table (36), complete conformity in physician diagnosis and the decision support system diagnosis is observed.

Fuzzy logic allows the software variables of the decision support system to be members of different sets, simultaneously and with different degrees. In 5 articles, the fuzzy logic method with Mamdani (37-39) and Sogno (40) fuzzy models and the fuzzy clustering algorithm (31, 41) were used. The parameters accuracy, specificity and AUC for the Sogno (40) fuzzy model and also the KAPPA parameter for the FCM algorithm in article (41) were calculated. For articles in which the Mamdani model was used, evaluation results of the system were reported qualitatively by phrases such as "accuracy is very good".

Natural language processing is a tool for identifying vo-

cabulary and their mapping to concepts. The medical records of patients' progress are a big store of clinical data that are used in intelligent systems. This method has been applied in three intelligent systems, for which the applicable algorithm included: Definitive type1, Definitive type 2, possible type 1, possible type 2 (42) and PERL (43, 44). Table 2 showed that the efficiency scales of sensitivity and specificity and positive prediction value of these algorithms are very high.

The neural network method is obtained from biological characteristics of the human brain and the individuals reasoning method. In four articles, different neural network models were used such as MLP (45-47), LVQ (46), RBF (46,48) and neural net clamping (49). According to Table 2, the RBF neural network in article (46) had the highest accuracy. Also, the MLP neural network with the FFBP learning algorithm in the articles had very high sensitivity, specificity and accuracy.

The SVM method was applied alone in two articles and in combination with other methods in two other articles. This method is easy, but its average sensitivity and accuracy in articles (50, 51) was 0.7. In 6 articles, a combination of different reasoning methods have been used that included a combination of rule-based and case-based methods (23, 24), a combination of rule-based and fuzzy logic methods (31), a combination of artificial neural network, statistical analysis and decision tree methods (45) and a combination of SVM, statistical analysis and neural network methods in studies (48, 52). According to Table 2, the efficiency of combining reasoning methods was very high.

4. DISCUSSION

By applying different reasoning methods, intelligent computer systems help to diagnose MS more accurately. Each reasoning method has certain capabilities and limitations; hence yielding different efficiencies and applicability's in the diagnosis of this disease.

The rule-based method is one of the best applications of disease diagnosis. This method manages well-defined problems with knowledge-based texts; however, it has limited flexibility. To overcome such a weakness, case-based methods are used. The case-based method is more suitable for domains in which rules and relations among parameters are unknown. The diagnosis of rare and complicated disorders like MS was one of these domains. In a review study on "Intelligent and knowledge-based computing systems", benefits such as modularity and combination and overall description of the results have been considered for the rule-based method, and benefits such as ease of knowledge acquisition, learning from experiences, automatic system updating and error management have been mentioned for the case-based method.

Natural language expressions are ambiguous in the medical domain and are used abundantly. The existing uncertainty in this domain has resulted in complexity for the production of medical intelligent systems. Certainty factors and the method of confronting uncertainty are very important characteristics of the fuzzy logic method that have made it unique (56, 57). In review studies on "Fuzzy logic: A simple solution for complexities in neurosciences?" and "Intelligent and knowledge-based computing systems", fuzzy logic was introduced as a solution for uncertainty problems and resulted in simplifying the knowledge presentation process and minimizing calculation complexities. Extracting knowledge and specifying fuzzy rules were difficult and tiresome, requiring a great amount of experience and skills.

Among the neural networks, FBP, LVQ, and RBF were increasingly being used to classify medical data. Learning algorithms in the neural network method are effective tools for calculating and data mining in education data and their generalization. In a review study on "Neural Networks for Medical Diagnosis", it has been stated that this method has applications in domains in which system output is dependent on numerous unknown inputs. The neural network method was suitable for diagnosing MS because the diagnosis of this disease was done based on many decision parameters and these parameters were various in different patients. A review study on "Intelligent and knowledge-based computing systems" has reported on the limitation of non-clarity in the neural network structure.

The natural language processing method analyzes medical records and identifies MS patients in the primary steps of the clinical course of disease using simple algorithms. Moreover, this method increases diagnosis accuracy and the positive prediction value. However, classification models used well-defined signs and symptoms and did not benefit from terms existing in the clinical notes.

The genetic algorithm in a big and very complicated problem space is seeking for a correct and fast solution, while minimizing the problem space. This approach is applied repeatedly to extract characteristics and classifications. This algorithm requires much calculation and a large memory and may not find the most optimal answer.

Some intelligent systems used a combination of reasoning methods. Rule-based systems along with case-based systems completely simulate the decision-making process of the physician. Experts' knowledge is a combination of objective knowledge obtained from the texts and subjective knowledge resulted from the individual's experiences. Objective knowledge is in the form of rules and subjective knowledge includes a combination of cases. The combination of these two methods improved problem solving ability and diagnosis accuracy, simplified the extraction of knowledge, and increased the cost-effectiveness of the system.

Articles that applied the rule-based method have suggested that fuzzy rules and weighing out rules be used to solve the uncertainty problem, the combination that was used in the first article. A combination of neural networks, fuzzy logic and genetic algorithm help to minimize problem space complexity such as MS diagnosis with different signs and symptoms.

According to the results of this review, in intelligent systems of MS diagnosis, the rule-based method had the highest application. In 27% of the studies, the rule-based method was applied and then, in 20%of studies the fuzzy logic method and in 18% of the studies the neural network method was applied. In the rule-based method, the backward chaining technique, in the neural network method, the multilayer Perceptron network, and in the fuzzy logic method, the Mamdani fuzzy model was used for diagnosis. In a review study of "Intelligent and knowledge-based systems", 35% of the studies also applied the rule-based method.

Table 2 shows that the model-based and evidence-based methods had the highest amount of efficiency among the knowledge-based methods. The Kappa variable for them was equal to one. According to interpretation of Kappa, Landis and Koch table (36), knowledge-based methods had good efficiency and the decision support system for MS diagnosis made decisions similar to an expert physician. In the fuzzy logic method, due to various efficiency evaluation scales, the Mamdania and Sogno models and fuzzy clustering algorithm efficiency cannot be compared in MS diagnosis.

Results showed that due to similarities in the nature of fuzzy logic and the medical domain, fuzzy systems were useful for MS diagnosis. In a reported review study on "Fuzzy logic: A simple solution for complexities in neurosciences?" fuzzy logic has been noticeably successful in diagnosis, management and prediction of neurological disorders.

In the neural network method, RBF and FFBP networks had the largest amount of efficiency incorrectly diagnosing MS. The RBF neural network automatically finds the relation between inputs and outputs and provides a correct classification of patient's information. In a review article entitled, "Neural Networks for Computer-Aided Diagnosis in Medicine",it has been noted that neural network efficiency is based on neural network model selection and selecting the learning algorithm and training data set and conformity between the network model and algorithm. The SVM method was less efficient compared to other methods because if the number of characteristics and signs and symptoms of a disease such as MS are high, they do not map the multi dimension space adequately enough. However, due to the simplicity of this method, it has been used alone and in combination with other methods.

The number of selected articles in this review article was limited due to lack of availability of the full texts. In addition, the calculated efficiency scales were different in various articles. On the other hand, in some articles, evaluation results of system efficiency have been described qualitatively with phrases such as "increasing efficiency" and "accuracy is very good". Therefore, the efficiencies of some applied methods and algorithms were not comparable with each other.

Values recorded in Table 2 showed that the neural network method was more efficient than other reasoning methods in diagnosing MS. Generally, it can be concluded that today, reasoning methods have been highly efficient in diagnosing and predicting clinical MS and can be used in assisting the clinical decision support system to help physicians and patients in the correct and timely diagnosis of this disease.

It is suggested that these reasoning methods can be applied to intelligent systems to diagnose other brain disorders and to compare the results with each other. Nowadays, image processing methods, genetic data processing and analytical methods of the electroencephalogram have been applied in the diagnosis and prediction of this disease, and their efficiency results can be compared and generalized with the results of this review study.

5. CONCLUSION

The aim of this study was to provide a general viewpoint on the developments in different methodologies in the intelligent system reasoning of MS diagnosis. The rule-based method was more applicable than other reasoning methods due to its modularity and rule integrity in the knowledge-based system. Then, the fuzzy logic method was applied more due to its unique capability to solve uncertain problems and simplify the knowledge presentation process and minimize the calculation complexity for complex diagnosis of MS. In addition, the neural network methods were applied to diagnose MS due to their powerful calculation capability in a complex problem space.

All reasoning methods had a high efficiency in diagnosing MS, but the efficiency of these methods was different with regard to their characteristics. The neural network method had higher efficiency than other reasoning methods in MS diagnosis. The fuzzy logic method performed successfully in disease diagnosis due to its medical nature, particularly in neurological disorders. The Kappa scale value showed that there was complete conformity between the intelligent diagnosis system and expert neurologist diagnosis. The SVM method was less efficient for MS diagnosis than other methods because of its inaccurate mapping in large and complex problem space. Surely, all reasoning methods had some limitations. In the rule-based reasoning method, there was inflexibility and some problems in acquiring knowledge, and updating and maintaining it. The neural network method works like a black box and parameter specification requires a lot of experience for better performance. In the fuzzy logic method, knowledge extraction, set specification and fuzzy membership functions and fuzzy rules definition were difficult and exhausting. In order to overcome these limitations, a combination of these methods was used to improve the system ability in accurately diagnosing MS. In general, we can conclude that computer methods and techniques have the potential to be applied in clinical practices and research in MS and other neurological disorders.

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