Review Article:

Difficulties of Diagnosing Alzheimer's Disease: The Application of Clinical Decision Support Systems

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ABSTRACT

Context: Alzheimer's disease is one of the most common causes of dementia, which gradually causes cognitive impairment. Diagnosis of Alzheimer's disease is a complicated process performed through several tests and examinations. Design and development of Clinical Decision Support System (CDSS) could be an appropriate approach for eliminating the existing difficulties of diagnosing Alzheimer's disease. **Evidence Acquisition:** This study reviews the current problems in the diagnosis of Alzheimer's disease with an approach to the application of CDSS. The study reviewed the articles published from 1990 to 2016. The articles were identified by searching electronic databases such as PubMed, Google Scholar, Science Direct. Considering the relevance of articles with the objectives of the study, 29 papers were selected. According to the performed investigations, various reasons cause difficulty in Alzheimer's diagnosis. **Results:** The complexity of diagnostic process and the similarity of Alzheimer's disease with other causes of dementia are the most important of them. The results of studies about the application of CDSSs on Alzheimer's disease diagnosis indicated that the implementation of these systems could help to eliminate the existing difficulties in the diagnosis of Alzheimer's disease. **Conclusion:** Developing CDSSs based on diagnostic guidelines could be regarded as one of the possible approaches towards early and accurate diagnosis of Alzheimer's disease. Applying of computer-interpretable guideline (CIG) models such as GLIF, PROforma, Asbru, and EON can help to design CDSS with the capability of minimizing the burden of diagnostic problems with Alzheimer's disease.

Keywords: Alzheimer's disease; Dementia; Diagnosis; Clinical Decision Support System; Computer-Assisted Diagnosis

Context

With increasing the social welfare and the improvement of economic and cultural indicators as well as the development of health facilities, the number of older adults are increasing [1].Therefore, aging diseases, more than any other period, have become prevalent in most countries across the world, and it has imposed enormous health and economic problems on societies. Alzheimer's disease is one of the aging diseases which affects individuals' life dramatically[2,3].Alzheimer's disease is a chronic neurodegenerative disease that was first discovered in 1906 by a German neurologist Alois Alzheimer [4, 5]. The condition often occurs in individuals over the age of 65 and gradually and progressively leads to the destruction of brain cells [5, 6]. Alzheimer's disease is one of the most common causes of dementia and results in an impairment of

cognitive functions in the individuals. The most common initial symptom of this disease is a gradually impairment of remembering new information [5, 6]. The occurrence of memory impairment harms the patient's social and personal functions and may result in depression, anger, and aggression [7, 8]. In the more severe phase of Alzheimer's disease, the person's motor abilities disappear, in a way that patients need assistance to do their daily routines, such as eating or walking [8,9]. Alzheimer's disease is not curable and usually causes a patient's death five to ten years after the onset of the disease [5, 10].

The accurate and early diagnosis of Alzheimer's disease is important and leads to better management and cost reduction of the disease [4, 11, 12]. The diagnosis of Alzheimer's disease is difficult especially at the early stages. The definitive diagnosis of the disease is possible using the autopsy of patients after death or through sampling the patient's brain, which is rarely used because of its invasiveness [13-17]. There is currently no single and simple test for the diagnosis of this disease. Alzheimer's disease is diagnosed through a complicated process by performing multiple tests and examinations [6, 12, 15, 16]. Therefore, the detection of Alzheimer's disease is done by eliminating possible causes [15]. Different reasons that cause difficulties in diagnosis include: The Complexity of the Diagnosis Process, Similarity of Alzheimer's Disease with other Causes of Dementia, Physicians Facing with Large Amount of Data, Physicians Limited knowledge or use of Medical Guidelines, The Inherent Complexity of the Alzheimer's Disease, and The disuse of Alzheimer's diagnosis paper-based guidelines by physicians [4, 6, 8, 12, 15, 18-30].

Given the challenges of Alzheimer's diagnosis, the development of Clinical Decision Support System (CDSS) could be regarded as a key approach towards eliminating the aforementioned difficulties [18, 19]. CDSSs are computer systems that support physicians and other healthcare providers when making decisions. These systems provide physicians with required information, recommendations, reminders, and warnings at the time of their decision based on available information about patients and applying the knowledge and rules of medicine in the system support diagnostic and therapeutic approaches [4, 31, 32]. The CDSSs aim to reduce medical errors, an improve decision-making in different field of medicine [4].

Nowadays, the design and implementation of CDSS have received increasing attention by researchers, and numerous studies have been conducted on the impact of CDSS. For example, in a systematic review, researchers reviewed articles between 1980 and 2010. CDSSs were categorized into four groups of diagnostic systems, automatic warning system, disease management systems, and drug delivery control systems. The results of this study indicated that CDSSs can improve the quality of care and reduce medical errors as well as can help saving time and money [33, 34]. In another study, Garg et al. studied one hundred CDSSs. The results showed that in 64% of cases CDSSs led to improving decision making [35]. In another study, Kuatomo et al. studied seventy implemented CDSSs. The results indicated that the systems were successful in 68% of cases [36]. According to the results of studies, CDSSs are considered as supportive tools which can improve decision making, patient safety, care quality and minimize costs [37, 38].

In the design of CDSSs, researchers have used various methods and techniques that can be categorized into two general categories of knowledge-based CDSSs and non-knowledge-based CDSSs. Knowledge-based CDSSs are produced based on existing medical knowledge, and in designing these group of systems, the logic and human reasoning methods are used in decision making. With respect to knowledge-based CDSSs, an attempt is made to simulate the process of physicians' decision-making by the computer [39, 40]. Technically, the knowledge-based CDSSs are composed of 3 parts, including knowledge base, inference engine, and user interface [39]. The knowledge base contains knowledge, rules, and compiled data about a subject or a disease. This information is structured and is usually in the form of IF-THEN rules. The inference engine or argumentation mechanism includes the formulas that obtain results by grasping the existing rules in the knowledge base and combining it with the patient data. The communication mechanism is for

entering patient information and showing the obtained results to the user. Clinical guidelines can be applied to create knowledge-based CDSSs [9].

Non-knowledge-based systems are the other type of CDSSs that unlike the knowledge- based systems use a branch of artificial intelligence called machine- learning, enabling the system to learn and recognize patterns based on the past experiences and available medical data [3,32]. The non-knowledge-based CDSSs operate based on a modeling which in its turn stands on the existing data [39, 40]. Due to the use of machine learning techniques such as Support Vector Machines (SVM) and genetic algorithm, the non-knowledge-based CDSSs have limited interpretability and the description of inference method is also difficult, and these resulted in low acceptance of non-knowledge-based systems among physicians [39].

In general, due to the advantages of CDSSs, there have also been developed CDSSs in the diagnosis of Alzheimer's disease. In 2015, Oluwafemi al. created an expert system for diagnosing neurodegenerative diseases, including Alzheimer's disease. The results of the evaluations showed that the system successfully diagnosed neurodegenerative disorders [41]. In 2014, a system, called PredictAD was developed to help the early diagnosis of Alzheimer's disease. Researchers in this CDSS used a machine learning method called The Disease State Index (DSI). The results of the evaluation indicated the capability of this system in accurate and rapid recognition of Alzheimer's disease [15]. In another study, researchers developed a CDSS called ODEI to diagnose Alzheimer's. In this knowledge-based system, the Spanish medical guidelines and the existing ontologies had been used. In addition to being a CDSS, this system, as a research tool, supported physicians to determine the most relevant parameters for diagnosing Alzheimer's disease [4]. In another study, an intelligent diagnostic approach was proposed for developing a CDSS for Alzheimer's disease. In this study various psychological tests used to diagnose Alzheimer's were combined by applying multiple algorithms such as genetic algorithms. The results of the evaluations showed that this system facilitated the diagnosis of Alzheimer's disease and was more efficient and effective in detecting Alzheimer's disease compare to other existing psychological tests [22].

In this paper, the difficulties with the diagnosis of Alzheimer's disease are reviewed, and the application of Clinical Decision Support Systems (CDSS) are discussed in this field.

Evidence Acquisition

In this study, data were collected through search in CINAHL, Science Direct, ProQuest, PubMed and Google Scholar databases. The search terms included, but not restricted to, Clinical Decision Support System, Expert System, Diagnosis, Alzheimer Disease, and Dementia. The retrieved articles were published from 1990 to 2016 (184 articles). The title and abstract of the retrieved articles were initially reviewed in relation to the aim of the study and the duplicate articles, and the articles that their full text were not accessible, as well as articles that were not in English were removed from the review. The contents of the articles were then checked, and ultimately 29 articles were selected for analysis. The inclusion criteria were as follows: studies concerning difficulties of Alzheimer's diagnosis, studies on the difficulties of dementia diagnosis, CDSSs that were associated to the diagnosis of Alzheimer's disease or dementia, studies concerning the effect of CDSS on diagnosing Alzheimer's disease. The exclusion criteria were as follows: studies concerning the difficulties in diagnosis of other causes of dementia, CDSSs that were associated to the diagnosis of other causes of dementia; CDSSs that were only related to Alzheimer's disease treatment.

RESULTS

Overall, according to the aim of the study, the findings are presented into two sections. The first sections deals with the difficulties and problems of diagnosing Alzheimer's, and the second section presents information about developing and implementing CDSSs for diagnosis Alzheimer's disease.

Difficulties and problems with Alzheimer's diagnosis

Of the 29 studies reviewed, 20 were related to the difficulties with diagnosing Alzheimer's disease. Difficulties facing the diagnosis of the disease are presented in Table 1.

Table 1. Difficulties in Alzheimer's disease diagnosis

Difficulties in Alzheimer's diagnosis	Studies	Frequency
The Complexity of the Diagnosis Process	[6,8,12,15,18-24]	55%
Similarity of Alzheimer's Disease with other Causes of Dementia	[12,14-16,21,25-28]	45%
Physicians Facing with Large Amount of Data	[4,15,19,21,29]	25%
Physicians Limited knowledge or use of Medical Guidelines	[22,25,27,29,30]	25%
The Inherent Complexity of the Alzheimer's Disease	[6,25,27,29]	20%
The disuse of Alzheimer's diagnosis paper-based guidelines by physicians	[25,27,30]	15%

The *applications* of CDSS in diagnosing Alzheimer's disease

Sixteen studies indicated the application of CDSS in the diagnosis of Alzheimer's disease. In some of the studies, the diagnostic difficulties were also remarked. The findings are seen in Table 2. In 13 studies, the developed CDSSs were evaluated the effects of the systems on Alzheimer's diagnosis. The results of these studies showed that the generated CDSSs facilitated the diagnosis process and help doctors diagnose the disease more accurately. In three studies, the evaluation was not practically performed on the CDSS, but the researchers, emphasized the positive effects of these systems on Alzheimer's diagnosis through reviewing the relevant literature [2, 4, 23]. Among the reviewed studies, only one study evaluated the user satisfaction with the CDSS. The findings of this study showed that, the user satisfaction of the designed system has a crucial role in successfully implementing the system [42].

Table 2. Research on CDSSs for diagnosing Alzheimer's disease

Study	CDSS type	Findings
Do Amaral et al. (1996) [43]	Knowledge-based	In 73.6% cases, the designed system had recognized mental illnesses, including Alzheimer's disease.
French et al. (1997) [44]	The use of machine learning techniques	Neural networks can be effective in diagnosing Alzheimer's disease.
Perez et al. (1998) [21]	The use of machine-learning techniques	The system facilitated Alzheimer's disease diagnosis.
Gregory (2004) [29]	The use of machine learning techniques	The designed system was seen as effective in solving diagnostic difficulties.
Oteniya et al. (2005) [23]	The use of machine learning techniques	The designed system can help physicians to diagnose correctly and easily.
Iliffe et al. (2005) [44]	Knowledge-based	The system facilitated diagnosis of Alzheimer's disease.
Lindgren (2008) [42]	Knowledge-based	The system facilitated diagnosis of Alzheimer's disease.
Duchesne et al. (2010) [48]	The use of machine learning techniques	The system was suggested to be efficient in analyzing large volumes of data and help physicians to diagnose Alzheimer's disease.
JC et al. (2011) [24]	The use of machine learning techniques	The designed system helped physicians to diagnose Alzheimer's disease.
Mattila et al. (2014) [15]	The use of machine learning techniques	The designed system was reported as efficient in the early and accurate diagnosis of Alzheimer's disease.
Sanchez et al. (2014) [4]	Knowledge-based	The designed system was found as efficient in the early and accurate diagnosis of Alzheimer's disease.
Yen et al. (2014) [22]	The use of machine-learning techniques	The system accelerates and facilitates the diagnostic process.
Seixas et al. (2014) [2]	The use of machine-learning techniques	Bayesian networkscan be effective in facilitating Alzheimer's disease diagnosis.
Ben Nasser et al. (2014) [47]	The use of machine-learning techniques	in 89% of the cases, the system correctly diagnosis and accelerates the diagnosis process
Oluwafemiet al.(2015) [41]	Knowledge-based	The designed system can facilitate diagnosis
Bhagya et al. (2016) [46]	The use of machine-learning techniques	The system can diagnose Alzheimer's disease with high accuracy

The review of the studies indicated that a variety of methods and techniques were used in relation to the CDSSs development. In five studies, the developed CDSSs were knowledge-based [4, 41-44]. In other studies, machine learning techniques such as neural networks, Bayesian networks were used for system development [2, 15, 22-24, 45-48].

According to the literature review, the CDSSs developed were different in terms of scope. In five studies, CDSSs were for diagnosis of dementia [23, 29, 42, 47], and two systems for psychiatric disorders and neurodegenerative, including dementia and Alzheimer's disease [41, 43]. In two studies, the designed systems were capable of supporting care in addition to supporting the diagnosis of diseases, [42, 44].

DISCUSSION

The review of the studies revealed that diagnosis of Alzheimer's disease is complicated and difficult. Some organizations and institutions have provided guidelines such as DSM, NINCDS-ADRDA and EFNS to help physicians in diagnosing Alzheimer's more accurately and efficiently [49-51]. Generally, the use of medical guidelines in the patient care process has many benefits for patients and physicians, and result in reduction of medical errors and improvement of the quality of care [52, 53]. The applications of existing diagnostic guidelines concerning Alzheimer's disease can also be efficient in the accurate diagnosis of the disease and elimination of the existing issues. Despite the benefits of diagnostic guidelines, physicians are facing difficulties when using paper-based guidelines. These include inaccessibility, bulkiness, hardness and time-consuming nature of guidelines [25, 27, 30].

The CDSSs can eliminate a main part of the difficulties noted. These systems can analyze a large amount of data and make the complicated process of Alzheimer's diagnosis easier and can help physicians to diagnosis the disease more efficiently and accurately. As studies indicated, a variety of techniques were used to generate CDSS for Alzheimer's disease. Some of the CDSSs were non-knowledge-based and had been designed using machine learning techniques such as neural networks. In this type of CDSSs, the inference and diagnosis method of Alzheimer's disease is not clear, and this issue could result in system use and user satisfaction [39]. The other sort of CDSSs for Alzheimer's diagnosis were knowledge-based and were designed based on current medical guidelines [42, 43]. Given the benefits of using medical guidelines, the development of CDSS based on existing diagnostic guidelines appears to be a preferred approach towards developing systems [54, 55]. The guideline-based CDSSs could help to eliminate the limitations associated with the paper-based guidelines. The systems of this type could help physicians to go through the diagnosis process more conveniently and accurately. The guideline-based CDSSs compare to the non-knowledge-based systems have high interpretability, as these are designed according to the medical knowledge and guidelines that are commonly approved and accepted by physicians. The inference engine and the decision-making process of these systems are explicit and these are resulted in more user satisfaction and more straightforward implementation. In the design and implementation of guideline-based CDSSs, the identification of the decision-making process and the extraction of available knowledge in the guidelines, and eventually converting the paper-based guideline to a computer-interpretable guideline (CIG), are very important and play a pivotal role in the success of these systems [54]. Concerning the diagnosis of Alzheimer's, due to the difficulties and complexities of the diagnostic process, the extraction of knowledge from the existing diagnostic guidelines is troublesome and challenging, and this process requires active participation of physicians and field specialists. Concerning the CIG development, there are several models such as GLIF, PROforma, Asbru, and EON [54-56]. These models could facilitate the process of converting paper-based guidelines to efficient CIG.

CONCLUSION

The development of CDSSs based on existing diagnostic guidelines, can be a solution for difficulties experiencing by physicians when facing patients with neurodegenerative diseases

such as Alzheimer's disease. Extracting the knowledge from guidelines and designing diagnostic algorithms can play a significant role in the success of these systems. It is suggested to use CIG models to convert the existing diagnostic guidelines to CIG, as this approach could help to make the diagnosis process more efficient and accurate.

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