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Advancements in Imaging Biomarkers for Early Diagnosis and Monitoring of Alzheimer's Disease: Comprehensive Review

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Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss. Increasing prevalence necessitates early and accurate diagnosis, as current treatment options are limited and primarily symptomatic.

Methods: This comprehensive review examines contemporary imaging biomarkers used for the early diagnosis and monitoring of AD. Emphasis is placed on structural and functional neuroimaging techniques, particularly magnetic resonance imaging (MRI) and positron emission tomography (PET). The review categorizes biomarkers according to the "A/T/N" classification system, which includes amyloid (A), tau (T), and neurodegeneration (N) components.

Results: Key findings indicate that amyloid deposition is often the earliest detectable change, while tau accumulation correlates more closely with clinical symptoms of cognitive decline. Innovative methodologies, such as voxel-based morphometry and diffusion tensor imaging, enhance the sensitivity of MRI in identifying structural brain changes. PET imaging with novel tracers, including those for synaptic density and iron accumulation, shows promise for early detection and monitoring disease progression. Despite advancements, existing biomarkers face challenges regarding specificity and reliability, which can hinder their clinical utility.

Conclusion: The review underscores the critical role of imaging biomarkers in the early detection and ongoing monitoring of Alzheimer's disease. While current imaging techniques provide valuable insights,

further research is required to validate new biomarkers and improve existing methodologies. The development of robust, non-invasive biomarkers is essential for enhancing early diagnosis and facilitating timely therapeutic interventions.

Keywords: Alzheimer's Disease, Imaging Biomarkers, Neuroimaging, PET, MRI.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurological condition characterized by memory loss, cognitive decline, behavioral alterations, and ultimately mortality [1]. Alzheimer's disease is the predominant cause of dementia and is anticipated to impact over 152 million individuals by 2050. The illness is neuropathologically defined by the accumulation of aberrant proteins, leading to the development of extracellular senile plaques and intracellular neurofibrillary tangles (NFTs) [3,4]. Senile plaques typically include neurotoxic amyloid-β (Aβ) [5], whereas neurofibrillary tangles (NFTs) consist of aberrant hyperphosphorylated tau aggregates [6,7]. While the role of aberrant protein deposition in Alzheimer's disease (AD) is acknowledged, the precise pathophysiology of AD remains intricate, and a conclusive diagnosis can only be confirmed post-mortem by histological staining of the brain. At present, Alzheimer's disease is the only cause of death in the top ten worldwide fatalities for which no effective therapeutic intervention exists, and there are no approved medications to impede disease development [10]. Consequently, significant effort is dedicated to elucidating the pathophysiology of Alzheimer's disease for the development of treatment medicines [11].

In Alzheimer's disease, neuropathological alterations transpire up to thirty years prior to the clinical onset of the condition [12]. The primary pathogenic occurrence in Alzheimer's disease is the deposition of Aβ, which facilitates the development of senile plaques. Similarly, hyperphosphorylation leads to the formation of neurofibrillary tangles (NFTs), resulting in neuronal death, cerebral atrophy, neurotoxicity, and eventually cognitive deterioration [7]. In 1991, Braak and Braak delineated the progression of NFTs across the brain and identified six distinct phases [3]. The Braak stages correlate with the proliferation of NFTs from transentorhinal regions (stages I/II) to limbic areas (stages III/IV) and neocortical regions (stages V/VI) as Alzheimer's disease advances.

The aforementioned processes succeed and overlap, so AD is seen as a continuum with pathological alterations and clinical manifestations according to the disease stage [13] (Figure 1). Given that damage from these events may exceed a certain neuropathological threshold, rendering therapy ineffective, it has been proposed that therapeutic drugs should aim to prevent neurodegeneration during the asymptomatic period of Alzheimer's disease before it escalates in severity [14,15,16]. Consequently, precise and accurate procedures are essential for diagnosing Alzheimer's Disease in the early or preclinical phase [1]. Currently, research emphasizes the identification of biomarkers—physiological, chemical, or anatomical parameters—that accurately represent certain pathopsychological processes in Alzheimer's disease (AD) [17]. These biomarkers may be classified into three distinct categories according to the kind of pathology they monitor. In the "A/T/N" system, "A" denotes biomarkers that assess Aβ accumulation, "T" signifies biomarkers that are sensitive to tau, and "N" represents biomarkers indicative of neurodegeneration [18]. This system is flexible and may be perpetually augmented as new biomarkers emerge [19].

An optimal biomarker is cost-effective, simple to assess, and non-invasive, thereby minimizing patient damage. Additionally, an effective biomarker has elevated sensitivity and prediction capabilities for the particular disease occurrence [15]. Ultimately, biomarkers may serve as a diagnostic instrument for early illness detection, so enabling the postponement of disease development or perhaps hindering its clinical presentation [20,21]. Furthermore, the longitudinal assessment of these biomarkers may provide insights into disease development and facilitate the evaluation of the efficacy of disease-modifying therapies.

This study focuses on biomarkers that may be monitored using structural or functional neuroimaging methods, including magnetic resonance imaging (MRI) and positron emission tomography (PET). This

study aims to provide an overview of proven biomarkers for the early diagnosis and longitudinal monitoring of Alzheimer's disease, while also discussing their viability and possible limitations. Initially, we elucidate contemporary biomarkers for the early detection of Alzheimer's disease and the longitudinal assessment of disease development. This study evaluates these biomarkers about their diagnostic value, advantages, and limits. We present novel biomarkers and imaging approaches that provide promising outcomes for the early diagnosis and longitudinal monitoring of Alzheimer's disease. In conclusion, we encapsulate our results and provide future insights.

2. Modern Early Diagnosis of Alzheimer's Disease Utilizing Imaging Techniques

As the prevalence of Alzheimer's disease rises owing to an aging demographic, significant efforts have been dedicated to the early diagnosis of the condition. A variety of approaches have been evaluated, including cognitive assessments, MRI imaging, and cerebrospinal fluid sampling [22]. This section examines the imaging modalities and corresponding biomarkers used in the early diagnosis of Alzheimer's disease.

The first applications of imaging modalities in Alzheimer's Disease (AD) were computed tomography (CT) and magnetic resonance imaging (MRI), which were primarily used to rule out other causes of dementia rather than to facilitate early diagnosis of AD. Subsequently, imaging methods were used as corroborative evidence to validate the clinical diagnosis of Alzheimer's Disease (AD). These strategies concentrated on the neuronal damage and degeneration facets of Alzheimer's disease [1]. Currently, imaging methods concentrate on either detecting amyloid deposition or assessing neurodegeneration [23,24].

3. Innovative Approaches, Utilization of Imaging Modalities and Biomarkers in Alzheimer's Disease Research

Given the absence of an effective treatment for Alzheimer's disease (AD) and the lack of an ideal biomarker for detecting AD from its initial stages to advanced manifestations, considerable effort is dedicated to discovering innovative techniques, identifying new biomarkers, and enhancing existing methods for early diagnosis and longitudinal monitoring of AD. This section succinctly examines innovative processing methods for established techniques, potential new biomarkers for monitoring Alzheimer's disease, and unique uses of imaging techniques aimed at effectively diagnosing and tracking Alzheimer's disease.

4. Innovative Processing Methodologies for Established Techniques

Enhancing the methodologies that analyze acquired data is a means to augment the therapeutic utility of current procedures. In neuroimaging using MRI, enhanced clinical value has been achieved by the use of several morphometric techniques for data analysis. Neuroimaging data from MRI scans are often stored as voxel matrices, necessitating various approaches for data processing. Furthermore, significant emphasis has been placed on developing novel data-driven techniques for the analysis of PET images.

5.1. Voxel-Based Morphometry

The predominant data-driven technique for T1-weighted MRI imaging is voxel-based morphometry (VBM), which automatically segments brain tissue into white matter, gray matter, and cerebrospinal fluid (CSF) [25]. It converts T1-weighted individual brain scans into a standardized reference template. VBM subsequently quantifies variations in concentrations of distinct brain tissues by comparing voxels across numerous brain regions [26]. In Alzheimer's disease, VBM is used to measure atrophy and to autonomously differentiate Alzheimer's patients from those with mild cognitive impairment and healthy controls [27].

5.2. Deformation-Based Morphometry

A physiologically relevant approach previously referenced is DBM, whereby all brain volumes are converted into a standardized template brain [28]. Unlike VBM, DBM preserves the great resolution of MRI images [28]. Deformation fields, which encapsulate the spatial discrepancies of the voxels between the imaged brain and the template brain, are used for statistical analysis instead of the voxels themselves.

Consequently, DBM exhibits greater sensitivity to nuanced alterations in brain tissue composition compared to VBM. Furthermore, data from various investigations, imaging apparatus, and research institutions may be analyzed impartially [29].

5.3. Tensor-Based Morphometry

Tensor-based morphometry (TBM) quantifies localized variations in the gradients of deformation fields that align pictures with the template brain [30]. TBM may be used in several examinations, ranging from the voxel level to comprehensive whole-brain analysis. Furthermore, because of its almost automated nature, TBM is preferred in extensive MRI research, including clinical trials.

5.4. Pattern-Based Morphometry

Pattern-based morphometry (PBM) is another kind of morphometry, originating from voxel-based morphometry (VBM) and deformation-based morphometry (DBM) [31]. This data-driven approach employs an algorithm rooted in sparse dictionary learning and, unlike VBM, can identify multidimensional patterns that delineate group differences, making PBM a valuable instrument for comparing various brain areas. While PBM seems to be a viable processing strategy for heterogeneous diseases, more study into its robustness and applicability to different neuroimaging modalities is essential for widespread implementation.

5.5. Empirical Approaches

With advancements in technology, there has been a recent focus on using extensive datasets to develop data-driven models that enhance the processing of PET scans. The influence of aging on specific brain areas evaluated by FDG-PET has been adjusted utilizing a data-driven methodology [32]. Furthermore, data-driven analysis of tau PET scans revealed spatial patterns of radiotracer 18F-AV1451 signal clusters in contrast to pathology-based techniques, indicating the superiority of data-driven approaches in assessing radiotracer data [33]. Additional research comparing traditional methods with data-driven approaches is essential to fully use the benefits of data-driven techniques in neuroimaging.

6. Innovative Consequences of Imaging Methodologies

Alongside the development of new strategies to enhance the diagnostic efficacy of existing imaging techniques, there is a rise in the innovative uses of alternative imaging modalities. While structural MRI with T1-weighted images remain the gold standard in Alzheimer's disease research, other MRI sequences seem to have promise.

Diffusion tensor imaging (DTI) is a sophisticated kind of diffusion MRI. This approach quantifies the displacement of water molecules in three dimensions to assess the integrity of biological tissue [34,35]. In AD, DTI has been used to assess the integrity of brain areas by the calculation of mean diffusivity [36]. Furthermore, DTI has proven valuable in elucidating the architecture of white matter [33], and numerous studies have indicated a correlation between white matter integrity and disease severity, implying that white matter degeneration should be considered a pathological biomarker of AD for early diagnosis [37-39]. To fully use DTI as a diagnostic instrument in AD, the precise correlation between disease severity and white matter tracts must be investigated [35].

Functional MRI (fMRI) is a non-invasive imaging technology that provides insight into the functional integrity of brain networks associated with various cognitive domains [23,40]. fMRI use the blood-oxygen-level-dependent (BOLD) signal to assess neuronal synaptic activity. fMRI may be used in two ways: resting state (rs) fMRI, which assesses fluctuations in BOLD signals during periods of rest, or task-related fMRI, when subjects engage in various cognitive activities [33]. Given that seriously damaged individuals may lack the capacity to execute these activities, rsfMRI might be a more viable method for monitoring disease development in advanced stages [23]. Despite the shown clinical use of fMRI in examining the default mode network [41-44], its widespread clinical application is hindered by constraints, including poor signal-to-noise ratio [34].

Optical coherence tomography (OCT) is another intriguing imaging tool used in Alzheimer's disease research; nevertheless, there is still no agreement about its application. Recent studies have associated pathological alterations in the retina with Alzheimer's disease [45]. These alterations include Aβ plaques, attenuation of the retinal nerve fiber layer (RNFL), loss of ganglion cells, and decreased vessel density. Given that OCT is a non-invasive, rapid, and cost-effective technology [46], several studies have explored its advantageous role in Alzheimer's disease research. Despite the proposed utility of Aβ accumulation in the lens, along with the analysis of RNFL thickness and ganglion cell loss as diagnostic indicators for Alzheimer's disease, the reliability of these markers remains contentious due to the potential influence of other underlying conditions, such as glaucoma, that may induce similar pathological alterations. Nonetheless, the practicality and cost-efficiency of OCT make it a compelling imaging modality for future exploration in applications related to AD.

7. Novel Biomarkers

For several years, the emphasis of Alzheimer's disease research has been on atrophy, glucose metabolism, and the imaging of Aβ deposition and tau accumulation. Nonetheless, since none of these biomarkers is unequivocally superior for diagnosing Alzheimer's disease (AD) and monitoring its evolution, research is directed toward discovering new biomarkers that accurately represent the advancement of AD. Numerous novel biomarkers have been introduced throughout the years.

Synaptic vesicle glycoprotein 2A (SV2A) is proposed as a clinically valuable marker in Alzheimer's disease, indicating synaptic density [9]. This protein resides in the cell membrane of secretory vesicles and given that SV2A is universally expressed in the brain, diminished levels of SV2A may serve as a potential biomarker for synaptic loss in Alzheimer's disease. 18F-UCB-J is a PET radiotracer recognized for its sensitivity to synaptic loss, as its altered uptake in gray matter correlates with changes in SV2A expression and reduced synaptic density [47,48]. Despite the encouraging findings, further validation of this and other radiotracers is essential to fully use the therapeutic potential of SV2A in Alzheimer's disease [9].

There is growing evidence that the receptor for advanced glycation end products (RAGE) modulates the neurotoxicity of Aβ in Alzheimer's disease (AD) [49]. The interaction of RAGE with Aβ leads to the generation of reactive oxygen species, which facilitate the development of senile plaques and neurofibrillary tangles. Furthermore, RAGE levels are markedly elevated in Alzheimer's disease participants compared to cognitively healthy controls [50]. Consequently, it has been proposed that RAGE serves as a significant biomarker in the first phases of Alzheimer's disease. 11C-FPS-ZM1 is a radiotracer used for PET imaging of RAGE in the brain [51]. Given that RAGE overexpression is thought to precede Aβ plaque formation, PET imaging of RAGE with 11C-FPS-ZM1 might serve as an effective instrument for the early identification of Alzheimer's disease [49].

Excessive iron buildup in certain regions of the brain is increasingly associated with Alzheimer's disease [52]. While iron is essential for homeostasis and is integral to several biological processes, excessive iron buildup in subcortical and deep gray matter nuclei has been linked to Alzheimer's disease [53]. Numerous investigations have used quantitative susceptibility mapping (QSM) to measure the local magnetic susceptibility obtained from MRI images resulting from deposits of both Aβ and iron [52,54,55]. The QSM application for detecting iron has been clinically valuable in evaluating the correlation between Aβ accumulation and iron load [56]. The identification of iron by QSM may assist in imaging Aβ for the early diagnosis of Alzheimer's disease [57-59].

8. Conclusions and Prospective Outlooks

This study examines the use of imaging tools for the early diagnosis and ongoing monitoring of Alzheimer's disease. Alzheimer's disease is a neurodegenerative disorder characterized by pathological alterations that transpire decades prior to the onset of clinical symptoms. The condition is marked by the development of senile plaques, neurofibrillary tangles, and ensuing synaptic loss and neurodegeneration. Despite the widespread impact of Alzheimer's Disease on the global population, no curative medicine currently exists. Given that disease-modifying medicines are likely most advantageous in the first phases of

the illness, early diagnosis of Alzheimer's disease is crucial. Moreover, longitudinal observation of illness development is essential for enhancing comprehension of pathophysiology and establishing clinical objectives for prospective therapies. Numerous biomarkers have been suggested for the early diagnosis and ongoing monitoring of Alzheimer's disease; however, each of these biomarkers has limits in terms of specificity, reliability, and sensitivity.

Aβ deposition is one of the first indicators of Alzheimer's disease; nevertheless, there is little agreement on the precise role of Aβ accumulation in the disease's pathophysiology. Furthermore, comprehensive research on Aβ over time has shown that Aβ levels attain equilibrium, rendering Aβ a dubious biomarker for tracking disease development. Tau buildup is considered to be more physiologically linked to the symptoms associated with neurodegeneration in Alzheimer's disease. Imaging studies using tau PET tracers have shown encouraging results; nevertheless, further validation of these tracers is necessary compared to Aβ-PET imaging to establish tau-PET imaging as a dependable instrument in Alzheimer's disease. Furthermore, longitudinal investigations on various phenotypes of Alzheimer's disease demonstrated variation in the topographic patterns of tau accumulation throughout the brain. This variability may provide extra benefit; nevertheless, a more comprehensive examination of these distinct tau propagation patterns is necessary. General imaging modalities, like FDG-PET and structural MRI, have been used in Alzheimer's disease research; however, these methods primarily assess prevalent pathology alterations rather than features particular to Alzheimer's disease. Brain atrophy, assessed using structural MRI, is not exclusive to Alzheimer's disease pathology and becomes apparent only after significant neurodegeneration. FDG-PET is used to assess glucose absorption in the brain. In Alzheimer's disease, synapse loss results in hypometabolism, which correlates with reduced glucose absorption. Nonetheless, diminished glucose metabolism is not exclusive to Alzheimer's disease; it may also manifest after strokes and cerebral injuries. Moreover, a growing body of data indicates that glucose absorption is indicative of astrocytic activity rather than neuronal activity.

Currently, there is no definitive biomarker for the early detection of Alzheimer's disease and the monitoring of its development over time. Moreover, these biomarkers depend on neuroimaging methods that need high-quality and costly equipment, rendering them impractical for extensive population studies. Therefore, a thorough study of Alzheimer's disease is essential for early diagnosis and ongoing monitoring of the condition. Given that tau-PET is the most promising instrument for diagnosing and monitoring illness progression, research should concentrate on the validation and advancement of both current and novel tau radiotracers. Moreover, comprehensive investigation into novel uses of alternative imaging methods is essential to address the constraints associated with widespread scanning of huge populations. Ultimately, existing methods need considerable protein buildup or neurodegeneration for detection. Given that elevated levels correlate with increased disease severity and diminished therapeutic efficacy, it is crucial to uncover new biomarkers that signify the pathogenesis of Alzheimer's disease in its first stages to facilitate the development of disease-modifying medicines.

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التطورات في المؤشرات الحيوية التصويرية للتشخيص المبكر ومراقبة مرض الزهايمر: مراجعة شاملة

المستخلص

الخلفية :مرض الزهايمر (AD) هو اضطراب تنكسي عصبي تدريجي يتميز بتدهور معرفي وفقدان الذاكرة. مع تزايد انتشاره، يصبح التشخيص المبكر والدقيق ضرورة ملحة، حيث إن الخيارات العلاجية الحالية محدودة وتقتصر في الغالب على تخفيف الأعراض

الطرق :تستعرض هذه المراجعة الشاملة المؤشرات الحيوية التصويرية المعاصرة المستخدمة للتشخيص المبكر ومراقبة مرض الزهايمر. يركز التحليل على تقنيات التصوير العصبي الهيكلية والوظيفية، وخاصة التصوير بالرنين المغناطيسي (MRI) والتصوير المقطعي بالإصدار البوزيتروني (PET). تُصنف المؤشرات الحيوية وفقًا لنظام التصنيف"A/T/N" ، الذي يشمل أميلويد(A) ، وتاو(T) ، والتنكس العصبي.(N)

النتائج :تشير النتائج الرئيسية إلى أن ترسب الأميلويد غالبًا ما يكون التغيير الأول القابل للكشف، بينما يرتبط تراكم بروتين تاو بشكل أوثق بالأعراض السريرية للتدهور المعرفي. تُعزز منهجيات مبتكرة، مثل قياس الكثافة باستخدام فوكسلات والتصوير الموزع باستخدام التنسور، من حساسية الرنين المغناطيسي في تحديد التغيرات الهيكلية في الدماغ. كما أظهر التصوير المقطعي بالإصدار البوزيتروني باستخدام متتبعات جديدة، بما في ذلك تلك المتعلقة بكثافة المشابك العصبية وتراكم الحديد، وعودًا للكشف المبكر ومراقبة تقدم المرض. ومع ذلك، تواجه المؤشرات الحيوية الحالية تحديات تتعلق بالتخصص والموثوقية، مما قد يعيق فائدتها السريرية.

الاستنتاج :تؤكد المراجعة على الدور الحاسم للمؤشرات الحيوية التصويرية في الكشف المبكر والمراقبة المستمرة لمرض الزهايمر. وعلى الرغم من أن تقنيات التصوير الحالية توفر رؤى قيمة، فإن هناك حاجة إلى مزيد من الأبحاث للتحقق من صحة المؤشرات الحيوية الجديدة وتحسين المنهجيات الحالية. يُعد تطوير مؤشرات حيوية قوية وغير غازية أمرًا ضروريًا لتعزيز التشخيص المبكر وتسهيل التدخلات العلاجية في الوقت المناسب.

الكلمات المفتاحية :مرض الزهايمر، المؤشرات الحيوية التصويرية، التصوير العصبي، التصوير المقطعي بالإصدار البوزيتروني، التصوير بالرنين المغناطيسي.