Molecular diagnosis and drug development in both Alzheimer's and Parkinson's diseases

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Alzheimer's disease (AD) and Parkinson's disease (PD) are neurodegenerative diseases that are caused by brain degeneration and lead to severe memory decline. According to the World Health Organization, the world's elderly population will reach 2 billion by 2050. The number of patients with AD and PD is increasing with the aging of the population. Currently, AD is the third leading cause of disability and death among the elderly after cardiovascular and cerebrovascular diseases and malignant tumors. A new case of Alzheimer's occurs every 3 seconds worldwide, and by 2050, the number of AD cases is expected to reach approximately 152 million. In addition, 5.7 million people have PD worldwide. PD receives untimely treatment and exhibits a high rate of delayed diagnosis and low rate of treatment. In this review, we aim to introduce readers to various diagnostic methods for AD and PD and the progress in the development and research of related drugs to assist in the early diagnosis, evaluation, and drug treatment of AD and PD.

Keywords: Neurodegenerative diseases; biological markers; drug development; Alzheimer's disease; Parkinson's disease.

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Background information

Neurodegenerative diseases are caused by the loss of neurons and/or their myelin sheaths, which are worsen over the time and present dysfunction [1]. Neurodegenerative diseases can be classified into acute or chronic categories with the acute mainly including cerebral ischemia, brain injury, and epilepsy, and the chronic including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis, spinocerebellar ataxias, and Pick's disease [2]. Neurodegenerative diseases have long courses and hidden onset. Their main clinical manifestations are the loss of cognitive function and the disorder of motor behavior that progressively aggravate with the incidence increasing with age [3]. The common clinical symptoms of AD include memory loss, language disorders, visual spatial dysfunction, executive disorder, depression, anxiety, and other neuropsychiatric symptoms [4, 5]. Patients with AD not only have reduced daily living ability but also demonstrate significantly decreased social communication ability which may be caused by pathological changes in neurons (loss), glia (hyperplasia), and nerve fibers (formation of senile plaque tangles) [6]. At present, the drugs used in the clinical treatment of AD, such as donepezil and memantine, mainly improve symptoms. However, there is no drug that can

delay or stop the progression of AD [7]. For the PD, although studies have shown that tremor is the first symptom presented by 75% of patients with PD, 15% of patients with PD do not exhibit tremor during the whole course of the disease. Most of patients with PD show static tremors, bradykinesia, myotonia, abnormal posture, and gait [8]. However, a recognized and accurate early objective diagnostic index for such neurodegenerative disease does not exist. Until now, there is lacking effective methods for preventing and organizing the occurrence and development of neurodegenerative diseases [9]. Drugs used for the treatments of both AD and PD include anticholinergic agents, levodopa preparations, dopaminergic receptor agonists, and catechol-O-methyltransferase inhibitors [10]. Relevant data show that, in 2018, approximately 50 million people suffered from dementia worldwide. By 2050, this number will increase by three times to 152 million. The global social costs related to dementia reached $1 trillion US dollars in 2018 and will increase to $2 trillion by 2030 [11]. Statistical data from the World Parkinson's Association show that the incidence of PD among people over 65 years old is 1.7% and that among people over 70 years old is 3% - 5%. At present, 5.7 million patients have PD worldwide [12]. The mechanisms of neurodegenerative diseases are not fully understood yet. These diseases are mostly treated through drug therapy, which is used mainly to slow disease progression, but less effective [13]. Therefore, finding biomarkers for early diagnosis and treatment targets and developing new drugs have become the focus and hot spot of research on neurodegenerative diseases.

Diagnosis of Alzheimer and Parkinson diseases

The final diagnosis of neurodegenerative diseases mainly relies on the biopsy of brain tissue specimens or autopsy and the detection of related misfolded protein deposits and changes in specific brain histopathology [14-17]. The diagnosis of neurodegenerative diseases is complicated because there has no effective alternative clinical diagnostic method [18], and the brain biopsy is difficult to carry out conventionally in clinical settings given its trauma and high risk while autopsy is not popular in many countries. Therefore, in addition to autopsy and biopsy, neurodegenerative diseases can be diagnosed on the basis of the three following aspects.

1. Diagnosis based on clinical symptoms

The new research-based criteria for the diagnosis of AD introduced by the International Working Group (IWG) in 2007 present a conceptual framework for introducing biomarkers into the diagnosis of AD. These diagnostic criteria and the subsequent National Institute of Aging–Alzheimer's Association (NIA–AA) criteria were designed to cover the entire course of the disease from its asymptomatic phase to its most advanced stage. Their most important potential clinical application is to achieve early intervention in the prodromal phase of the disease and to facilitate the secondary prevention of AD in the preclinical phase. In the practical research applications of these criteria, a base has been found for establishing consistency that truly reflects the nature of AD criteria [19, 20]. Accordingly, biomarker studies have helped clarify the potential value of different biomarkers in the diagnosis of AD [21]. Research data have highlighted the potential values of cue recall tests for the assessment of situational memory impairment and the relevance of the hippocampus and its associated structural atrophy, as well as a renewed and an improved understanding of the values of cerebrospinal fluid (CSF) biomarkers including their relevance to pathology, and their importance. The interpretation of amyloid PET data has been improved, and its relevance to pathology has been demonstrated. Additional new ligands have been introduced and clarified. Over the past 14 years, IWG and NIA–AA have established diagnostic criteria for AD. These criteria well define the clinical phenotype of AD, integrate biomarkers into the diagnostic process, and cover the entire spectrum of the disease [22].

Paroxysmal slow wave events (PSWEs) in the brain can be used to identify and quantitatively assess abnormal neural activity in the cortex and reflect the extent of blood–brain barrier damage. PSWEs can be applied as diagnostic indicators for brain diseases, such as AD and epilepsy, and as pharmacodynamic indicators for the treatment of blood–brain barrier injuries with drugs or antiepileptic drugs. The pathological transformation of the blood–brain barrier may be a potential mechanism for the occurrence of neurological diseases and therapeutic target [23].

The revised latest diagnostic criteria for PD have been published by the Movement Disorder Society (MDS). Comparison with the UK Brain Bank criteria revealed that in the MDS criteria, the diagnostic role of nonmotor symptoms has been expanded and diagnostic certainty has been classified (diagnosed as PD and most likely PD). The primary core criterion for the diagnosis of PD is the presence of motor retardation and, at least, one of the two main signs of stationary tremor or ankylosis. All core master signs must be examined in accordance with the method described in the MDS-sponsored revision of the Unified Parkinson's Disease Rating Scale [24]. Given that the pre-symptoms of PD are not obvious, patients are often already in the middle and late stages of PD by the time that various clinical indicators are observed. If patients with early PD are treated promptly, the potential for delaying the onset of the disease is great. Thus, the early diagnosis of PD is essential. Patients with PD are clinically diagnosed on the basis of the latest criteria by MDS including observable motor symptoms that are predominantly associated with PD in addition to other conditions, such as sleep disturbance, olfactory disturbance, cognitive impairment, and other nonmotor symptoms. Among these symptoms, sleep disturbance has been recognized as one of the universal symptoms of PD and can precede the appearance of motor symptoms [25]. Studies have shown that patients in the early stages of PD have developed localized electro-encephalograms (EEG) activity alteration. Some scholars have identified small sample EEG classifications based on wavelet scattering and LSTM neural networks. Multiple sample EEG classification recognition and LSTM EEG classification recognition combining transient frequency and power spectral entropy feature extraction were performed and correlated. The F1 values and accuracy of these classification methods were compared. The experimental accuracy in the classification of EEG and normal EEG signals is over 92% with good results for PD. Thus, this method provides new ideas for early diagnosis of PD patients [26].

2. Diagnosis based on biological markers

Similar to the diagnosis of cerebrovascular diseases, epilepsy, multiple sclerosis, and other diseases, the diagnosis of AD and PD made by a physician mainly depends on the clinical data of history and signs. There is no method with high specificity and sensitivity [27]. In recent years, with the development of biological markers, a series of neurobiochemical, molecular imaging, and neurogenetic markers has been developed and applied in the diagnosis of AD and PD, which has considerably improved diagnosis [28].

Patients with AD dementia may present characteristic CSF manifestations, namely, decreased Aβ and elevated total tau and P-tau [29]. Therefore, CSF can be used as a diagnostic marker for AD dementia, and characteristic changes in AD (decreased Aβ42 and increased tau protein) can also be applied to predict the outcome of MCI. The following methods are commonly used in the clinical diagnosis and antidiastole of AD, which include (1) structural MRI that can be used to detect regional or whole encephalatrophy due to axonal degeneration, synapse, and cell death by measuring the volume of the hippocampus and medial temporal lobe [30]; (2) 18F-FDG PET that can examine and evaluate the changes in synaptic function in patients with AD. The patients with dementia may exhibit decreased glucose metabolism in their temporal parietal and upper temporal areas or posterior temporal area, posterior cingulate cortex, and anterior wedge; (3) 18F-AV-45 PET

that can demonstrate significant or peak amyloid deposition in patients with early or late MCI, respectively [31].

In recent years, circular RNA (circRNA), a new class of endogenous noncoding RNA, has been found with a covalent closed-loop structure formed by reverse splicing [32], which is different to the structure of linear RNA such as mRNA, microRNA, and lncRNA. circRNAs are highly expressed in the nervous system and enriched in the synapses [33]. The AD correlation and potential disease impact mechanisms of AD-associated circRNAs have been investigated via relative importance analysis, co-expression network analysis, and miRNA binding site prediction analysis. The results showed that changes in circRNAs can better reflect AD characteristics than the two known factors, namely, the number of APOE4 alleles (the most commonly used genetic risk factor for AD) and the proportion of neuronal estimates. In addition, AD-related circRNAs are co-expressed with known AD genes, and these circRNAs have potential microRNA binding sites that can be used to predict microRNA for AD-based targets and as peripheral biomarkers of pre-symptomatic and symptomatic AD and other potential neurodegenerative diseases [34].

The neurofibrillary light chain (NfL), a component of the cytoskeleton, is mainly expressed in large-diameter myelin axons [35]. Mouse model studies on NfL have found that changes in body fluids are associated with brain damage, encephalatrophy, and multiple neurological diseases including neurodegenerative diseases. A study using a single-molecule array (Simoa) platform to test serum NfL via a hypersensitive immunoassay, a cognitive test, and MRI examination (calculating encephalatrophy ratio) demonstrated that serum NfL concentration was elevated in mutant carriers, and the degree of elevation was associated with disease stage and symptom severity. Therefore, serum NfL may be a viable biomarker for early AD-related neurodegeneration [36].

AD can be diagnosed by using exosomes in peripheral blood as biomarkers. The experiment was divided into two stages, namely, discovery and validation, and the possible markers in the peripheral blood and CSF of the same subjects were systematically observed and compared. The results showed that the levels of Aβ, T-tau, and P-tau in the peripheral blood neurogenic exosomes of patients with AD had significantly increased and were highly correlated with their levels in cerebrospinal fluid. These results indicated that exosomes reflected the pathophysiological changes of the brain and that the diagnostic efficacy of exosomes was equivalent to that of CSF. An AD diagnostic model was established by combining Aβ42, T-tau, and P-tau and was used to evaluate the complexes of the three biomarkers via logical regression analysis. This model revealed that the complexes of exosome biomarkers had higher diagnostic efficiency than that of individual biomarker [37].

The concept of α-synuclein in the pathogenesis of PD has been widely mentioned in genetic and proteomic studies. Early studies have found that variant rs356219 of α-synuclein is associated with increased α-synuclein transcription and content [38, 39]. Recent studies have proven that α-synuclein, the RPTOR gene, and the RPS6KA2 gene have epistatic interactions in modulating the age of onset of PD. Moreover, the dysfunctional activation of the mTOR pathway contributes to the aggregation of α-synuclein and the pathological transmission of PD in the brain. Meanwhile, genetic variation in the mTOR pathway can interact with α-synuclein risk variants. These phenomena provide new ideas for the discovery of new biological markers and potential epistatic interactions [40].

Additionally, relevant studies have found that damage to mitochondrial function during neurodegenerative diseases and before neuronal death leads to sequential damage to peripheral organelle function, thus leading to the release of the stress response factor FGF21 and to mitochondrial damage. In many cases, damage to communication between organelles leads to the

emergence of stress responses, and chronic cellular stress has important implications in the occurrence of neurodegenerative diseases. Therefore, FGF21 is an important molecular marker for the early diagnosis of AD and PD [41].

Skin is the largest organ of the human body. It has a high degree of innervation and shares a common embryonic origin with the brain. Therefore, skin can be used as a reliable biomarker for the diagnosis of neurodegenerative diseases [42]. α-Synuclein aggregates are present in epidermal peripheral nerve endings and cutaneous appendages in patients with PD, while phosphorylated tau protein aggregates are present in skin fibroblasts in patients with AD [43]. The feasibility of applying misfolded cutaneous proteins as clinical diagnostic biomarkers for neurodegenerative diseases need to be further identified.

3. Diagnosis based on genetic testing and gene identification

The distribution of the polymorphisms of the sporadic AD-predisposing gene APOEε4 in the population is associated with the risk of AD pathogenesis. Some studies have found that the AD risk of individuals with an APOEε4 allele is three times higher than that of noncarriers, whereas that of carriers with two APOEε4 alleles is 14 times higher [44]. Given the above correlation, gene detection can provide a reference for the diagnosis of AD. Relevant studies have shown that the BACE1-AS gene presents high specificity and high transcriptional activity in the brains of patients with AD [45]. Furthermore, the results of PCR product electrophoresis, gene sequencing, and target gene extraction illustrate that the BACE1-AS gene is of great value in the early diagnosis of AD [46].

In 1996, α-synuclein mutation was identified as the genetic etiology of PD. Since then, mutations in a variety of genes, such as parkin, DJ-1, PINK1, LRRK2, and ATP13A2, have been further identified via linkage reaction and site cloning, thus revealing the diversity of the causes of PD [47].

Progress in the development of drugs for AD- and PD-based neurodegenerative diseases

Given that the pathogenesis of neurodegenerative diseases has not been studied clearly, the treatment of these diseases has been a difficult problem. In recent years, with the rapid development of molecular biology, neurobiology, and behavioral science, studies on this group of diseases have made new discoveries. These findings not only provide abundant information for the elucidation of disease mechanisms, but also new ideas and action targets for finding corresponding therapeutic drugs [48, 49].

1. Progress of drug development research on AD

Drugs for AD treatment are classified into four categories in accordance with the mechanisms of actions, which include acetylcholinesterase inhibitors (ACheIs), noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists, and drugs acting on Aβ and tau proteins. At present, drugs in the first two categories, such as donepezil, galantamine, and rivastigmine from ACheIs, and memantine hydrochloride from noncompetitive NMDA receptor antagonists, are mainly applied in the clinic [50].

Current research has confirmed that intestinal flora imbalance is closely linked to autism, depression, PD, AD, and other diseases. A new understanding of the pathogenesis of AD has also been obtained that neuroinflammation induced by intestinal flora disorder is an important pathogenesis of AD. Sodium oligomannate capsule (GV-971) made from low-molecular acid oligosaccharides derived from marine brown algae extracts is the first new Chinese drug applied to target the brain–gut axis for the treatment of mild to moderate AD and improve cognitive function [51].

A second important pathological tau protein in the brains of patients with AD has been demonstrated to be zippered in an animal model for the first time. Neurological inflammatory response is completely eliminated in drug-

treated tau mice via the blockage of the leukotriene pathway and the inflammatory process in the brain; this effect thus allows tau damage to be reversed [52]. Ziluton, a drug used to treat asthma by blocking 5-lipoxygenase to inhibit leukotriene formation, was first introduced in 1996 by Abbott Laboratories. It is now sold by Cornerstone Therapeutics Inc. under the brand names Zyflo and Zyflo CR, which are indicated for asthma prevention and chronic treatment in adults and children 12 years and older.

In a phase II clinical trial, BAN2401, an anti-Aβ fibrin monoclonal antibody for the treatment of mild AD, was found to significantly clear Aβ plaques and decelerate cognitive decline [53].

Aβ-induced neurodegeneration is considered as the main pathological mechanism of AD, and inhibiting β production or promoting β clearance is one of the promising therapeutic strategies in anti-AD research [54]. Studies on APP/PS1 double transgenic AD mouse models and cells have revealed that the natural product arctigenin (ATG) from Arctium lappa (L.) can inhibit Aβ production by inhibiting the expression of β-site amyloid precursor protein cleavage enzyme 1 and promote Aβ clearance by inhibiting AKT/mTOR signaling and activating the AMPK/Raptor pathway. In addition, in AD mice, ATG can greatly reduce elderly plaques, hinder Aβ formation, and effectively alleviate memory impairment. These results indicate that ATG has considerable potential as an anti-AD drug [55].

Ginkgo biloba extract (GBE), a plant pharmaceutical preparation, has been widely used in the treatment of central nervous system diseases and cardiovascular diseases [56]. GBE can effectively alleviate the symptoms of AD by reducing Aβ formation and deposition and inhibiting Aβ neurotoxicity [57]; reducing tau protein phosphorylation [58, 59]; increasing acetylcholine levels [60]; providing antioxidant and mitochondrial function protection [61]; protecting the blood–brain barrier [62, 63]; exerting an antiapoptotic effect and promoting differentiation [64-66]; exhibiting an anti-inflammatory effect [67]; maintaining endoplasmic reticulum homeostasis [68]; and showing anti-NMDAR effects [69].

Fucoidan has shown to exert a neuroprotective effect in an AD model of drosophila [70].

Human-induced neural progenitor cells (iNPCs) have been proven to effectively improve the cognitive function of AD mice by repairing the neural networks of the host hippocampus through functional integration. The existence of synaptic transmission between foreign and host neurons differentiated by neuroprecursor cells has been proven for the first time. In AD mice, iNPCs can be functionally integrated into the neural networks of the host hippocampus to repair damaged neural networks and improve synaptic plasticity, subsequently significantly improving learning and memory function. The above illustrates the feasibility of using iNPCs for AD cell replacement therapy and provides new strategies and directions for the treatment of AD [71].

Testosterone levels gradually decline in men with age. Low plasma testosterone level is a risk factor for poor cognitive function in old men and is significantly associated with the risk of AD in old men [72, 73]. In humans and rodents, testosterone depletion reduces cognitive performance, whereas supplementation with testosterone improves cognitive performance. Low testosterone levels in the brain and blood are associated with increased Aβ levels and those in the male brain are associated with the increased risk of developing AD [74]. Moreover, in AD, testosterone levels decrease before the appearance of cognitive impairment and neuropathological changes. Related data on patients with prostate cancer show that long-term androgen deprivation therapy is associated with the risk of cognitive impairment [75] and AD [76, 77]. At the same time, testosterone can counteract Aβ-induced mitochondrial dysfunction and increase mitochondrial energy generation under this pathological condition

[78]. A clinical evaluation of 265 subjects over the age of 60 showed that testosterone had a neuroprotective effect in patients with AD [79].

Intracranial administration can be achieved while alleviating AD symptoms by using an exosome-packed curcumin vector. Exosome-packed curcumin can efficiently penetrate the blood–brain barrier to enter brain tissue and inhibit tau phosphorylation and thus has great potential in targeted drug delivery for AD treatment and neurological recovery [80].

2. Progress of drug development research on PD

Wild-type GCase might also be a potential therapeutic target. GBA1 gene mutation is the most common genetic risk factor for PD. GBA1 encodes GCase, which degrades the fatty molecule glucose ceramide (GC). C5aR1 is a protein component receptor from a small portion of the complement system (a part of the immune system) called C5a that drives inflammation in several different types of immune cells. The occurrence of neurodegenerative diseases begins with GBA1 gene mutation, which drives the extensive accumulation of GC in immune cells. Thus, the activity of GCase is closely related to neuronal function. Mutations associated with PD can render GBA1 dysfunctional and produce deformed GCase. These effects results in the accumulation of toxic proteins in neurons that produce dopamine [81]. Experiments on mice showed that the small molecule S-181 can cross the central nervous system to enhance the activity of wild-type GCase in brain tissues, reduce the accumulation of α-synuclein and GCase lipid substrates, and improve lysosomal dysfunction [82].

In mice, *Agaricus blazei* extract protects against rotenone-induced dopaminergic degeneration and apoptosis. It blocks the rotenone-mediated diminution of dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT 2) expression, as well as the downregulation of Bcl-2 and the upregulation of Bax, caspase-3,-6,-8, and caspase-9. Some data indicate that *A. blazei* extract plays an important role in regulating the expression and promoting apoptosis and anti-apoptosis effects of DAT, VMAT2, and other proteins in PD. Therefore, *A. blazei* extract has a potential neuroprotective effect in PD therapy [83].

α-Synuclein aggregates and mitochondria have been identified as the major components of Lewy bodies [84, 85]. The inhibition of α-synuclein aggregation and reduction in mitochondrial damage have become one of the key entry points for the treatment of neurodegenerative diseases, such as PD. Molecular chaperones interact dynamically with α-synuclein in vitro. Six highly dispersed molecular chaperones identify a typical sequence in the N-terminal and a segment around Tyr39 in α-synuclein to hinder the aggregation of α-synuclein at the atomic level. Models can be used to predict the changes in molecular chaperones, α-synuclein activity, or cell level and can then be applied in preventing and treating neurodegenerative diseases, such as PD. Moreover, molecular chaperones with protective effects on α-synuclein can be used to treat neurodegenerative diseases, such as PD [86]. α-Synuclein aggregation leads to Lewy body formation, which in turn induces PD [87]. However, α-synuclein is indispensable for the human body. It plays a key role in the regulation of DNA repair: α-synuclein and DNA damage response elements are confocal in human cells and mouse brains, thus helping promote nonhomologous end-connection responses. Accordingly, increased DNA double-strand breaks (DSBs) in mice with knocked out genes that express α-synuclein can then be saved by the transfer of the human α-synuclein gene [88]. Meanwhile, α-synuclein aggregation in the cytoplasm reduces α-synuclein levels in the nucleus; this effect consequently increases DSBs and leads to programmed cell death through the loss of nuclear function. On the basis of the association of PD with DNA damage due to oxidative stress, a new approach has also been proposed: the provision of new therapeutic regimens for diseases caused by Lewy bodies via targeting α-synuclein-mediated DNA repair mechanisms [89].

In the early stage of PD, chronic inflammation occurs in the microglia in the brains of patients with PD due to the accumulation of α-synuclein [90, 91]. Some studies have found that the NLRP3 inflammasome is upregulated in the brain of patients, especially in areas where dopaminergic cells have been lost. The small-molecule inhibitor MCC950 can block the activation of the microglial inflammasome NLRP3 in the brain, thus reducing the inflammatory activity of microglia, preventing the loss of brain cells, and allowing neurons to function normally. These effects significantly improve motor function. Therefore, the NLRP3 inflammasome plays a key role in PD-like pathology. Therefore, this molecule is expected to be a viable therapeutic target for alleviating neurotoxic α-synuclein accumulation and dopaminergic neuronal damage [92].

SynuClean-D can bind closely to the protofibrils formed by α-synuclein. It exhibits a strong profibrotic decomposition activity that not only significantly reduces the aggregation of α-synuclein with A30P and H50Q variants in vitro but also prevents the misfolding and amplification of circulating α-synuclein. These effects subsequently effectively reduce the production of protofibrils and the number of Lewy bodies. After the release of the abnormal aggregation of α-synuclein in the synapse, synuclean-D can also restore synaptic motor activity [93]. Thus, SynuClean-D is expected to be used as a new molecule for PD therapy.

Sirtuin, an NAD^+-dependent histone deacetylase, is thought to have protective effects on aging-related diseases, such as cardiovascular, cerebrovascular, and neurodegenerative diseases. Given that the seven different subtypes of SIRT2 proteins promote neurodegenerative diseases, such as AD, PD, and HD, SIRT2 inhibitors have neuroprotective effects [94]. Resveratrol (RSV) is a natural polyphenolic compound with antioxidant, anticancer, anti-inflammatory, and antiaging properties. RSV acts as an antioxidant by enhancing antioxidant enzymes through the blood–brain barrier. It is also involved in SIRT1-mediated longevity extension activity, which in turn reduces glial activation and contributes to increasing hippocampal neurogenesis. RSV can also reduce amyloid precursor protein expression and improve spatial working memory. Given that RSV is an antioxidant, it can be used safely as an oral drug [95].

IP6 has a neuroprotective effect on 6-OHDA-induced dopaminergic cell damage. Its protective effects may be associated with mitochondrial alterations and the induction of apoptotic pathways, the downregulation of calcium levels, and the aggregation of α-synaptic nuclear proteins [96]. IP6 is considered as an alternative therapy for neurodegenerative diseases due to its capability to cross the blood–brain barrier of brain tissue [97].

Discussion

This review mainly presents the diagnostic system of AD and PD in neurodegenerative diseases and the progress of drug development research on AD and PD (Figure 1). AD and PD can be diagnosed on the basis of three aspects including internationally common clinical diagnostic criteria, new biomarkers, and genetic testing and identification. The clinical diagnostic criteria for AD cited in this review were co-established in 2014 by IWG and NIA-AA and can well define the clinical phenotype of AD and increase the specificity of AD diagnosis. The PD clinical diagnostic criteria mentioned in this review are included in the latest revised version published by the MDS. Moreover, new biomarkers have considerably improved the diagnostic level of neurodegenerative diseases. In addition to characteristic CSF presentations, such as decreased Aβ and elevated total tau and P-tau, found in studies on AD biomarkers, the presence of 18F-FDG PET and 18F-AV-45 PET can also reflect the occurrence of AD. Biomarkers, such as circRNA, NfL, and exosomes, have been shown to provide a reliable basis for the diagnosis of AD. CircRNAs, a new class of endogenous noncoding RNA, can be used as markers of AD because of their high expression in

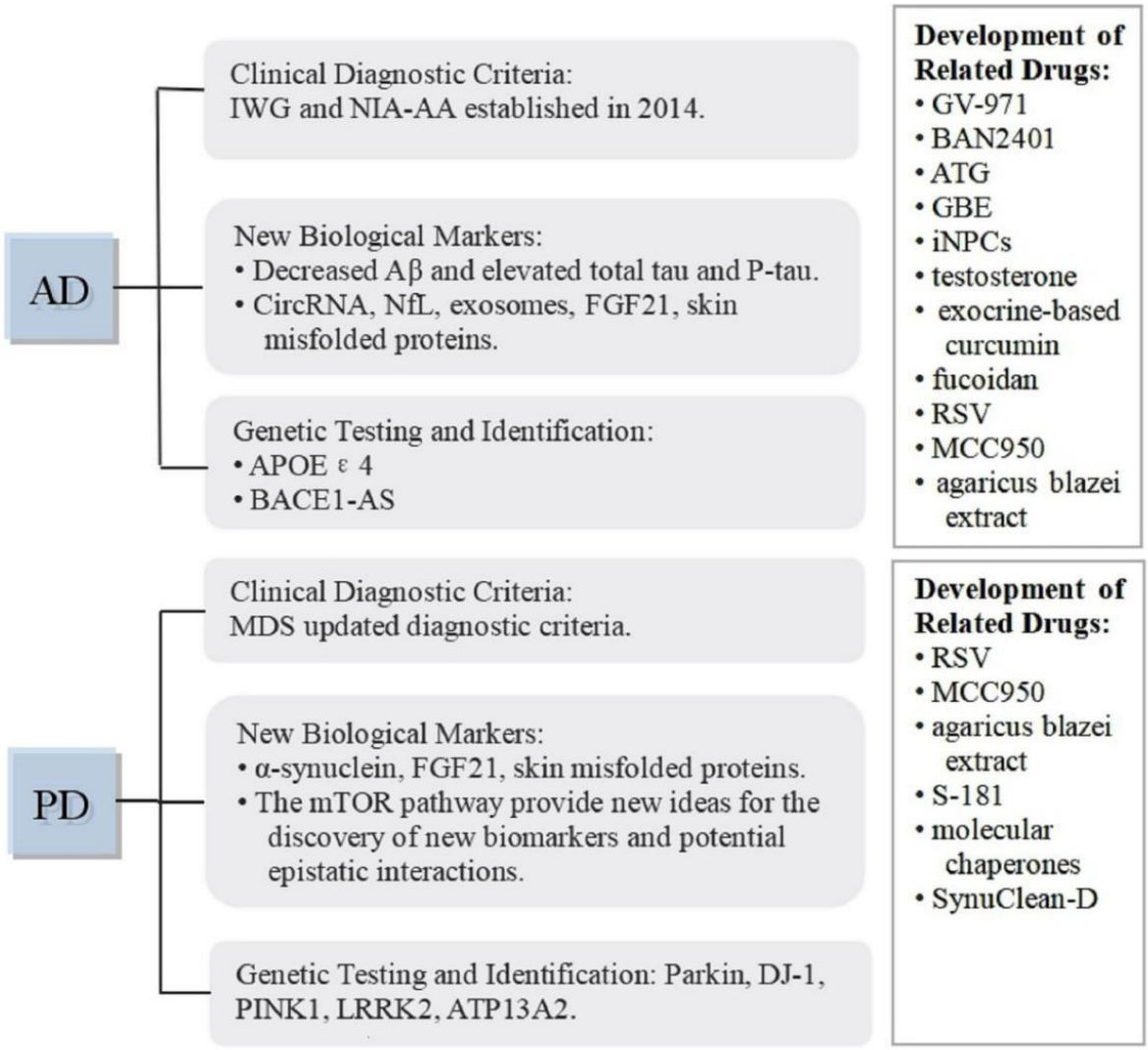

Figure 1. Diagnosis and Drug Development of AD and PD.

the nervous system, enrichment in synapses, and co-expression with known AD genes. Thus, their changes can well reflect the characteristics of AD. NfL is an integral part of the cytoskeleton, and relevant experimental results have shown that NfL in body fluid can be used as a viable biomarker in the diagnosis of AD. In recent years, studies on exosomes have also provided a new idea for the diagnosis of AD. The levels of Aβ, T-tau, and P-tau in neurogenic exosomes in the peripheral blood of patients with AD are significantly increased and highly correlated with their levels in CSF. Exosomes in peripheral blood can reflect the pathophysiological changes of the brain, and their diagnostic efficacy is equivalent to that of CSF and higher than that of individual biomarkers. The concept of α-synuclein has been widely mentioned in studies on PD biomarkers, and abnormalities in the function of α-synuclein can lead to Lewy body disease and production. Given that Lewy body production is known as the main cause of PD, pathological changes in α-synuclein, as a biomarker of PD, can be used for the diagnosis of PD. Additionally, the dysfunctional activation of the mTOR pathway contributes to the aggregation and pathological transmission of α-synuclein in the brain. The interaction between the mTOR pathway and α-synuclein provides new ideas for the discovery of new biomarkers and potential epistatic

interactions between biomarkers in PD. Meanwhile, stress response factor FGF21 and misfolded skin proteins can be used as the biomarkers of neurodegenerative diseases, such as AD and PD. Damage to mitochondrial function leads to the release of stress response factor FGF21, and chronic cell stress has an important effect on the occurrence of neurodegenerative diseases. Therefore, stress response factor FGF21 is an important molecular marker for the early diagnosis of diseases, such as AD and PD. α-Synuclein aggregates are present in epidermal peripheral nerve endings and cutaneous appendages in patients with PD, and phosphorylated tau protein aggregates are present in skin fibroblasts in patients with PD. These phenomena further demonstrate the feasibility of using misfolded skin proteins as biomarkers for the clinical diagnosis of neurodegenerative diseases. In addition to basic clinical diagnostic criteria and new biological markers, the testing and identification of relevant genes can provide a reliable basis for the diagnosis of neurodegenerative diseases. The distribution of APOEε4 gene polymorphism in the population is associated with the risk of AD pathogenesis and carrying high numbers of APOEε4 alleles is associated with the increased risk of developing AD dementia. The high specificity and transcription of the BACE1-AS gene in the brains of patients with AD suggest that BACE1-AS gene detection may provide a basis for the diagnosis of AD. In addition, mutations in a variety of genes, such as parkin, DJ-1, PINK1, LRRK2, and ATP13A2, generated through linked reaction and site cloning techniques cause PD.

Given that the pathogenesis of neurodegenerative diseases has not been clearly studied, the treatment of such diseases has become a difficult problem. Currently circulating drugs in the market can only play a role in mitigation and improvement but cannot achieve a curative effect. In recent years, research on neurodegenerative diseases has provided new ideas and action targets for finding corresponding therapeutic drugs (Figure 2). The most commonly used drugs for relieving the symptoms of AD are AChels and NMDA receptor antagonists. GV-971, which targets the brain–gut axis, has become a new drug for AD treatment. It is suitable for the treatment of patients with mild to moderate AD and provides new ideas for the pathogenesis of AD. A phase II clinical trial demonstrated that in mild AD, the BAN2401 antibody significantly clears Aβ plaques and slows cognitive decline. Aβ-induced neurodegeneration is a well-known pathogenesis of AD, and ATG can effectively alleviate memory impairment in AD mice by inhibiting Aβ production. GBE, a variety of plant medicine, can effectively relieve the symptoms of AD through many ways. Moreover, iNPCs can repair the hippocampal neural loop in AD mice through functional integration. This effect can effectively improve the cognitive function of mice and then relieve AD symptoms. The neuroprotective effects of related drugs have been used to prevent or relieve AD symptoms. Fucoidan has a neuroprotective effect in a drosophila AD model, and testosterone has neuroprotective effects in AD patients. Exosome-packed curcumin can efficiently penetrate the blood–brain barrier to enter brain tissue and inhibit tau phosphorylation. Thus, this treatment modality has great potential in targeted drug delivery for the treatment of AD and neurological recovery. The analysis of a large number of experimental results has shown that wild-type GCase may also be a potential therapeutic target and that the small molecule S-181 can cross the central nervous system, thereby enhancing the activity of wild-type GCase in brain tissues, reducing the accumulation of α-synuclein and GCase lipid substrates, and improving lysosomal dysfunction. *A. blazei* extract protects against rotenone-induced dopaminergic degeneration and apoptosis in mice. Molecular chaperones can interact dynamically with α-synuclein in vitro and at the atomic level. This interaction, in turn, hinders the aggregation of α-synuclein and contributes to the prevention and treatment of PD. Given that α-synuclein is indispensable for the body, PD can be treated by targeting α-synuclein-mediated DNA repair mechanisms. Moreover, the NLRP3 inflammasome reduces

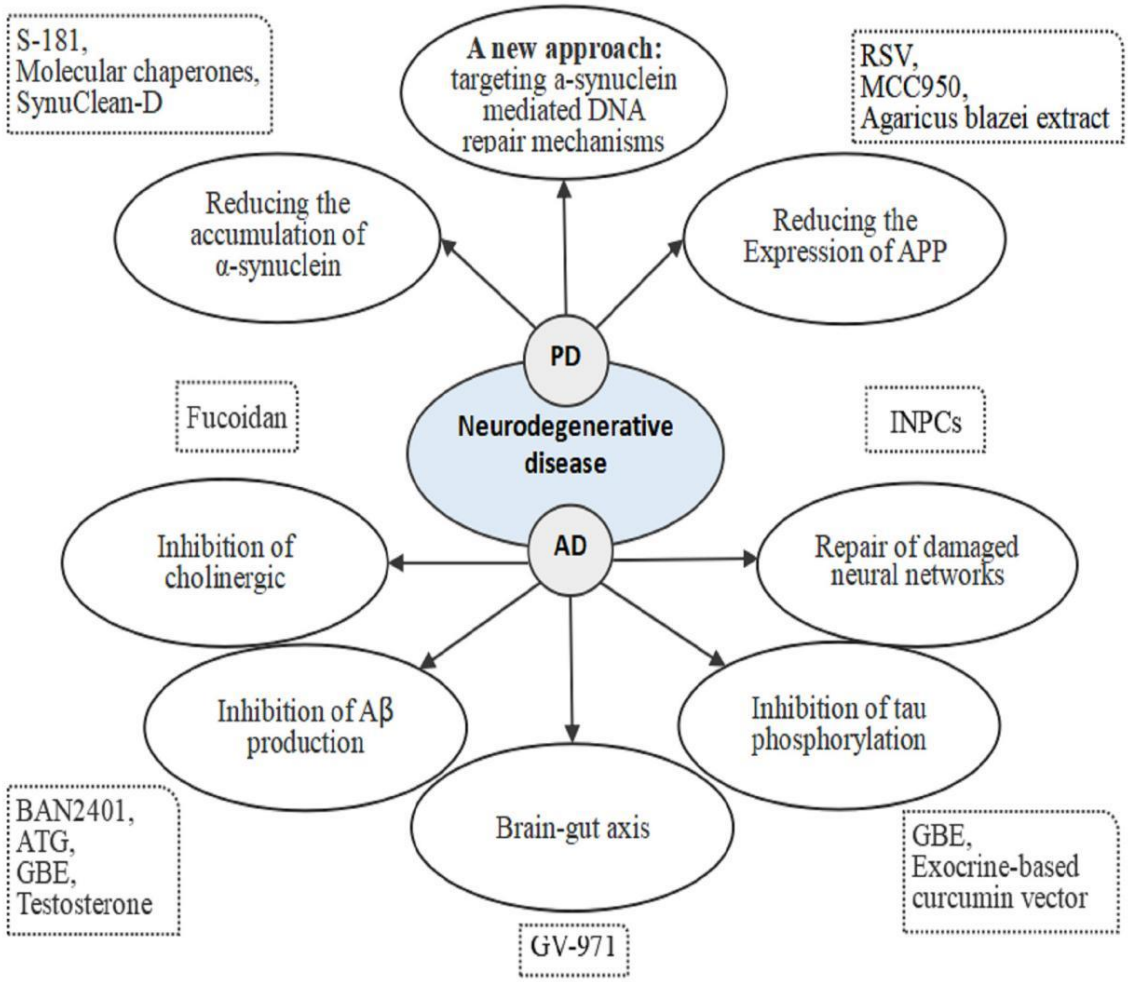

Figure 2. Advances in the development of drugs for neurodegenerative diseases such as AD and PD.

inflammatory activity in microglia, blocks brain cell loss, and reduces neurotoxic α-synuclein accumulation and dopaminergic neuronal damage. SynuClean-D can not only restore synaptic motor activity, but also prevent the misfolding and circulating amplification of α-synuclein and subsequently effectively reduce the production of primary fibers and reduce the number of Lewy bodies to alleviate PD symptoms. The SIRT2 protein promotes neurodegenerative diseases, such as AD, PD, and HD. Thus, SIRT2 inhibitors have neuroprotective effects. IP6 is also considered an alternative therapy for neurodegenerative diseases because it can cross the blood–brain barrier of brain tissue.

Conclusion

This systematic review shows that existing international diagnostic standards are constantly updated along with research on AD/PD. The diagnostic standards for AD and PD can be combined with other auxiliary methods to clarify diagnostic steps, increase diagnostic efficiency, and decrease diagnostic error rates. This review also lists a series of new drugs, which need to be further researched, for neurodegenerative diseases. These drugs provide new ideas for research on neurodegenerative diseases, the development of new drugs, and the establishment of drug targets.

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