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Chronic Diseases and Translational Medicine

REVIEW

Early detection of Alzheimer's disease using the MEMORIES mnemonic

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Abstract

The rising incidence and death rates linked to Alzheimer's disease (AD) highlight an urgent issue. Genetic screening is celebrated as a significant advancement for its early detection capabilities, pinpointing those at risk before the emergence of symptoms. Yet, the limited availability of these technologies highlights a critical gap in widespread application. This review pivots to the potential of presymptomatic clinical assessments as a readily available, economical, and simple strategy for early detection. Traditionally, AD diagnosis relies on the late-stage identification of cognitive deterioration, functional impairments, and neuropsychiatric symptoms, coinciding with advanced brain degeneration. Conversely, emerging research identifies early indicators preceding significant degeneration, manifesting years before clinical symptoms. We introduce a mnemonic, MEMORIES, to categorize these prodromal: Metabolism changes, Eye/visual impairments, March (refer to gait disturbances), Olfactory dysfunction, Rhythm (blood pressure and heart rate), Insensitivity of the tongue, Ears (hearing loss), and Stool alterations. Recognizing these prodromal through clinical examinations provides a valuable strategy for initiating preventative actions against brain degeneration. This approach advocates for broadening the screening lens beyond genetic screening to encompass clinical evaluations, enhancing early detection and intervention opportunities for AD.

KEYWORDS

Alzheimer's, clinical settings, prodromal

Highlights

- Prodromal AD: An alternative when genetic screening is unavailable.
- Prodromal stages precede brain degeneration in AD.
- MEMORIES: A tool for early prodromal AD assessment.

1 | INTRODUCTION

Global age-standardized prevalence of Alzheimer's disease (AD) at 119.0 per 100,000 individuals aged 30–64, equating to approximately 3.9 million affected individuals in this age group worldwide.[1] Individuals with dementia, including Alzheimer's, face a significantly elevated mortality risk, with a 3- to 10-fold higher rate compared to those without dementia.[2] The diagnosis of AD encompasses both clinical manifestations and laboratory assessments, with early detection strategies, including genetic screening, being a topic of extensive discussion. However, genetic screening is often inaccessible to everyone due to its high cost, lack of expertise, religious principles, cultural beliefs, and limited availability at specialized centers.[3] This underscores

the need for alternative methods to genetic screening for the early detection of AD.

The clinical signs that manifest early before the onset of AD in a clinical setting have not been thoroughly explored. Clinical indicators of AD encompass cognitive deterioration, difficulties in performing daily tasks, and neuropsychiatric manifestations like apathy, aggression, anxiety, and hallucinations. Although instances of euphoria are rare, these symptoms generally emerge with the onset of AD.[4,5] Unfortunately, diagnosing AD at this stage is considered late for preventive interventions, as the disease progresses irreversibly, leading to significant brain degeneration.[5] This highlights the critical need for the identification and understanding of early clinical signs to potentially halt or slow the progression of AD.

In the subclinical phase of AD, a spectrum of prodromal symptoms emerges, playing a pivotal role in the disease's early detection within a clinical context. These early manifestations encompass a broad range of symptoms, including autonomy impairment with notable effects on the cardiovascular system, motor dysfunctions such as gastrointestinal disturbances and altered gait, alongside sensory deficits affecting vision, olfaction, taste, and hearing, in addition to metabolic dysregulation. To facilitate the recollection of these prodromal symptoms, the mnemonic "MEMORIES" is introduced, representing Metabolism change, Eye/visual impairments, March (indicating gait disturbances), Olfactory dysfunction, Rhythm (pertaining to alterations in blood pressure and heart rate), Insensitivity of the tongue, Ears (hearing loss), and Stool changes. This mnemonic is designed to streamline the recall process for healthcare professionals, facilitating the recognition of these diverse yet interconnected symptoms.

This review explores prodromal phase of AD, shedding light on the pathophysiological mechanisms that lead to these early symptoms before the disease's full manifestation and mnemonic to memorize the prodromal. By concentrating on these early signs, the review endeavors to improve the preventative, memorizing, and simplifying measures implemented by clinicians and physicians in healthcare settings, with the goal of slowing the progression of AD.

2 | SEARCH STRATEGY AND SELECTION CRITERIA

The references for this review were sourced from multiple academic databases such as PubMed, Google Scholar, ScienceDirect, Wiley Online Library, and SpringerLink, as well as through reviewing the reference lists of relevant articles. The research utilized precise search terms like "Alzheimer," "early onset OR prodromal," and specific mechanisms of interest such as "gustatory." The selection was restricted to articles published in English, with no constraints on the publication date.

Metabolism change (M)

A study spanning 40 years has shown that declining body mass index (BMI) trends are linked to an increased risk of dementia in later life. Individuals who showed patterns of increasing BMI in early to mid-life followed by a decline in later mid-life were found to be at a significantly increased risk of dementia—ranging from 1.5 to 10.0 times higher—compared to those whose BMI did not decline.[6] A meta-analysis supports this discovery, indicating that 32.52% of elderly individuals with dementia were malnourished, and 46.80% were at risk of malnutrition.[7] Interestingly, the tendency towards malnutrition or reduced BMI among individuals with dementia cannot be attributed to diminished dietary intake. Instead, it is associated with an increased metabolic rate. This conclusion is supported by a study that compared 71 patients with AD, 52 individuals with mild cognitive impairment (MCI), and 96 control subjects, revealing that those diagnosed with AD and MCI exhibited a higher resting energy expenditure (REE) compared to the control group.[8]

The hypermetabolic state noted in AD is associated with an increased activity in oxidative phosphorylation, fueled by the upregulation of mitochondrial complexes I, IV, and V. This enhanced activity, while contributing to higher metabolic rates, also makes cells more prone to oxidative damage and calcium (Ca2+) overload. Such conditions lead to imbalances in intracellular Ca2+ levels, resulting in neuronal dysregulation (Figure 1).[9]

In the early stages of the disease, the hypermetabolic state may initially cause an increase in BMI due to low leptin levels, which further leads to imbalances in intracellular Ca2+ levels, ultimately resulting in neuronal dysfunction and dyshomeostasis. However, as the disease advances, the excessive accumulation of amyloid-beta (Aβ) may disrupt hypothalamic leptin signaling, resulting in weight loss.[10] As the amyloid burden escalates, the condition deteriorates further. Notably, the trend of declining BMI may commence as early as 3 months in mouse models, preceding the formation of amyloid plaques. This phase is characterized by decreased weight, significantly reduced adiposity, low levels of plasma leptin, and heightened energy expenditure, all occurring without alterations in feeding behavior.[10]

3 | AUTONOMIC IMPARMENT

3.1 | Rhythm (blood pressure and heart rate) (R)

Heart rate variability (HRV) denotes the fluctuations in the intervals between heartbeats, originating from the sinus node. It mirrors the intricate balance between the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS). Although a decline in HRV is a normal part of aging, a marked reduction

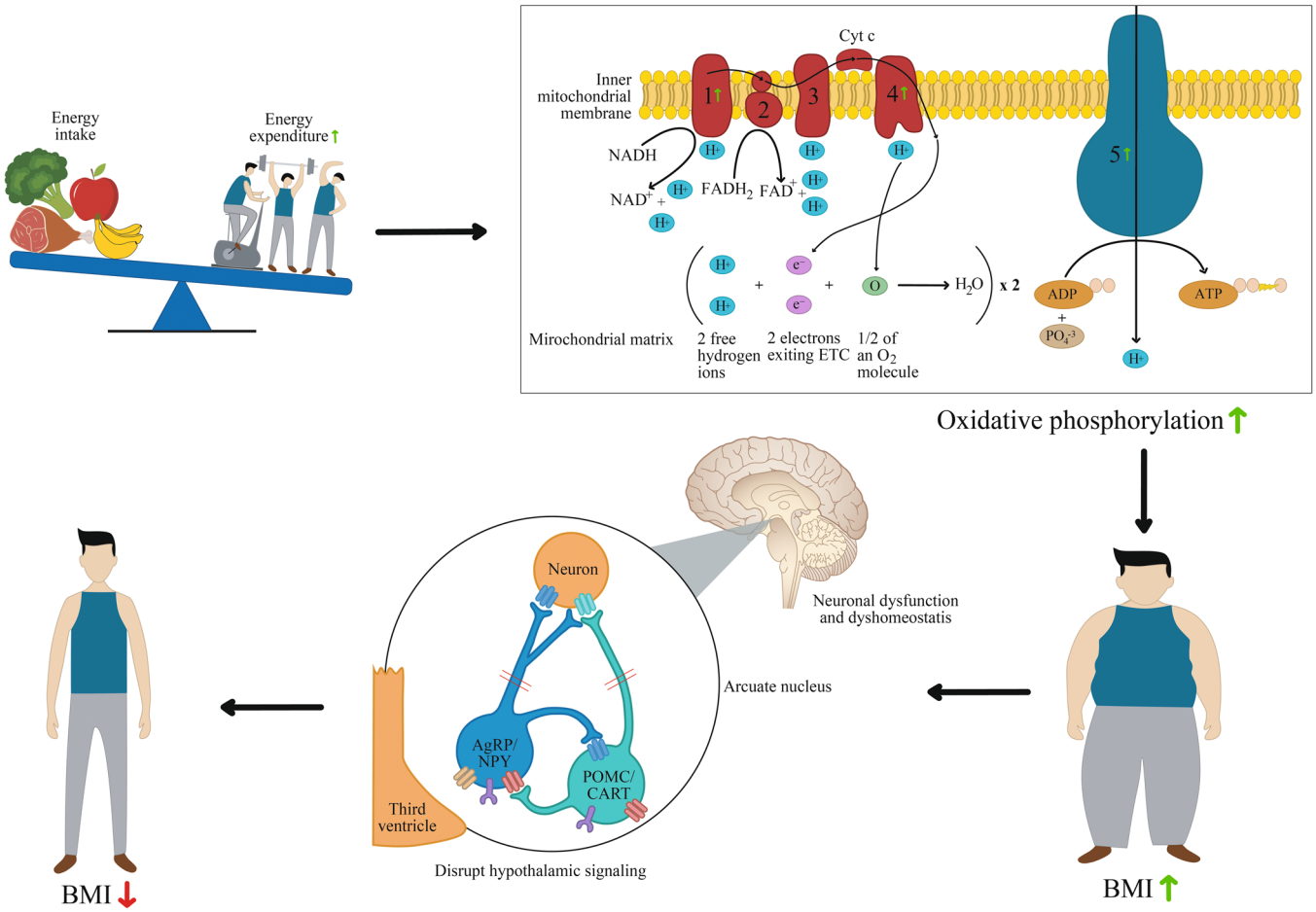

FIGURE 1 Metabolic dysfunction mechanism in early AD. Initially, a hypermetabolic state leads to increased BMI due to reduced leptin levels, causing intracellular Ca2+ imbalances and neuronal dysregulation. As the disease progresses, amyloid-beta accumulation disrupts hypothalamic leptin signaling, leading to weight loss.

signals dysfunction within the ANS. Traditionally, HRV has been evaluated using electrocardiography (ECG).[11] However, with advancements in technology, it is now possible to monitor one's HRV at home using wearable devices such as smartwatches and pulse oximeter.[12] These modern tools offer an accessible means to track and understand the state of the ANS in daily life.

A meta-analysis has demonstrated that patients with dementia exhibit significantly lower resting HRV, indicating diminished parasympathetic function and overall variability compared to control subjects. Diagnostic subgroup analysis showed that HRV was significantly lower in individuals with mild cognitive impairment and in patients diagnosed with Dementia with Lewy Bodies (DLB), when compared to control subjects. Particularly, HRV in patients with DLB was significantly reduced relative to those with AD,[13] suggesting that HRV may serve as a useful method to distinguish DLB from AD in patients with mild cognitive impairment.

In another vein, blood pressure variability (BPV) has been explored as an alternative modality to HRV.[14] Studies have determined that individuals with the highest BPV and the lowest HRV faced a doubled risk of developing AD in the future, compared to those with the lowest BPV and highest HRV.[14] This relationship is underpinned by clinical studies which have shown that biofeedback, which stimulates vagus-nerve pathways, can modulate HR. Specifically, conditions that increase HR were found to decrease plasma Aβ levels, while lower HR conditions increased Aβ levels. Decreases in Aβ were linked to reductions in gene transcription indicators of β-adrenergic signaling, establishing a connection to the noradrenergic system.[15] This suggests that alterations in HRV and BPV may reflect an imbalance in ANS activity (Figure 2). Additionally, it is noteworthy that Aβ, specifically Aβ40 and Aβ42, which are known to accumulate in the brain in AD, are also present in the heart, further linking cardiovascular function to AD pathology.[16]

4 | MOTORIC IMPAIRMENT

4.1 | Stool changes (constipation) (S)

Chronic constipation impacts around 20% of the general population, with its prevalence being notably

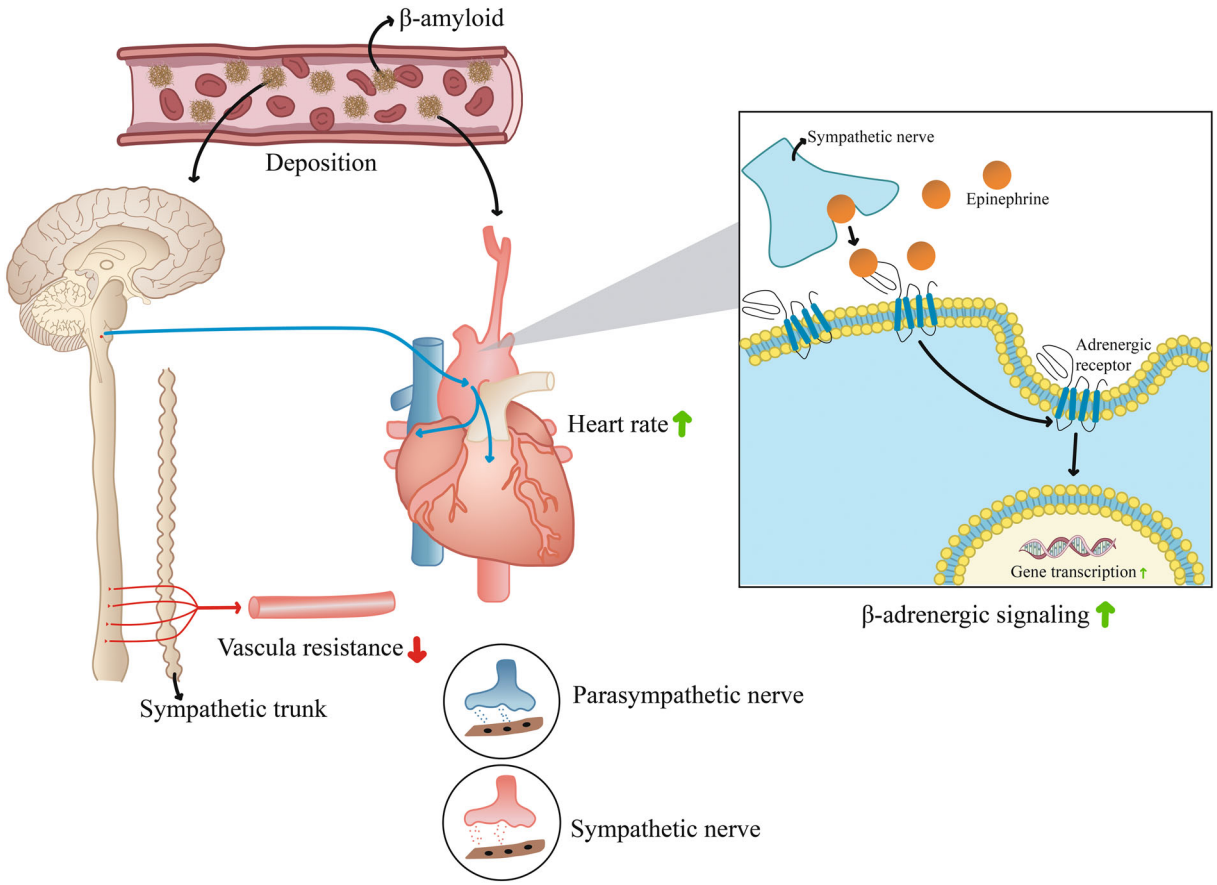

FIGURE 2 Dysregulation of blood pressure and heart rate mechanisms. Aβ circulation and deposition in the brain and heart disrupt autonomic nervous system balance by affecting gene transcription related to β-adrenergic signaling. This disruption leads to aberrant sympathetic and parasympathetic activities, affecting vascular resistance and heart rate. Consequently, there is an increase in blood pressure accompanied by a decrease in heart rate.

higher among the elderly,[17] indicating that aging is a contributing factor to constipation. Further research has demonstrated that individuals with constipation exhibit a 2.7 times faster decline in cognitive function compared to those without constipation in the context of MCI and AD.[18] Furthermore, baseline serum homocysteine levels were found to be significantly higher in the group suffering from constipation compared to those without constipation.[18] Constipation is also found as an early symptom of Parkinson's disease (PD).[19] However, in PD, constipation is associated with severe pain, fluctuating pain, nocturnal pain, and radicular pain.[20] This type of pain linked with constipation in PD has not been reported in AD, suggesting a distinct difference in how constipation manifests in PD compared to AD.

Laxatives have long been a conventional treatment for constipation. Interestingly, a study observed that over a median follow-up period of 12.8 years, the cumulative incidence rate of dementia per 1000 person-years was 2.75 for individuals who used laxatives, compared to 1.60 for those who did not use laxatives.[21] The study further included genetic assessments related to dementia risk, dividing genetic susceptibility into three categories (low, middle, and high) based on a standard genetic risk score. Compared to participants with low or middle genetic susceptibility who did not use laxatives, there was a 4.10-fold increase in the risk of dementia for individuals with high genetic susceptibility who used laxatives.[21] However, the study did not clarify the reasons for laxative use, which might be attributed to severe constipation.

The mechanism linking constipation with early signs of AD involves the gut-brain axis, where hyperhomocysteinemia (HHcy) is associated with an increased predisposition to dementia.[22] It is well known that HHcy, often observed in dementia, is linked to cardiovascular comorbidities. Cardiovascular disease is associated with HHcy, and the aging process also increases HHcy levels.[22] HHcy decreases intestinal motility through MMP-9-induced intestinal remodeling, resulting in constipation.[22] Furthermore, increased levels of reactive oxygen species (ROS), superoxide, and inducible nitric oxide synthase (iNOS), as well as heightened expression of ICAM-1 in the colon.[22] This

condition is associated with a reduction in the richness and diversity of the gut microbiome, mirroring findings in other conditions linked to alterations in the gut microbiome (Gut-Brain axis). These alterations include heightened levels of amyloid-beta and microglia in the brain, an increase in the transcription of genes linked to norepinephrine secretion and immune responses, and a reduction in the transcription of genes that play a role in bacterial defence within the colonic tissue (Figure 3).[23]

4.2 | March (refer to gait disturbances) (M)

In research involving 10-month-old Alzheimer's mouse models (specifically Tg2576 mice), an optimal age was selected for the investigation of early gait abnormalities preceding plaque formation in AD.[24] The study indicated that these mice exhibited significantly altered gait characteristics when compared to wild-type controls. This included differences in stride time, stride length, duty cycle, and the distribution of footfall patterns.[24] Gait disturbances noted in Tg2576 mice are likely due to cortical dysfunction caused by Aβ accumulation before the widespread formation of parenchymal Aβ plaques and vascular amyloid deposits.[24] This reflects the pattern of gait impairments linked to AD in humans, indicating that early cortical alterations from Aβ deposition may contribute to the observed motor deficits (Figure 4).

A meta-analysis examining the incidence of dementia in relation to gait decline found rates ranging from 5 to 21 per 1000 person-years.[25] Individuals presenting with only gait decline were identified to have a 2.1–3.6 times increased risk of developing dementia. In contrast, those experiencing both memory and gait decline faced a significantly higher risk, between 5.2 and 11.7 times, of

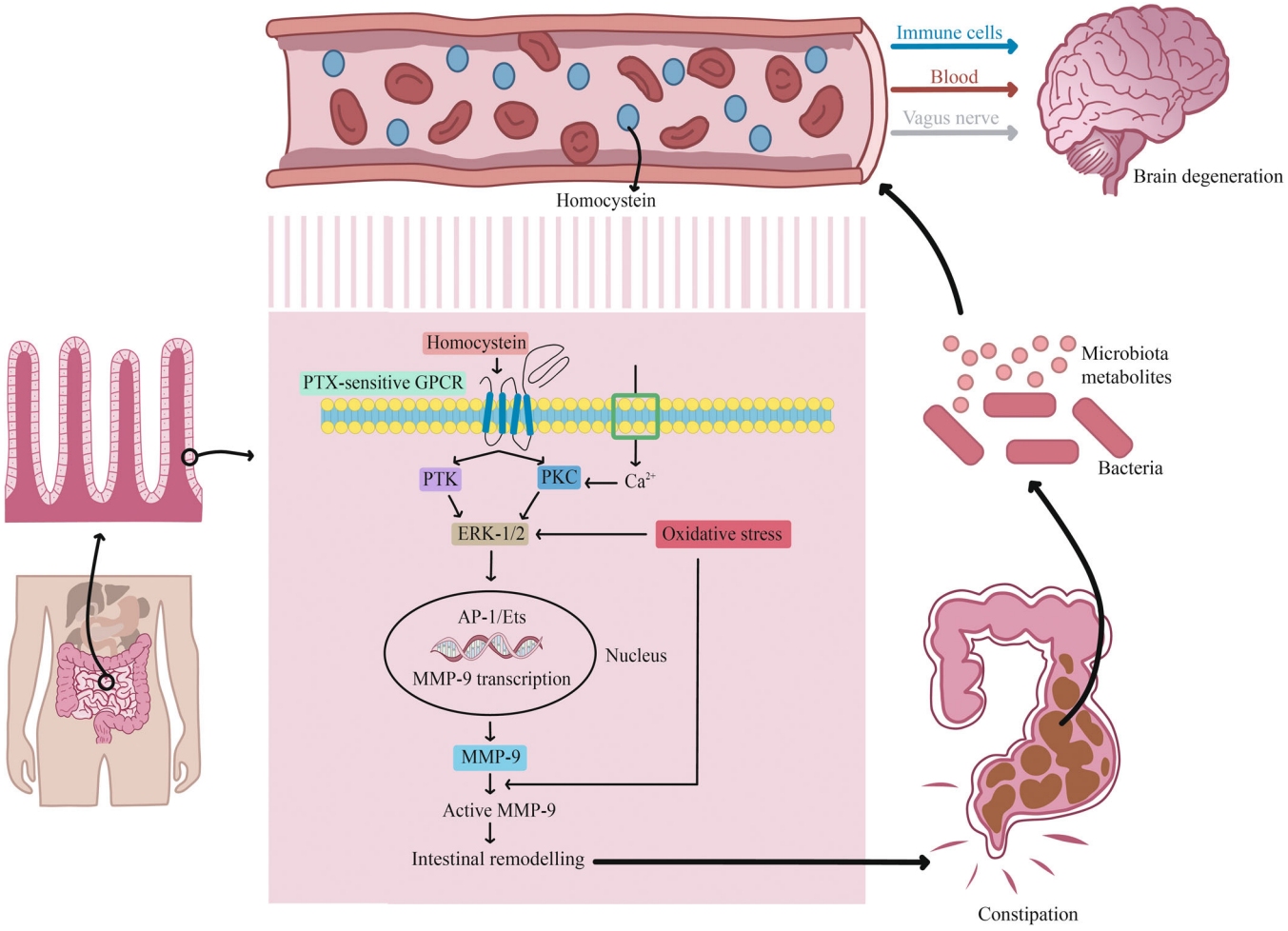

FIGURE 3 Constipation mechanism in Alzheimer's disease. Constipation in early AD involves the gut-brain axis, where hyperhomocysteinemia, linked to dementia risk, reduces intestinal motility via MMP-9-induced remodeling. This is compounded by increased oxidative stress and inflammation in the colon, characterized by elevated ROS, superoxide, iNOS, and ICAM-1 levels, contributing to gut microbiome alterations. These changes reflect broader gut-brain axis dysfunctions, including increased brain amyloid-beta and altered gene transcription affecting immune responses and bacterial defense.

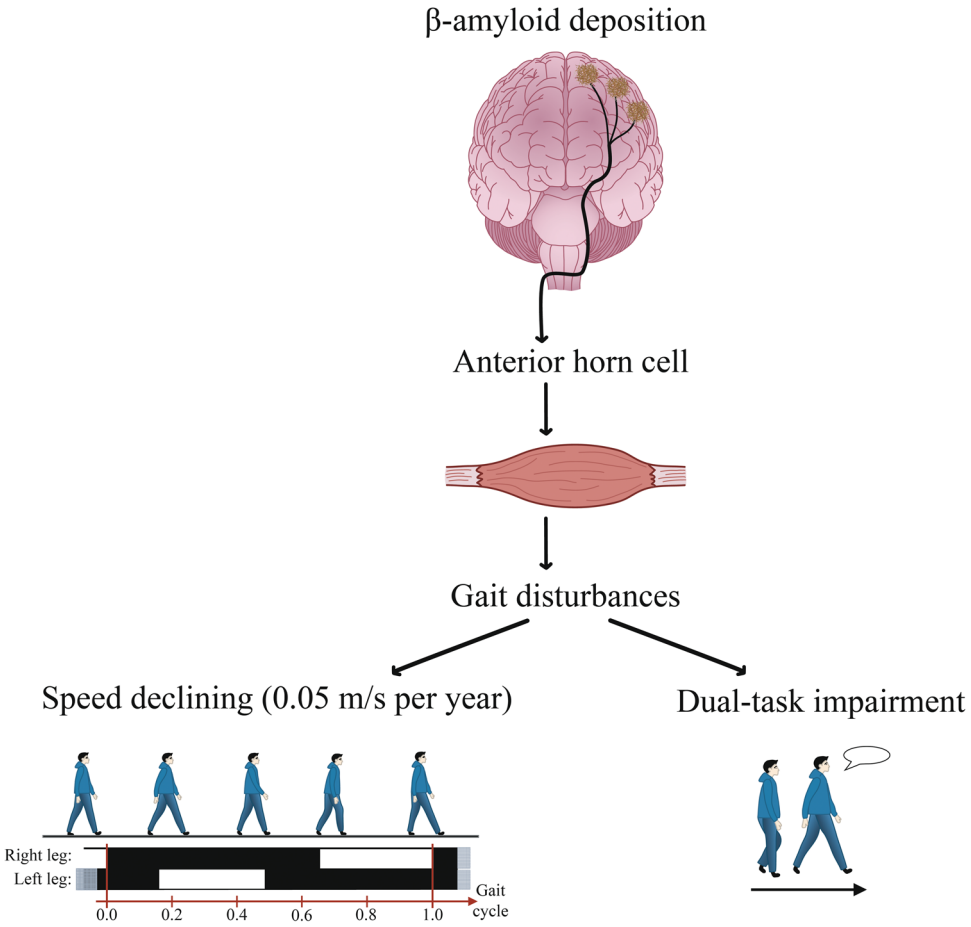

FIGURE 4 Gait disturbances mechanism in Alzheimer's disease. Gait disturbances in AD are attributed to cortical dysfunction resulting from Aβ accumulation, before extensive formation of parenchymal Aβ plaques and vascular amyloid deposits. This disruption leads to motor deficits mirroring human AD-associated gait impairments, suggesting that initial cortical changes due to Aβ deposition significantly affect mobility. Consequently, this decline impacts gait speed and the ability to perform dual tasks, such as walking while speaking.

developing AD over periods of 6.6 and 14.5 years.[25] This analysis used gait speed as a marker for gait decline, categorizing it as a decrease of 0.05 m per second or more annually.

Alternative approaches for evaluating gait, such as the dual-task method involving walking while engaging in conversation, have been suggested as early indicators of AD. Individuals in the early phases of AD exhibit gait impairments that intensify over time, particularly when undertaking tasks that demand a higher cognitive load.[26] Other alternative gait examinations include assessing high gait variability[27] and conducting videogrammetry analyses.[28] Videogrammetry analyses incorporate three distinct evaluations: the 10-m walk test, the timed up and go test, and the treadmill walk test. Among these, the treadmill walk test has not shown clinical significance in the early detection of AD.[28] However, these alternative gait assessments currently lack sufficient evidence.

Gait disturbances are also observed in the early stages of PD, with specific abnormalities noted. In PD, there is a pronounced decrease in gait speed, averaging a reduction of 0.17 m per second. Additionally, there are notable deviations in walking patterns, such as a reduced stride length, which occurs despite a higher cadence. Other abnormalities include reduced swing time and increased double support time, both of which contribute to decreased dynamic stability of gait. Moreover, reduced hip excursion in PD is likely accompanied by diminished knee extension during the terminal stance phase.[29]

5 | SENSORY IMPAIRMENT

5.1 | Olfactory dysfunction (O)

During the process of healthy aging, the prevalence of olfactory dysfunction (OD) was observed to be 24.8% among individuals aged 60–90 years, with 42% reporting the onset within the last decade.[30] This suggests that the onset of OD typically begins at the age of 60 during healthy aging processes. A meta-analysis has shown that the incidence of OD among individuals

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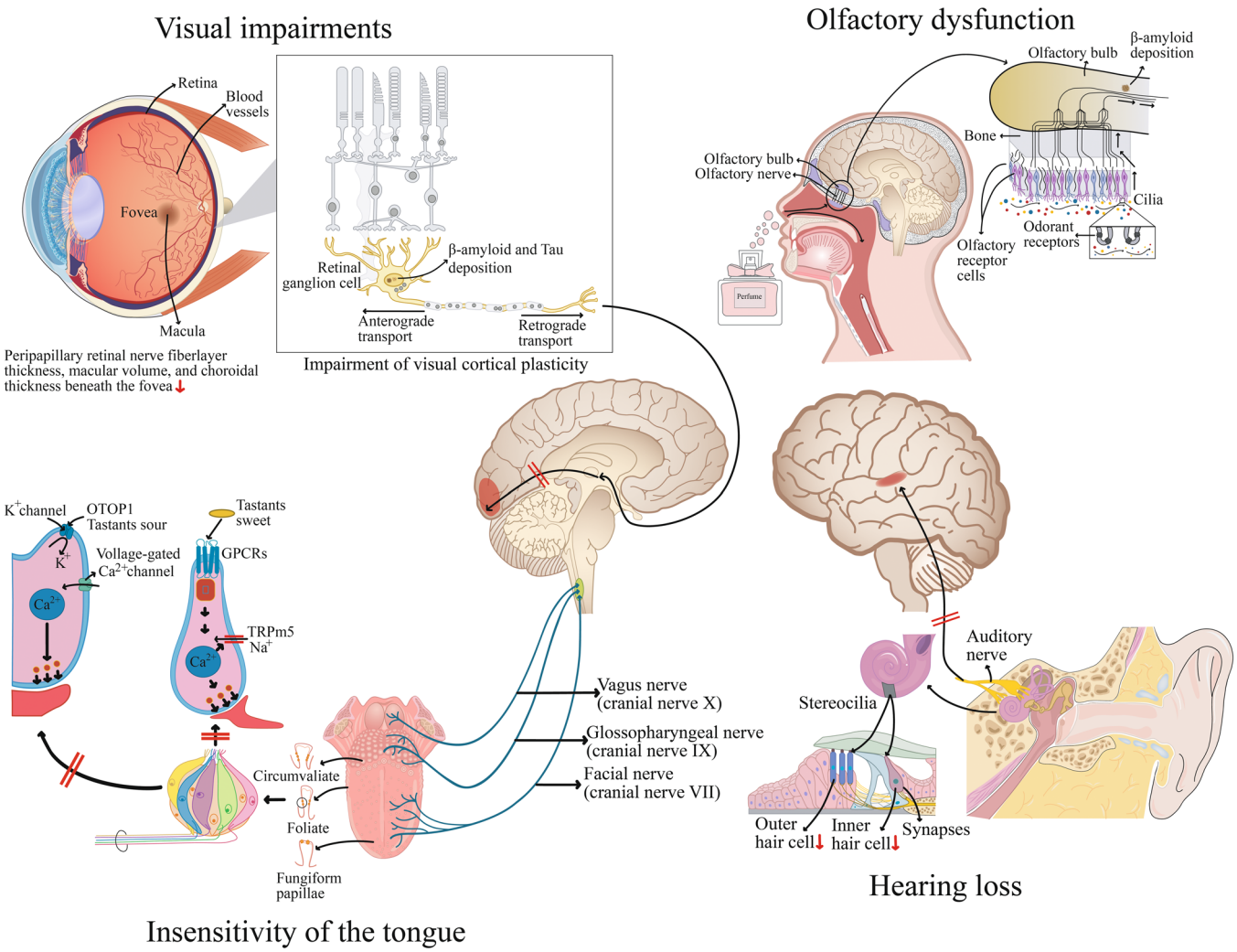

FIGURE 5 Sensory impairment mechanisms in Alzheimer's disease. Hearing loss arises from Aβ-induced neurotoxicity that disrupts the olfactory bulb's physiology and leads to cytoskeletal rearrangements, impacting intracellular signaling and structural stability. Taste insensitivity, especially to sweet flavors, is caused by dysfunction in TRPM5. Similarly, Aβ accumulation affects OTOP1, linked to sour taste perception. Visual impairments result from tau and Aβ buildup in the retina, particularly affecting retinal ganglion cells and impairing visual cortical plasticity. Lastly, hearing loss is linked to a reduction in inner and outer hair cells on the basilar membrane, with the overexpression of tau protein intensifying the impact of Aβ on hearing, contributing to a compounded sensory deficit.

aged 60–80 years is linked to a 2-3-fold increase in the risk of cognitive decline. For those aged over 80 years, the risk of experiencing cognitive decline escalates even further.[31]

Prospective cohort studies have indicated that OD often presents roughly 5 years before the emergence of mild cognitive impairment and 3 years before the diagnosis of dementia. Furthermore, the rate of decline in olfactory identification capabilities is more pronounced in individuals who develop dementia compared to those who do not.[32] Such evidence suggests that OD may be a significant early marker for the diagnosis of dementia, including AD. Additionally, this research has demonstrated a correlation between the presence of the APOE ε4 allele and OD, alongside an increased risk of developing dementia.[32] These findings highlight the significance of incorporating genetic assessments into screening protocols and early preventive measures for dementia. Although OD is an early indicator for diagnosing AD, it is also present at early onset of PD.[33] In AD, the impairment is primarily in odor detection, rather than odor recognition or detection thresholds. Conversely, PD affects olfactory functions more uniformly. Nevertheless, the impact on olfactory tests is more pronounced in AD, where significant differences between various olfactory assessments are observed.[34]

The mechanism behind OD in AD is attributed to the accumulation of Aβ within the olfactory circuit (Figure 5). Initially, Aβ deposition occurs in the vasculature of the olfactory bulb. During this early stage, the body activates defense mechanisms such as the upregulation of SEC. 14L2, GPM6A, and HIST2H2ACA and downregulated SMAP1 in response to Aβ aggregate-induced neurotoxicity to maintain physiology of olfactory bulb (OB).

Concurrently, there is an upregulation of inhibitory factors like PHF24 interneuron and DYNLL2, both of which are implicated in the trafficking of NMDA receptors to the postsynaptic site. Additionally, genes associated with Aβ deposition, including MARCKS, APP/PS1, and KIF2A, are involved in this process.[35,36]

The role of OD in the early stages of AD progression might be linked to abnormal impulse transmission. Aβ contributes to the disruption of specific protein mediators crucial for cytoskeletal rearrangements, leading to morphological changes or remodeling due to Aβ aggregate-induced neurotoxicity. This results in disturbances in intracellular signaling by influencing kinesin, causing an imbalance in axonal transport. The increase in DYNLL2 leads to aberrant axonal mitochondrial mobility and altered MARKCS-regulated phosphatidylinositol 4,5-bisphosphate (PIP2) levels and actin movement, resulting in abnormal endocytosis in vesicular trafficking. Smap1 acts on ADP-ribosylation factor 6, interacts with clathrin, and regulates clathrin-dependent endocytosis into clathrin-coated vesicles by lateral migration, aberrantly stabilizing NMDA receptor signaling. This process is further aggravated by the influence of PHF24 on GABAB-receptor signaling within the olfactory system, explaining the connection between OD and the early development of AD.[35]

5.2 | Insensitivity of the tongue (I)

Patients with AD are believed to suffer from gustatory dysfunction (GD) or insensitivity of the tongue. Yet, the reliability of this symptom as an early biomarker for AD remains under debate. Contrary findings from another study suggest that taste impairment in elderly individuals with cognitive decline may occur independently of factors known to affect taste perception, such as salivation, zinc levels, or the use of prescription drugs.[37] This study contrasts previous findings by showing that, in preclinical trials with mice aged 70 and 80 weeks, changes in taste sensitivity were evident by 70 weeks. However, alterations in short-term memory, as measured by spontaneous alternation behavior, were not detected until the mice reached 80 weeks, at which point a significant decline was observed,[38] indicating that the effects GD occurred first then cognitive functions manifest differently over time and give our perception that GD can be used as early biomarker.

Meta-analysis studies reveal that, compared to healthy controls, individuals with AD have significantly lower performance in overall taste sensitivity and the ability to identify flavors such as sweet, salty, sour, bitter, and umami. Notably, their ability to identify sour tastes is particularly impaired. This decline in taste sensitivity is also identified in the early stages of PD, where individuals with PD and MCI exhibit poorer detection of sweetness, sourness, and saltiness. In the AD group, the impairment is especially pronounced for sweet and sour flavors.[39] This observation indicates a progressive decline in taste function as cognitive impairment progresses from MCI to AD. Additionally, the worsening of dementia severity is associated with a decline in gustatory abilities.[40] Although aging can also affect gustatory function, in healthy aging, this function is not as impaired as in dementia, where the ability to taste sweet and sour flavors worsens significantly.[41]

The mechanisms driving this relationship are presently not fully comprehended. Recent studies have shed light on GD, revealing alterations in the functional connectivity among brain regions. These changes are not limited to areas directly involved in taste processing but extend to regions associated with cognitive functions.[42] A preclinical study using APP/PS1 transgenic mutant mice revealed a selective reduction in bitter taste sensitivity. This decrease was noted in the APP/PS1 mice, which also showed a diminished presence of TRPM5-expressing taste receptor cells in the circumvallate papillae on the tongue.[43] This result is seemingly contradictory to data from a meta-analysis that suggests a general deterioration in the perception of sweet and sour tastes in AD, not specifically bitter taste.[39] A potential mechanism for this could involve TRPM5, a channel known to be involved in the perception of both sweet and bitter tastes. The defect in taste perception primarily manifests in the sweet domain, with no significant impairment observed for sour tastes. Additionally, OTOP1, which is implicated in the perception of sour tastes, is also affected by Aβ accumulation (Figure 5).[44]

5.3 | Eye/visual impairments (E)

A meta-analysis has demonstrated that individuals experiencing eye or visual dysfunction (VD) are at a 47% higher risk of developing dementia and a 35% increased risk of developing cognitive impairment compared to those without VD. This study underscores the significant role of VD in contributing to the global burden of dementia, particularly among adults aged 50 years or older, with a pronounced impact observed in low-income countries. The link between VD and an increased likelihood of developing dementia became apparent within the initial 2 years after diagnosis and remained significant from 2 to 4 years thereafter. However, this increased risk did not extend beyond 4 years.[45]

In clinical evaluations, VD linked to AD includes diminished moderate and severe visual acuity as well as abnormalities in the retina. These retinal impairments involve a decrease in the thickness of the peripapillary retinal nerve fiber layer, the overall volume of the macula, and the thickness of the choroid beneath the fovea.[46,47] The underlying mechanism by which AD influences VD is attributed to the impairment of visual

cortical plasticity, primarily due to Aβ accumulation and retinal tau pathology.[48,49] Remarkably, the accumulation of tau in the retina is detectable as early as 3 months of age, preceding the onset of behavioral impairments in animal models. This initial tau pathology in the retina precedes tau aggregation in the brain, with tau buildup observed specifically in the soma and dendrites of retinal ganglion cells (RGCs). Conversely, there is a depletion of tau in RGC axons within the optic nerve. Alterations in tau phosphorylation and misplacement are closely linked to notable deficiencies in the transport of cellular materials along axons in the forward direction, occurring before the death of RGCs (Figure 5). Importantly, targeted reduction of endogenous tau using siRNA-based methods has demonstrated improvement in the transport of cellular materials along RGC axons and RGC dysfunction occurring before obvious nerve cell degeneration in AD.[49]

5.4 | Ears (hearing loss) (E)

Hearing impairment (HI), also known as hearing loss (defined as a speech-frequency pure tone average >25 dB), has been identified as a significant risk factor for AD, increasing the risk by 1.5 times over a period of 5 years. Specifically, individuals with HI are three times more likely to develop AD compared to those with normal hearing.[50] In addition to hearing loss, the existence of pre-existing tinnitus is linked with a 68% higher risk of early-onset dementia in young and middle-aged adults.[51]

Preclinical research using AD mouse models has shown that hearing loss, particularly at high frequencies, can occur as early as 2 months of age. This is significantly earlier than the spatial learning deficits typically observed at 6–7 months of age. This hearing loss is progressive, initially affecting high frequencies and subsequently extending to lower frequencies.[52] At 3–4 months of age, mice experience hearing loss across the entire range of frequencies. This decline in auditory function is attributed to a significant reduction in the number of both inner and outer hair cells located at the apical and basal ends of the basilar membrane.[53] Mechanistically, the overexpression of human microtubule-associated protein tau, a key pathological factor in AD, has been shown to synergistically exacerbate Aβ-induced HI (Figure 5).[54]

Our proposed mnemonic requires further exploration to analyze its precision in predicting AD. Many of our results, indicating the onset of AD before its occurrence, are derived from preclinical studies and therefore need confirmation through clinical studies. Clinicians should be careful, as prodromal symptoms are not exclusive to AD and can be found in other diseases. It is essential to identify specific characteristics in each mnemonic to ensure accurate diagnosis.

6 | CONCLUSION

In the context of diagnosing AD, clinicians should maintain a heightened index of suspicion when encountering patients presenting diminished capacity to discern sweet and sour tastes. A trajectory of BMI initially increasing followed by a subsequent decrease, progressive hearing loss across all frequencies, tinnitus, impairments in visual acuity and retinal function, OD, divergent responses in BPV and HRV—with BPV being markedly higher and HRV significantly lower, a decrement in gait speed exceeding 0.05 m per second annually or notable gait impairment, and constipation necessitating laxative intervention, should prompt consideration of AD. To aid in the recollection of these prodromal indicators, the mnemonic "MEMORIES" is proposed, encapsulating Metabolism change, Eye/visual impairments, March (indicating gait disturbances), OD, Rhythm (alterations in blood pressure and heart rate), Insensitivity of the tongue, Ears refer to hearing loss, and Stool changes indicative of constipation. This mnemonic serves as a comprehensive reminder to clinicians to consider these multifaceted symptoms when evaluating potential AD in patients.

AUTHOR CONTRIBUTIONS

Valentinus Besin, Farizky M. Humardani conceptualized the idea for the article, conducted the literature search, and performed the data analysis. Farizky M. Humardani drafted the manuscript and prepared all figures. Valentinus Besin critically revised the work.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

None.

ETHICS STATEMENT

Ethical approval was not required as this is a review of previously published studies.

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