Interdisciplinary Approaches to Deal with Alzheimer's Disease

Subjects: Others

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Alzheimer's disease is one of the most common neurodegenerative diseases in the western population. The incidence of this disease increases with age. Rising life expectancy and the resulting increase in the ratio of elderly in the population are likely to exacerbate socioeconomic problems. Alzheimer's disease is a multifactorial disease. In addition to amyloidogenic processing leading to plaques, and tau pathology, but also other molecular causes such as oxidative stress or inflammation play a crucial role. Unfortunately, all previous single-domain interventions have been shown to have limited benefit to patients. However, the latest studies indicate that combining these efforts into multidomain approaches may have increased preventive or therapeutic potential.

Alzheimer's disease | nutritional approaches | physical activity | socioeconomic factors | cognition-oriented treatment | communication | oral health | interdisciplinary approaches | multimodal intervention | multidomain intervention

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and is characterized by behavioral and cognitive impairments. It results in a loss of memory and acquired skills, as well as a decrease in participation in daily activities, communication skills, social interactions and quality of life leading to an increasing burden on caregivers [1][2]. The main histopathological hallmarks of AD are the severe accumulation of amyloid-β in extracellular neuritic plaques as well as intracellular neurofibrillary tangles (NFTs) in vulnerable brain regions such as the hippocampus and cortex [3]. Based on the onset of symptoms and pathological changes in the cortex and hippocampus, clinical AD stages can be classified into at least four phases. The pre-symptomatic/pre-clinical stage is asymptomatic despite early pathological changes in the cortex and hippocampal formation [4][5][6], followed by mild cognitive impairment (MCI). MCI shows limitations in some cognitive domains on functional examination without restrictions in the ability to cope with everyday life [7][8][9] but definite laboratory evidence, including biomarkers such as low amyloid-β and increased tau proteins in the cerebrospinal fluid [5]. Mild/early dementia due to AD is characterized by symptoms such as spatial and temporal disorientation, loss of memory and concentration, word-finding difficulties, and the development of depression. In the moderate stage of AD, increased memory loss, impairment of visuospatial abilities leading to difficulties in recognizing family members and friends, and problems with language and communication occur [5][6][10]. The final stage of AD, severe/late AD, is associated with severe

accumulation of NTFs and senile plaques in the entire cortex area, resulting in advanced functional and cognitive impairment, incontinence, dysphagia, and complete dependence on caregivers [5].

Currently (2020), AD is estimated to affect 55 million people worldwide. Global AD prevalence is predicted to increase to 139 million people living with AD by 2050 due to the aging population, making AD a major public health concern. Yet, to date, there are only two classes of approved drugs to treat persons with Alzheimer's disease (PwAD): Cholinesterase enzyme inhibitors and N-methyl-D-aspartate (NMDA) inhibitors. Acetylcholine-producing cells are destroyed in AD by different physiological processes. Treatment with acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine blocks the catabolism of acetylcholine, increasing acetylcholine concentration in the synaptic cleft and thus cholinergic transmission in the brain [5][11][12][13]. Overactivation of NMDA-receptors leads to increased intracellular calcium levels, promoting cell death and synaptic dysfunction. The use of partial NMDA antagonists such as memantine, which can be taken in combination with cholinesterase inhibitors, prevents NMDA-receptor overactivation and restores its normal activity [14][15]. However, these medications are only temporary effective in treating the symptoms of AD by improving quality of life but do not cure or prevent the disease.

Most AD cases occur sporadically (known as sporadic Alzheimer's disease, SAD) with the age of onset above 65 years. Less than 10% of AD cases are caused by genetic familial mutations leading to earlier disease onset, usually between the age of 30 and 60 (known as early onset Alzheimer's disease, EOAD or familial Alzheimer's disease, FAD). AD is considered a multifactorial disease as it is characterized by impairments in multiple cellular processes. In addition to cholinergic dysfunction and the well-known Abeta (Aβ) and Tau pathology of AD, inflammation, oxidative stress, as well as, e.g., alterations in lipid and energy metabolism are also involved in the pathogenesis of AD.

The Lancet Commission on dementia prevention, intervention and care [16] recently identified 12 potentially modifiable risk factors for dementia that account for around 40% of dementia cases worldwide. These include, among others, physical inactivity, low social contact, obesity, and associated diabetes. Frequent physical activity, promotion of communication to maintain social interactions, and a healthy diet to avoid the risks of obesity and diabetes may therefore affect neuropathological damage and cognitive reserve [16] and contribute to the prevention or delay of dementia. According to current literature, the intraoral condition could also represent such a modifiable risk factor [17][18][19].

Reducing modifiable risk factors, in addition to pharmacological interventions, is an important approach in dementia treatment. According to Spector and Orrell's biopsychosocial (BPS) model [20], dementia is a multifactorial disease in which psychosocial and biological processes are interrelated. Both domains include fixed, non-modifiable factors (e.g., age; education) and tractable, modifiable factors (e.g., physical health; social interaction, mental stimulation). Treatment plans should be tailored to the individual's needs. Factors amenable to change are identified with the aim of influencing them through medical and non-pharmacological interventions [20][21]. In recent years, non-pharmacological interventions have become increasingly important in the management of dementia and in the effort to improve living with dementia and maintain quality of life [1][7][22][23][24]. Non-pharmacological interventions

include evidence-based psychological, bodily, nutritional, digital or basic methods and approaches, that are individually selected and adjusted to the persons' needs in their courses of disease [7][24]. Among these, cognition-oriented treatments (COT) [1][24][25], physical activity [26], and diet [27] form an integral part.

2. Feasible Options

A large-scale meta-analysis and systematic review of more than 150 RCTs and more than 240 observational prospective studies identified evidence-based modifiable factors for the prevention of AD [28]. The Lancet Commission also recommends addressing risk factors that favor the development of dementia across the lifespan, as this can affect cognitive reserve and delay neuropathological developments [16][29]. For example, a reduction in oxidative stress or effects on mitochondria, in general, are known to be involved in physical activity and nutrition [30]. In this context, the effect of PGC-1α, a mitochondrial super-regulator, has been reported to be affected by AD and might be an interesting target for further studies [31]. Moreover, dietary interventions influence cellular energy metabolism and can therefore have an impact on synaptic plasticity [29], a parameter, which highly correlates with cognitive reserve and cognitive activity in general. Synaptic plasticity is further influenced by different lipids [32]. E.g., plasmalogens or phosphatidyl-choline in combination with choline/UMP-choline or DHA have been shown or are at least discussed to increase several synaptic markers such as synaptophysin or PSD95 [33][34]. There is growing evidence that combined dietary components show synergistic beneficial effects on AD pathology [35][36]. In general, interventions in the prodromal and early stages of AD may correct the deficiency of key nutritional elements that could otherwise lead to the loss of synapses and neurons [36].

Up to now, addressing only one risk factors or molecular mechanism has been proven to be not sufficient to deal with AD, making a multidisciplinary approach even more attractive. Therefore, multidomain interventions that target preventive, or early-stage disease show potential for delaying the onset of dementia [29][37][38][39][40][41][42], even with existing structural changes in the brain [43][44][45]. Physical activity and cognitive activities stimulate cerebral blood flow and the production of neurotrophic factors that influence hippocampal neuroplasticity [29][42][44]. Also, physical activity and dietary interventions are known to address similar mechanisms involved in AD. Dietary modifications combined with aerobic physical activity led to cognitive improvements in participants with elevated blood pressure [46]. Since high blood pressure is also a risk factor for the onset and progression of AD, combined nutritional approaches with specific physical activity are promising for AD. These are only a few examples that combine different approaches to adjust the dysregulated metabolic homeostasis in AD synergistically from different angles, resulting in an elevated beneficial potential with respect to AD compared to approaches based on a single intervention.

To improve cognition, multidomain interventions should comprise at least three modalities, one of which is a cognitive approach [29]. Up to now, cognition and physical training is the most common combination of the multidomain approaches [29][41][42][47]. Communication-based interventions and outcomes have rarely been considered in COT and in multidomain approaches so far, despite the fact that impaired communication can form a major burden in disease progression [48][49], and beneficial effects of COT are partly attributed to language activities and communicative interaction [50][51]. More recently, a person-centered approach with individually determined

goals has become prevalent in speech and language therapy [52][53][54]. Similarly, multidomain interventions with individualized contents achieve the greatest effect sizes [29]. In many studies, cognition is the primary outcome used to test the effectiveness of the intervention. Unfortunately, most of the chosen assessments or outcomes have little relation to the demands of daily living [29][55], but rather measure higher cognitive functions [308]. Future work should therefore consider communication skills as an outcome measure. Corresponding parameters would be, for example, the proportion of topic-related utterances and empty utterances or the global coherence in the discourse of people with dementia [56][57].

Nutritional interventions and educational support play an important role in supporting and counseling PwAD and their families throughout the course of the disease [38][58][59][60]. The success of psychoeducational interventions depends on clear communication of theoretical contents and the active involvement of carers in practice sequences to implement new skills [49][58].

Although there is a growing interest in interrelated biochemical processes in intraoral inflammation and the occurrence and progression of AD [61][62], there are few clinical studies investigating the effectiveness of oral treatment approaches in AD. Support of oral hygiene and health, prevention and diagnosis of periodontal disease are promising approaches in dementia care that have not yet been addressed in multidomain interventions but should receive more attention in the future [66][67][68][69]. Difficulties in recruitment include ethical issues, the health status of people with disabilities, lack of compliance, required involvement of relatives, treatment limitations, and economic issues [63][64][65]. However, oral treatment approaches are very promising to be integrated into a multidomain approach. In particular, approaches to nutrition, oral hygiene, mobility and masticatory function can be optimally coordinated and adapted to individual needs, which overall contributes to an improvement in the quality of life of PwAD. Sessions can take place in groups as well as individually and thus promote social activities, as is also recommended in this context [16]. In this context, diabetes mellitus, recently identified as an additional risk factor for the development of AD [70], should also be mentioned, even though the underlying mechanisms have not yet been clarified [71]. It is known that there is a bidirectional relationship between the presence of intraoral inflammation, especially periodontitis, and diabetes mellitus [72]. Thus, an improvement of the intraoral condition also fulfills the previously formulated need to implement a diabetes mellitus-protective lifestyle for AD prevention [28].

Taken together, treatments based on multicomponent or even multidisciplinary approaches revealed more pronounced benefits than single interventions. Therefore, we suggest a tight interlink between different treatment strategies resulting in an interdisciplinary approach, covering in particular nutritional counseling, supervised physical training, oral health, and cognitive-oriented communication intervention to maintain quality of life in AD. Although the reviewed literature is promising, further studies addressing these interdisciplinary aims are needed to prove effectiveness.

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