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Review

Overview of therapeutic targets in management of dementia

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ABSTRACT

Dementia is defined as a gradual cognitive impairment that interferes with everyday tasks, and is a leading cause of dependency, disability, and mortality. According to the current scenario, millions of individuals worldwide have dementia. This review provides with an overview of dementia before moving on to its subtypes (neurodegenerative and non-neurodegenerative) and pathophysiology. It also discusses the incidence and severity of dementia, focusing on Alzheimer's disease with its different hypotheses such as Aβ cascade hypothesis, Tau hypothesis, inflammatory hypothesis, cholinergic and oxidative stress hypothesis. Alzheimer's disease is the most common type and a progressive neurodegenerative illness distinct by neuronal loss and resulting cognitive impairment, leading to dementia. Alzheimer's disease (AD) is considered the most familiar neurodegenerative dementias that affect mostly older population. There are still no disease-modifying therapies available for any dementias at this time, but there are various methods for lowering the risk to dementia patients by using suitable diagnostic and evaluation methods. Thereafter, the management and treatment of primary risk elements of dementia are reviewed. Finally, the future perspectives of dementia (AD) focusing on the impact of the new treatment are discussed.

1. Introduction

Dementia is a syndrome in which there is an impairment of brain functions (memory loss and judgment), which affects or interferes with individuals' ability with daily functioning. In other words, dementia is a condition that reduces a person's capacity to function at work, at home, or in other social circumstances. Dementia, rather than being a disease in and of itself, should be considered an acquired condition with various possible causes. For instance, Alzheimer's disease, frontotemporal lobar degeneration and language cortex tumor can be responsible for dementia syndrome of progressive language loss. Dementia is thought to afflict up to 7% of adults (with age above 65 years) globally, with somewhat higher occurrence (8–10%) in advanced nations owing to long life expectancies [1]. Causative factors of this syndrome include aging (the biggest risk factor), changing genetics and systemic vascular disorders [2].

Abbreviations: AChEI, Acetylcholinesterase Inhibitor; AD, Alzheimer's Disease'; ALS, Amyotropic Lateral Sclerosis; Aβ, Amyloid Beta; CAA, Cerebral Amyloid Angiopathy; CBS, Corticobasal Syndrome; CDR, Clinical Dementia Rating; CSF, Cerebrospinal Fluid; CTE, Chronic Traumatic Encephalopathy; ESR, Erythrocyte Sedimentaion Rate; FTD, Frontotemporal Dementia; IVIG, Intravenous Immunoglobulin; MCI, Mild cognitive impairment; MMSE, Mini-Mental Status Exam; NFTs, Neurofibrillary Tangles; O-GlcNAc, O-linked N-acetylglucosamine; PET, Poitron Emission Tomography; TBI, Traumatic Brain Injury; VCI, Vascular Cognitive Impairment.

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Dementia is characterized into two major categories: 1) neurodegenerative (formerly known as irreversible); 2) non-neurodegenerative (potentially reversible) (Fig. 1). This heuristic is useful, although it is constrained by its simplicity. Patients with dementia can and often do have a number of both neurodegenerative and non-neurodegenerative disorders, all of which lead to impairment [3]. Diseases that deteriorate the cognitive function without altering everyday functioning, whether it is diagnosed early or later, are termed as "Mild neurocognitive disorder" (according to the DSM-V) and "mild cognitive impairment".

Neurodegeneration is considered as the primary cause of dementia in grown-up people. Prevailing degenerative dementias among the aged population include Alzheimer's disease, Lewy bodies and vascular dementia, frontotemporal lobar degeneration, and Parkinson's disease. On the other hand, vitamin deficiencies, underactive thyroid (also known as hypothyroidism), chronic abuse of alcohol, cognitive dysfunction with chemotherapy, normal pressure hydrocephalus, viral infections such as human immunodeficiency virus, subdural hematomas, brain tumor, traumatic brain injury (TBI), and psychiatric infirmities like anxiety and insightful depression are responsible for non-neurodegenerative mild cognitive impairment.

2. Diagnosis and evaluation

In the initial evaluation and diagnosis, the following four aspects should be considered:

1) A detailed record of past events (medical history)
2) A neurological investigation focusing on assessing the mental state
3) Screening of specific metabolic and physiologic problems (e.g., basic biochemistries, thyroid level, vitamin B12 and vitamin D level)
4) When possible, a structural brain scan is preferred over a CT scan.

Serological tests studies such as heavy metal screening, erythrocyte sedimentation rate (ESR), antibodies assessment (HIV and *Treponema pallidum*), and venereal disease assessment should be conducted on certain individuals.

The focus of the history data collection should be on determining the occurrence and onset of symptoms (e.g., sudden vs. gradual) and symptom development in terms of months or years. Creutzfeldt-Jakob disease (Prion disease in humans), for example, often advances quickly within a few weeks, whereas diseases such as Alzheimer's and frontotemporal lobar degeneration normally proceed slowly over time. Mental functioning domains (attention, memory, executive function, visuospatial ability, and socio- behavioral aptitude) should be assessed during a thorough mental status evaluation.

The Mini-Mental Status Exam (MMSE) is still a useful way of screening for dementia and assessing its severity; however, this test provides less information on some specific subjects, such as highly functional elders and individuals having light formal education [4]. Another test, the Montreal Cognitive Assessment, measures a wider range of cerebral domains and is subtler than MMSE in the early detection of neurodegenerative illness [5,6]. Apart from this, in certain circumstances where screening tests or clinical impressions are ambiguous, then additional evaluation testing (neuropsychological evaluation) can be beneficial.

3. Neurodegenerative dementia

Alzheimer's disease (AD): Alzheimer's disease is considered as the largest neurodegenerative dementia, which affects primarily the aged population (5–6% of those aged 65 and above, and up to 30% of those aged 85 and over) [7]. It is estimated that almost 5% of all cases of Alzheimer's disease have early onset, that is, in individuals younger than 65 years of age [8].

The disease often begins with a progressive loss of memory; however, in rare cases, behavioral, visuospatial, or linguistic symptoms prevail. Following the start of symptoms, the average survival period for Alzheimer's disease is 10–12 years. Recent models of Alzheimer's disease contain a "preclinical" period marked by the progressive deposition of amyloid beta (Aβ) protein Amyloid plaques (also called neuritic plaques or Amyloid plaques) and neurofibrillary tangles (NFTs) that begins 20 years by symptoms manifest [9,10]. Patients may demonstrate slight forgetfulness or occasionally repeat stories early on, as well as anger, apathy, or a depressed mood. Prodromal Alzheimer's disease, also known as mild cognitive impairment, is a stage in which subjects (individuals with disease) or members of the family detect symptoms prior to the occurrence of any functional impairment [11,12]. As the disease progresses, MRI scans of the brain may reveal atrophy of the medial temporal lobe, which affects the hippocampal areas with surrounding tissues. Moreover, fluorodeoxyglucose-PET scan indicates reduced brain glucose consumption in the brain (bilateral temporo-parietal) and an amyloid-Positron Emission Tomography (PET) scan demonstrates plaque deposition in various areas. Alzheimer's disease pathologic diagnosis is done by measuring the amounts of two proteins: phosphorylated tau protein and amyloid beta proteins in the preclinical phase, biological

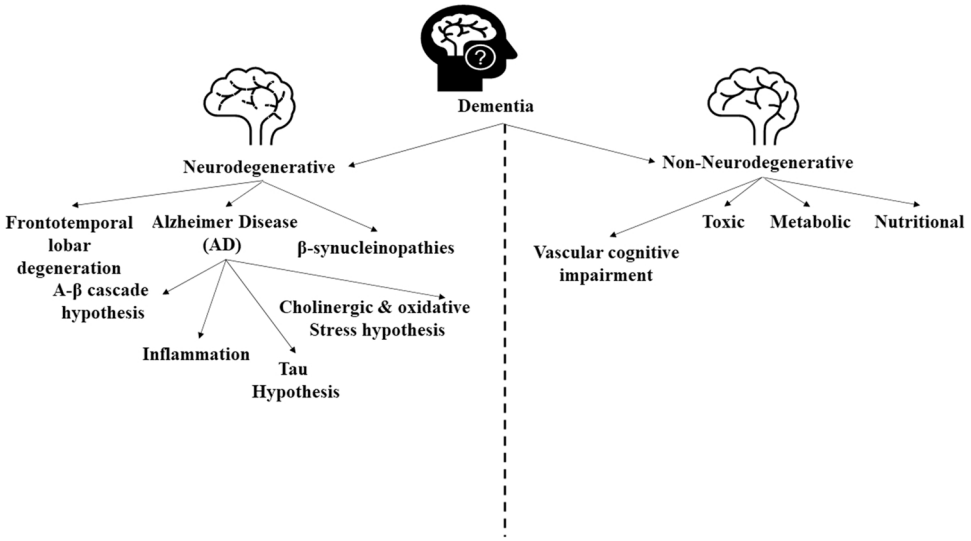

Fig. 1. : Various therapeutic targets in the management of dementia.

markers of cerebrospinal fluid show higher and reduced concentrations of these two proteins, respectively [13]. Alzheimer's disease currently lacks disease-modifying pharmacologic treatments or therapies.

Early diagnosis and therapeutic targeting of the underlying histology have been the focus of recent clinical and translational research [14]. The most prescribed drugs include cholinesterase inhibitors (like donepezil, rivastigmine, galantamine) and NDMA-receptor antagonists (memantine).

Even though these medications do not modify the general course of deterioration, they may ameliorate cognitive and behavioral symptoms for 6 months to several years [15,16]. According to a study, it has been found that people can not only lower the incidence of Alzheimer's disease but also, alter the rate with which the disease progresses just by changing to Mediterranean-style food habits, aerobic exercise on daily basis and participating in social [17,18].

3.1. Current theories concerning Alzheimer's disease and the development of drug therapies

Alzheimer's disease is regarded as a multifaceted condition with a range of underlying factors. The complete pathophysiology of Alzheimer's disease is still not clear because of the complexity of the human brain, a scarcity of appropriate animal models and other research tools.

Multiple theories relating to proteins (amyloid beta and Tau), inflammation, oxidative stress, and cholinergic neuron damage as a cause of Alzheimer's disease have been presented, resulting in a lot of work that has gone into developing anti-AD medications based on these concepts.

3.2. Amyloid beta (Aβ) cascade hypothesis

According to this hypothesis, accumulation of amyloid β protein/peptide (key component of plaques) the brain parenchyma is considered the management of Alzheimer's pathology. This accumulation leads to intraneuronal neurofibrillary tangles (NFTs), vascular damage, cell loss and dementia as well. Consequently, Amyloid peptides have long been considered a possible objective for Alzheimer's disease, which has been subjected to new treatment development for the past two decades [19]. Anti- Aβ therapy's (Fig. 2) most direct procedure is useful to restrict the production of Aβ through targeting secretase (β- and γ-) [20]. Targeting a crucial biological process that requires physiological substrates, like γ-secretase, is bound to have unwanted side effects because of its physiological substrate, the Notch signaling protein [21–23]. Similarly, targeting β-secretase is criticised for causing blindness and having a large catalytic pocket [24]. More critically, it has been seen that the majority of sufferers with sporadic AD do not have an excess of amyloid precursor protein. Furthermore, Aβ isoforms may have a crucial function in regulating the release of neurotransmitters at hippocampus synapses [25]. As a result, limiting Aβ production may provide a number of difficulties.

Immunotherapy clearance is an alternative option. Despite some benefits, such as decreased cognitive decline, ELAN's first active AD vaccine (AN1792) was withdrawn due to serious side effects, including meningoencephalitis [27–29]. In addition, when the performance of passive and active immunotherapy compared with each other, results revealed the active immunotherapy was significant. Numerous antibodies which target the Aβ, such as bapineuzumab (by Pfizer or Johnson & Johnson) [30,31] Crenezumab (by Genentech) [32,33], solanezumab (by Eli Lilly) [33,34] and ponezumab (by Johnson & Johnson or Pfizer) [35–37], have failed in clinical studies. Furthermore, passive immunotherapy helped alleviate some of the issues associated with active immunotherapy however, certain side effects which were predictable, like abnormalities relating to amyloid remained [38]. Scyllo-inositol [39] and tramiprosate [40,41], two small molecule Aβ binders, were also found to be clinical trial failures. Consequently, more doubt raises about this Aβ concept [42]. In fact, the failures may be partly explained by the approach of focusing on a specific functional sub-region of Aβ [43]. Furthermore, immunotherapy may have an effect on the human immune system, which could be useful or harmful (can cause unwanted effects). However, a research study outcome indicated a favorable connection between disease exacerbation and brain Aβ levels when deliberate by the Clinical Dementia Rating (CDR) in II trial phase with antibody aducanumab (Biogen) [44,45]. Even the solanezumab (Eli Lilly) phase III EXPEDITION3 trial, showed higher results in CDR-SB and positive effects on Mini-Mental State Examination and everyday actions [42,43,46,47]. Despite these drawbacks, immunotherapy may still be the most effective treatment for reducing the severity of AD neurodegeneration [48]. Amyloid cascade theory states that amyloid is the primary factor in Alzheimer's disease pathogenesis; also, its deposition is responsible for neurofibrillary tangles, cell death, dementia and vascular damage [49]. Despite the fact that most evidence still supports Aβ as the prime starter of multifaceted pathogenic cascade in AD, multiple findings suggest the role of Aβ as a trigger during the early stage of disease and seem to be essential but not needed in the later stages [50]. Recently, rapid advancements in collecting data and gaining knowledge about the development of toxic amyloid and systemic abnormalities of Aβ metabolism, will give new impetus and prospects for this intriguing strategy [51].

3.3. Tau hypothesis

Tau is also seen in neurofibrillary tangles, which are considered as intracellular symbol of AD. Tau, a microtubule-associated protein, functions as a supporting protein also known as a crucial regulator in neurons (particularly in axons). Accumulation of Tau leads to neurodegeneration by impairing axons of neurons in abnormal situations (Fig. 3). With the letdown of multiple Aβ-targeting medicines for AD, researchers are now paying more attention towards the therapeutic possibilities of tau targeting, especially when biomarker studies suggest tau pathology be more directly linked to the progression of the ailment [52].

Phosphorylation, lysine acetylation, arginine and lysine monomethylation, lysine dimethylation, lysine ubiquitylation, and serine are just a few of the changes that tau goes through. Modification of O-linked N-acetylglucosamine (O-GlcNAc) [54]. Increased tau hyperphosphorylation under pathological settings makes the protein susceptible to accumulation and lessens its affinity for microtubules, affecting neural plasticity. As a result, options for targeting tau consist of inhibition of tau accumulation (through tau vaccines), microtubules stabilization, and tau phosphatasesand kinases regulation. The majority of these initiatives, however, remained unsuccessful in medical trials. For instance, TRx0237, a tau accumulation blocker, was detected unsuccessful in phase III trials [55]. Active tau-targeted vaccines (ACI35 and AADvac-1) as well as inactive tau-targeted vaccines such as (RG6100 and ABBv-8E12) are presently being investigated in phase I and II clinical trials [56,57]. In persons having mild to moderate Alzheimer's disease (AD), intravenous immunoglobulin (IVIG), is the only passive vaccination evaluated in clinical trials phase III, which is unsuccessful to satisfy the key end goals [57]. Other tau-targeting methods for AD, such as microtubule stabilization and kinase and phosphatase manipulation, have only recently been investigated in preclinical research. The dearth of robust and reliable biological markers for analysis and response tracking; also, the narrowing of the blood-brain barrier makes tau-targeting therapy hard in general.

3.4. Inflammation hypothesis

The hallmarks of Alzheimer's disease are reactive gliosis and neuroinflammation. Emerging genomic and transcriptome investigations [58–60] have reinforced the notion that microglia-related pathways are crucial to the risk and pathogenesis of AD. According to mounting data, microglia plays a key role in the early synaptic loss, which is evolving as

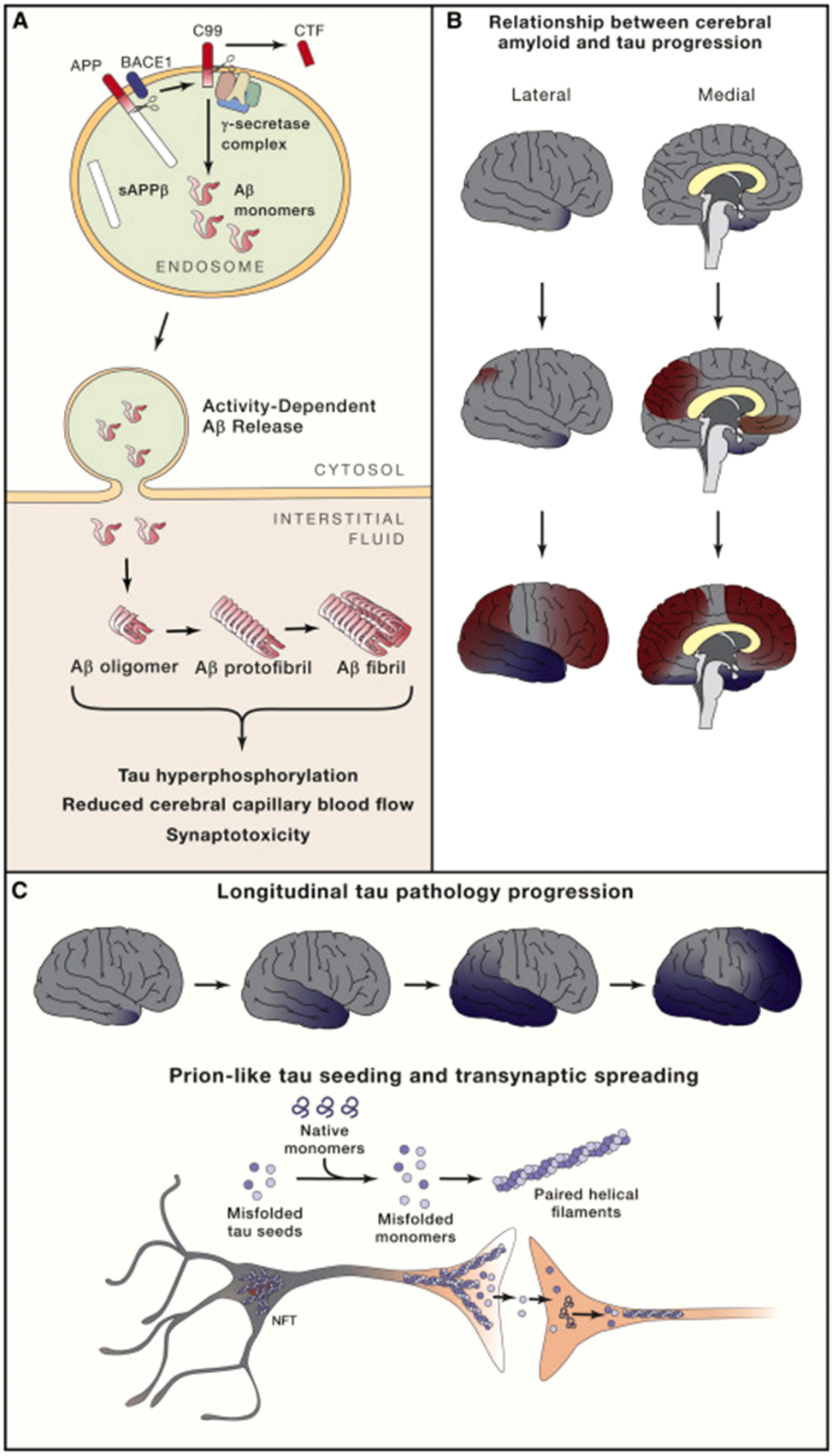

Fig. 2. : Roles of Amyloid beta (A) Production of Aβ from APP (B) Tau aggregation in brain (C) Spreading of tau in the brain.
Source: Reproduced with permission from [26] Elsevier Masson SAS publishes.

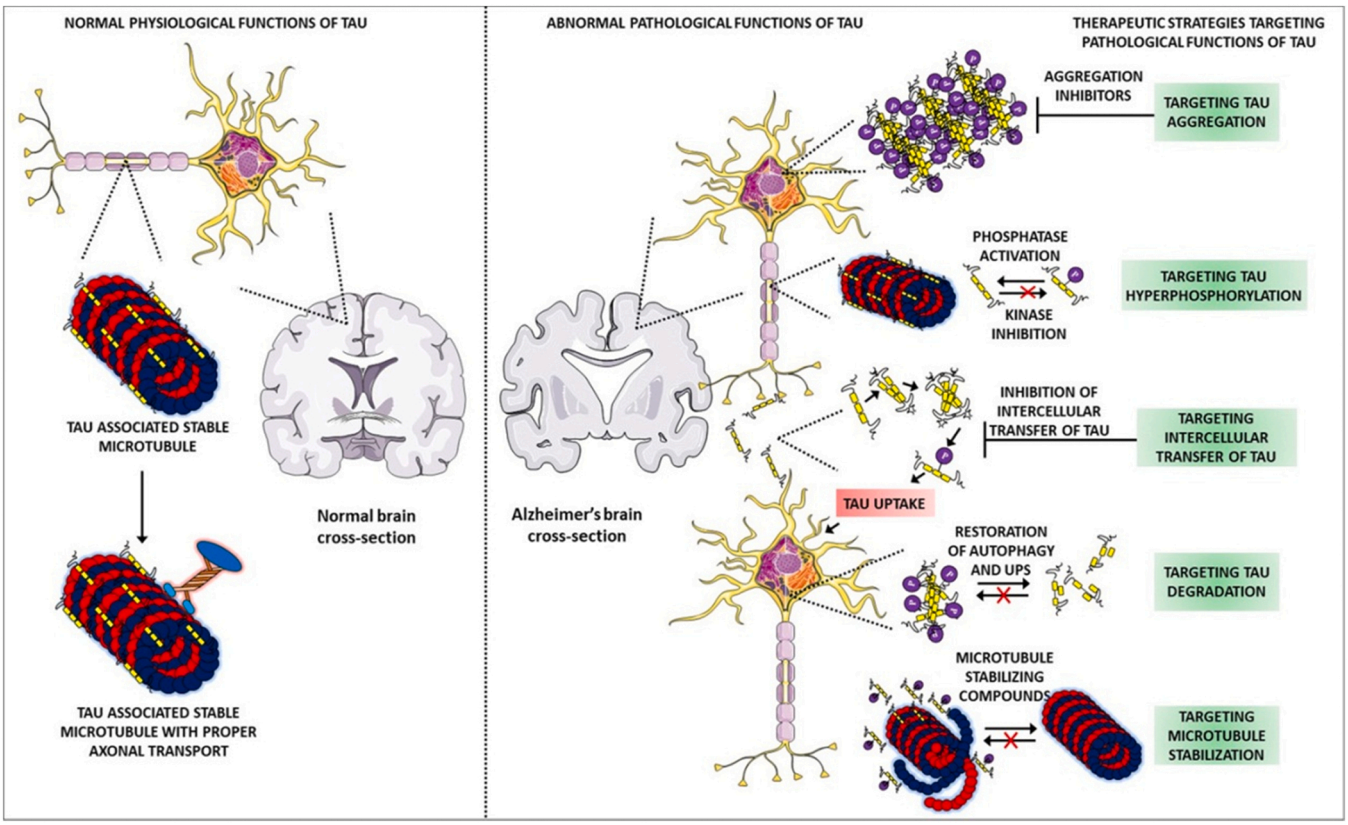

Fig. 3. : Comparison of normal and abnormal pathological functions of Tau proteins.
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a key participant in numerous neurodegeneration disorders such as AD, according to mounting data (Fig. 4). Apart from this, TREM2 and the complement system also account for early synaptic pruning [61,62]. Learning and memory are both driven by activity-dependent as well as long-term synaptic plasticity, which affects long-term memory [63]. Reactive microglia and astrocytes will then form a ring around amyloid plaques, secreting a number of pro-inflammatory cytokines. Those events are thought to be an important factor in the onset of Alzheimer's disease. In clinical trials, NSAIDs did not demonstrate adequate benefits because of the complex connection between native immunity and

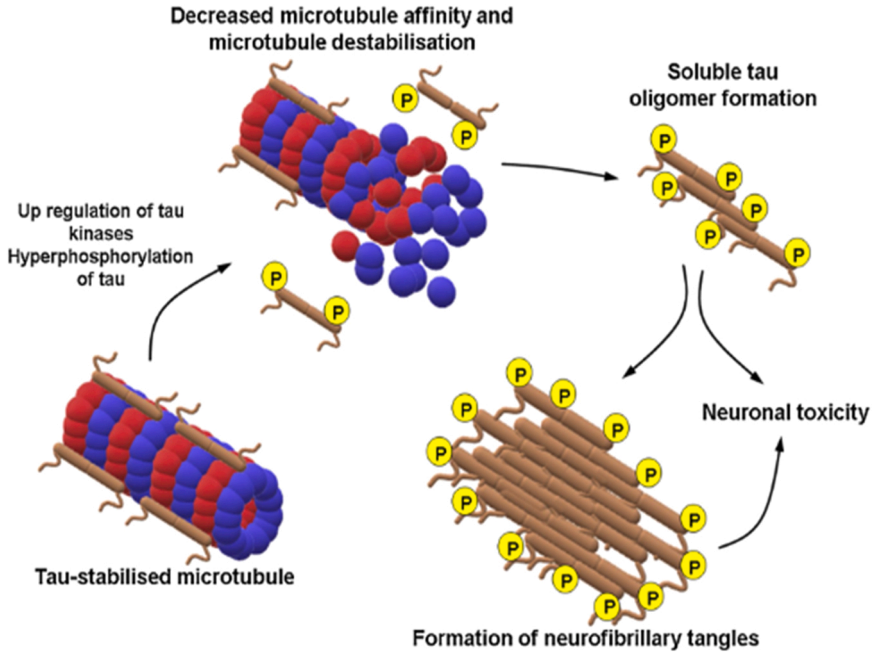

Fig. 4. : Formation of neurofibrillary tangles in brain.
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pathogenesis of AD, and depending on the situation, the immune system's response can be detrimental or beneficial [64,65]. However, recent findings showing PD-1 immune check-point inhibition decreases AD pathology and improves cognition in AD animal models [66,67] push us in the right direction for further research.

Current advancements in our knowledge have the fundamental mechanisms of microglia dys-function in pruning, plasticity regulation, and the neurogenesis is, paving the way for novel Alzheimer's disease treatment and diagnostic alternatives [69,70]. Targeting these abnormal microglial processes and restoring homeostasis could lead to new therapeutic paradigms for Alzheimer's disease. Given the complexity and diversity of roles of microglia in health and illness, novel biomarkers representing the activity of distinct microglia are urgently needed [71].

3.5. Cholinergic hypothesis and oxidative stress hypothesis

Neurotransmitter Acetylcholine (ACh), released from cholinergic neurons, plays a crucial role in a wide range of physiological functions such as attention, response to stress, learning process, memory, regulate the sleep cycle and sensory responses [72,73]. Cholinergic neuron death or disruption was thought to be a crucial pathogenic alteration linked to impairment in cognitive processes in AD (Fig. 5).

As a result, the cholinergic theory was initially investigated in the management of Alzheimer's disease with cholinesterase inhibitors. Tacrine, an inhibitor of acetylcholinesterase or cholinesterase, was the primary anti-AD medicine in clinical trials [75,76], but this was discontinued from the market in 2012 due to significant adverse effects (hepatotoxicity). Despite the fact that preventing cholinesterase is an indicative relief medicine with few benefits, it is now the most commonly accessible therapeutic therapy, providing hope to anxious Alzheimer's victims. Like Dopamine and 5-hydroxytryptamine, other neurotransmitter dysfunctions have a few studies, but not nearly as many as acetylcholine in Alzheimer's disease.

The oxidative stress hypothesis has a major role in Alzheimer's disease pathogenesis. The brain, in particular, uses more oxygen and undergoes mitochondrial respiration than other organs, increasing the risk of ROS exposure (Fig. 6). Indeed, AD is strongly linked to cellular oxidative stress, which has augmented oxidation of protein and glycol-oxidation, nitration and lipid peroxidation, and the increase of Aβ (also a risk factor of oxidative stress) [77–79]. It has been claimed that management with anti-oxidant chemicals would protect patients from oxidative signals and result in tissue damage. Oxidative stress is reported as a major symptom of AD, among others, antioxidants have been tested for their effectiveness in slowing the disease's progression. Hence, nowadays, it is used in combination with other drugs [80,81].

3.6. Frontotemporal dementia

The frontotemporal dementias (FTD), a neurodegenerative illness, are characterised by specific frontal and temporal lobe deterioration. Frontotemporal lobar degeneration is a pathological term that encompasses at least three distinct histologic subtypes: tau accretion, fusion in sarcoma protein and transactive response DNA binding protein [83]. These three subtypes are responsible to cause predominating clinical syndromes: behavioral variant FTD, primary progressive aphasia (language variant), progressive supranuclear palsy syndrome and corticobasal syndrome (CBS) [84]. Patients with FTD/ALS spectrum disorders (both frontotemporal lobar degeneration syndrome and amyotrophic lateral sclerosis) are rare [85]. FTD symptoms includes variant or obsessive behavior, changes in personality, and lack in empathy, frequent mood changes, loss of interest in normal daily activities, impaired judgement and mental inflexibility [86]. Primary progressive aphasia disturbs the ability to communicate, i.e. Impaired speech and language. Patients with this syndrome can have trouble understanding or word-finding, expressing their thoughts, and have articulatory disorders, syntax deficits, and conversation pauses [87]. Focused frontal or temporal lobe atrophy can be seen on MRI. Initial symptoms of the corticobasal syndrome include trouble with balance or coordination because of frequent falls, limb rigidity and apraxia, slowed movements, executive dysfunction, and change in behavior and later showed aphasia, "alien limb" phenomenon and gait decline [88]. The neck and trunk rigidity (axial rigidity), movement disturbance (postural instability with early falls), and eye movement limitation in upward or downward direction (vertical gaze palsy) are common symptoms of progressive supranuclear palsy syndrome, which leads to progressive motor and cognitive loss [89]. Additionally, other symptoms such as inflamed or damaged cerebellum and lack of accuracy or coordination of movement (cerebellar ataxia) and motor speech disorder (apraxia of speech) can also be present (Fig. 7).

Frontotemporal dementia, among types of degenerative dementias, is the third most prevalent after AD and dementia with Lewy bodies, and it accounts for 30% of all cases. Frontotemporal dementias are the

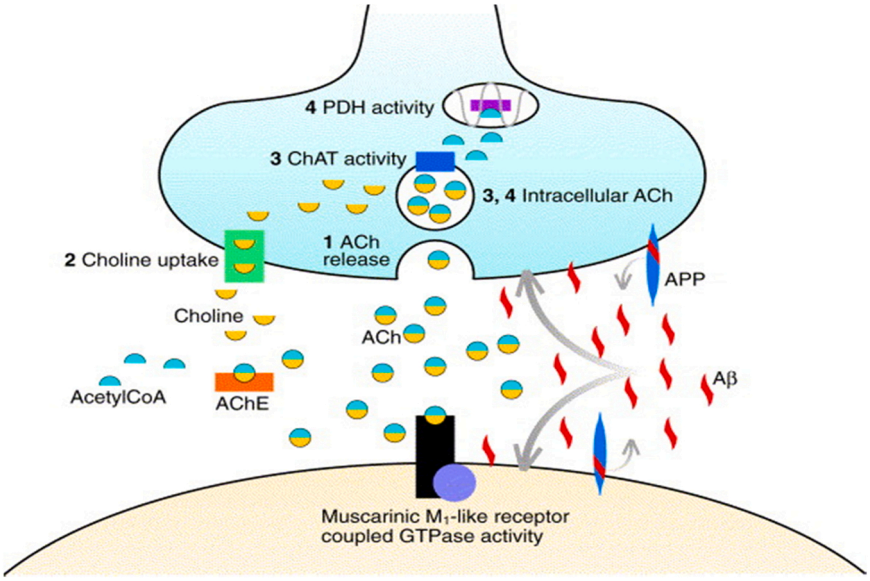

Fig. 5. : Cholinergic hypothesis.
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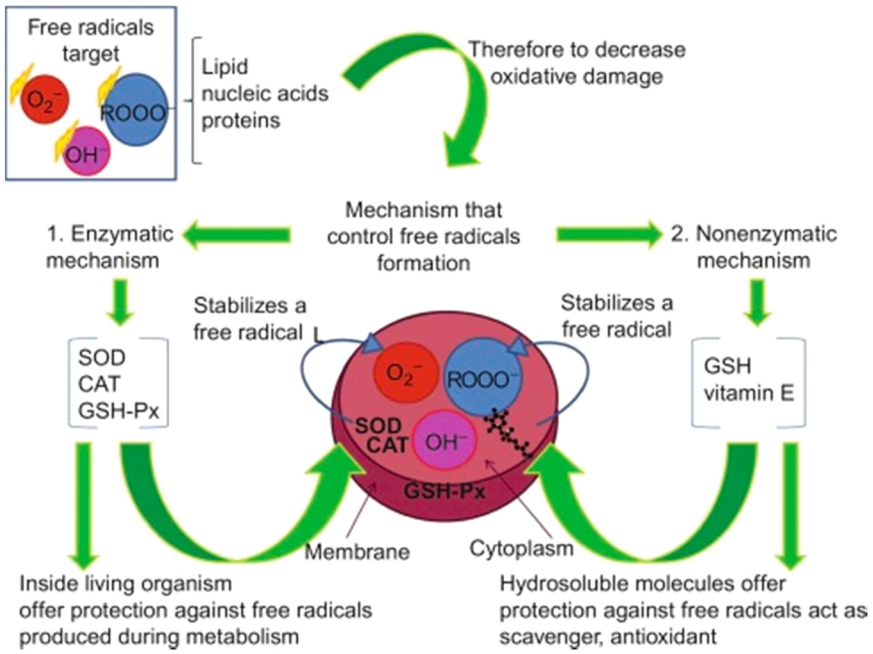

Fig. 6. : Mechanism to control free radicals in the Brain.
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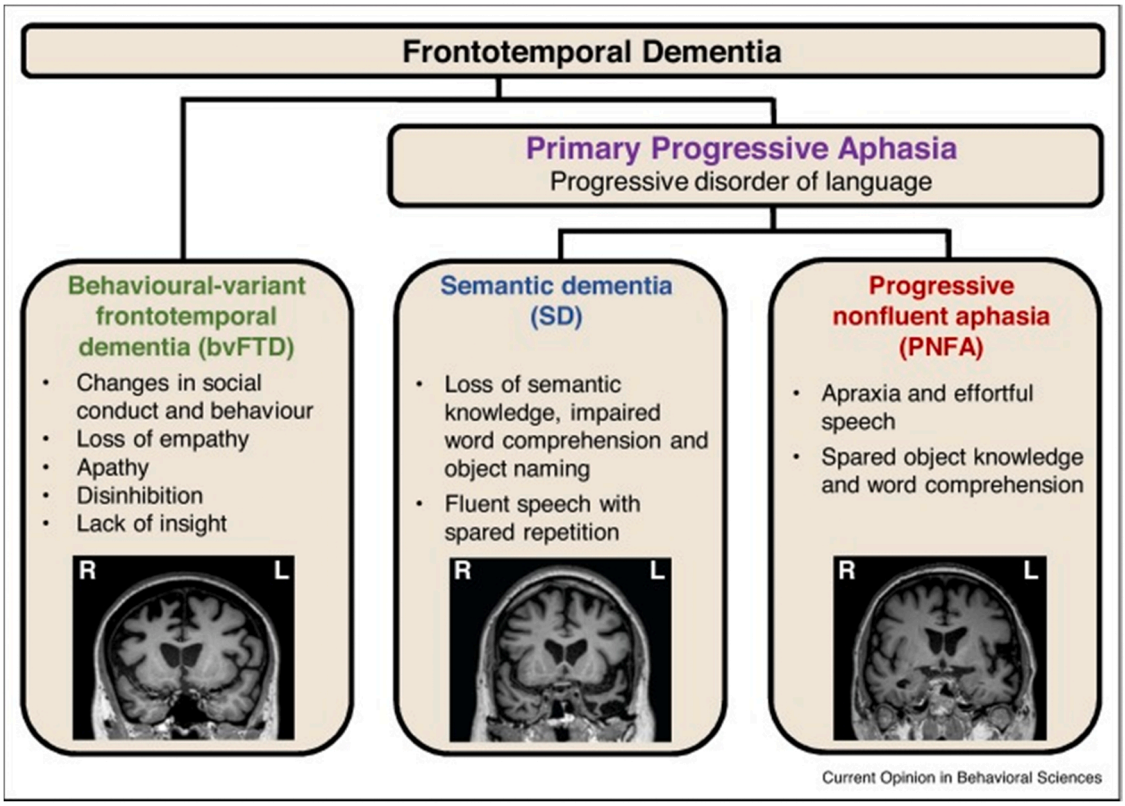

Fig. 7. : Showing different types of Frontotemporal dementia and their conditions in Brain.
Source: Reproduced with permission from [90] Elsevier Masson SAS publishes.

second most frequent dementia in people under 65, following AD, which accounts for over 20% of all the cases [91]. It can be treated by administering antidepressants and dopamine-modulating therapy, which are used to relieve neuropsychiatric and motor symptoms, respectively; however, dopaminergic medicines have seen to be less effective [92].

3.7. *The Alpha-synucleinopathies*

Abnormal buildup of alpha-synuclein accumulates in the nervous

system cells, including neurons, is a hallmark Alpha-synucleinopathies and several neurodegenerative disorders [93]. Dementia with Lewy bodies, Parkinson's disease, and multiple system atrophy are among these disorders. After Alzheimer's disease, dementia by Lewy bodies (Fig. 8) is the mainly prevalent neurodegenerative dementia [94]. It has variable cognition with substantially different attention and alertness levels, frequent visual hallucinations, dream-enacting behavior, and one or more parkinsonian symptoms (bradykinesia, posture instability, or rigidity) [95]. These difficulties (motor, mental and sleep problems) can all be signs of Parkinson's disease dementia, which develops in individuals suffering from Parkinson disease at least a year after the commencement of the disease.

In dementia with Lewy bodies and Parkinson's disease dementia, treatment with medicament, particularly with atypical antipsychotics, should be avoided altogether since they can exacerbate symptoms and produce unwanted effects such as neuroleptic sensitive reactions [97]. Multiple atrophy system (a subtype of alpha-synucleinopathy) is infrequent and characterized by Parkinsonism, cerebellar symptoms, pyramidal indications, and dysautonomia [98]. Hand or foot dystonia, as well as severe forward neck flexion (antecollis), are prevalent whereas non-motor symptoms like airway obstruction with noisy or high-pitched sound (inspiratory stridor), dysautonomia (postural hypotension and sexual dysfunction) and sleep disorder [99], appear months or years before motor symptoms in patients with multiple system atrophy. Dysautonomia is also common in Alzheimer's disease and Parkinson's illness. Although cognitive impairments in multiple system atrophy may be minor or nonexistent. Executive function deficits are the most common, but a memory, apraxia, and spatial impairments are all common [100]. Parkinsonism is a prevalent symptom of many dementias; that can be caused by primary and secondary pathology and its diagnosis needs previous records of diseases (history) and concomitant symptoms. Primary pathology such as atypical deposition of alpha-synucleinopathies, progressive supranuclear palsy and corticobasal syndrome;and secondary pathology for instance cerebrovascular ailments and CTE (chronic traumatic encephalopathy-mainly traumatic brain injury). CTE is a clinical syndrome that develops years after repeated concussions, lasts more than two years, and includes cognitive impairment, violent behavior with suicidal thoughts and emotional disturbance, in addition to Parkinsonism [101].

3.8. *Non-neurodegenerative dementia*

3.8.1. *Nutritional*

Dementia can develop when a patient's vitamin or nutrition levels become deficient or out of whack. In its early stages, severe thiamine (vitamin B1) deficiency can induce Wernicke encephalopathy, and if it progresses to persistent memory impairment, Korsakoff syndrome 5. Chronic alcoholics and individuals with inadequate dietary intake are

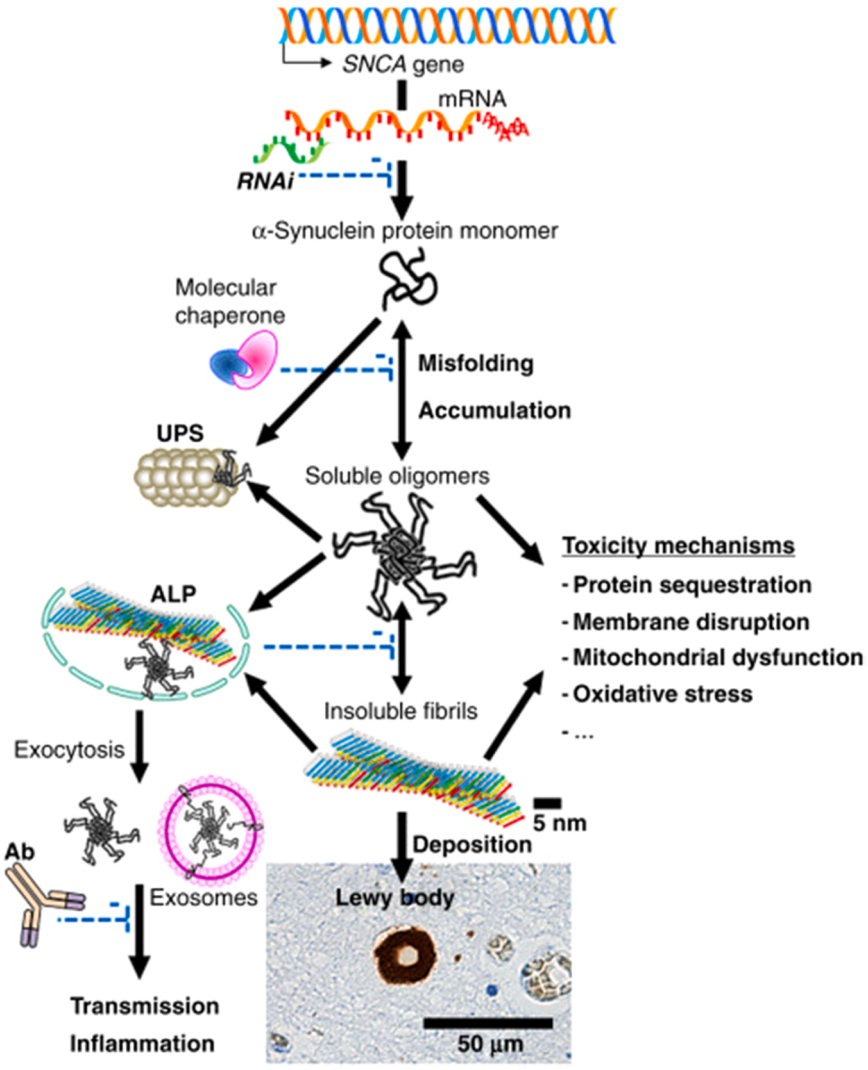

Fig. 8. : Formation of Lewy body in Dementia.
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the most likely to develop it. Wernicke encephalopathy is characterized by the necrosis of neurons lacking in thiamine and has trio clinical features: 1) difficulty in walking (gait ataxia), 2) delirium and 3) paralysis or weakness of the eye muscles (ophthalmoplegia), however only around 20% of patients exhibited all three features [102] (Fig. 9).

While the delirium of Wernicke encephalopathy resolves, having significant anterograde amnesia and less prominent retrograde amnesia, Korsakoff syndrome may appear weeks later of Wernicke encephalopathy since both are caused by thiamine deficiency but distinct from each other. Medicament for Wernicke encephalopathy is intravenous (i.v.) thiamine that must be administrated before the glucose as glycolysis uses B1 [104]. Even relative vitamin D insufficiency has been linked to an increased frequency of all dementia disorders, according to epidemiologic studies [105,106]. Moreover, pellagra, a form of dementia occurs due to less intake of folic acid and niacin-rich dietary sources.

3.8.2. Toxic

Excessive use of any medicament alone or in combination with another one can result in a cognitive deficit, either directly or indirectly through neurotoxic effects [107]. Anti-cholinergic drugs, such as cyclobenzaprine (muscle relaxant), tricyclic anti-depressants and oxybutynin, are especially found to be implicated. Besides, toxic substances (organophosphate insecticides), pollutants in the form of impurities, contaminants, toxins, and chemicals, and heavy metals (Fig. 10) can all produce non-progressive dementia syndromes [108], but they can also raise the likelihood of developing neurodegenerative dementia over time [109,110]. Dementia disorders have been linked to lead, mercury, arsenic, and manganese toxicity [111,112].

3.8.3. Metabolic

Hypothyroidism can cause or contribute to cognitive impairment and, in rare cases, dementia [114,115]. Mental health issues such as lack of motivation or interest (apathy), memory and attention loss, and depression are all indications of hypothyroidism (Fig. 11).

Psychosis, psychomotor slowness, and lethargy are all symptoms of severe hyperthyroidism or autoimmune thyroiditis [117–119]. Chronic uremia, liver ailments, parathyroid disorders, long-term hemodialysis ("dialysis dementia"), and Cushing syndrome are some metabolic conditions that can produce cognitive deficits in varied degrees [120]. Masses with cancer, long-term respiratory failure, heart failure, severe obstructive sleep apnea, paraneoplasticsyndrome and sickle cell anaemia can have cognitive deterioration [121–123].

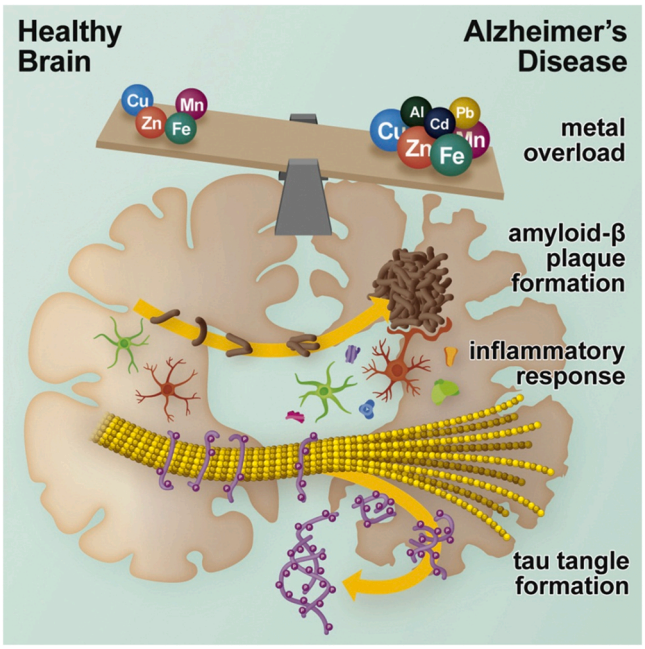

Fig. 10. : Various metals that induced AD.
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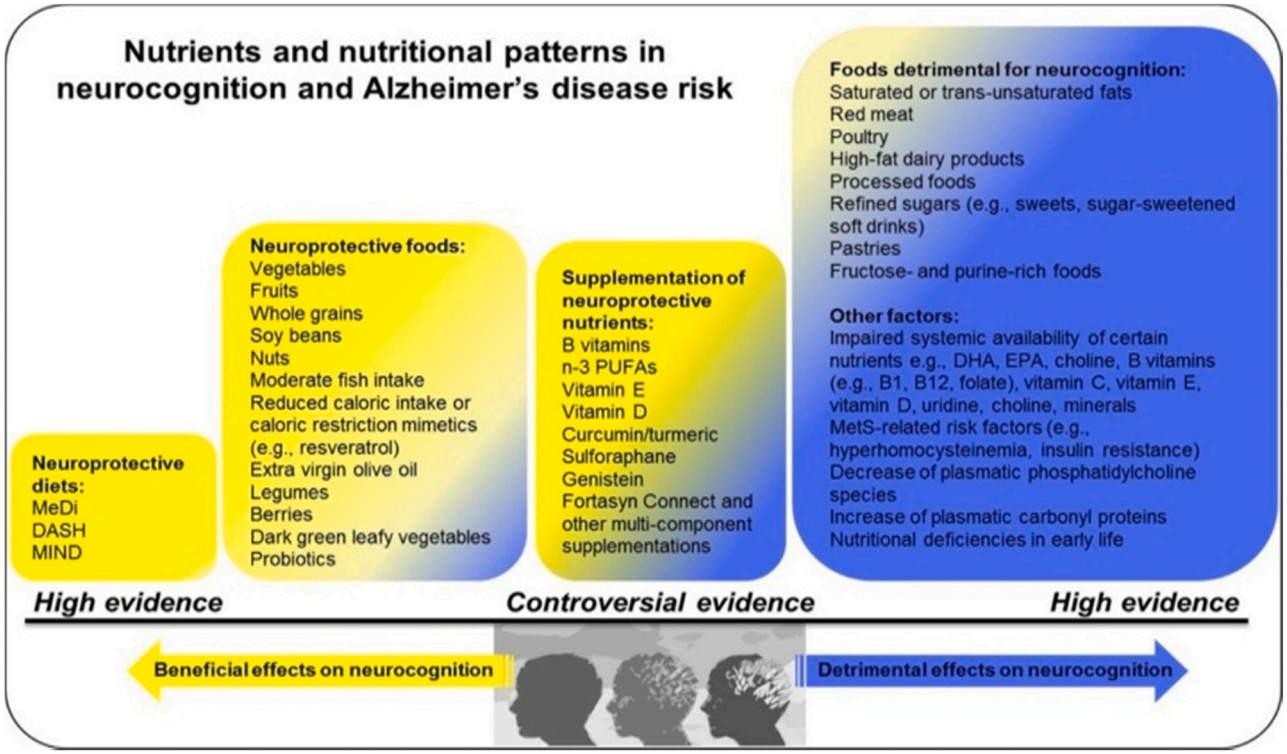

Fig. 9. : Nutrients and nutritional factors responsible for Dementia.
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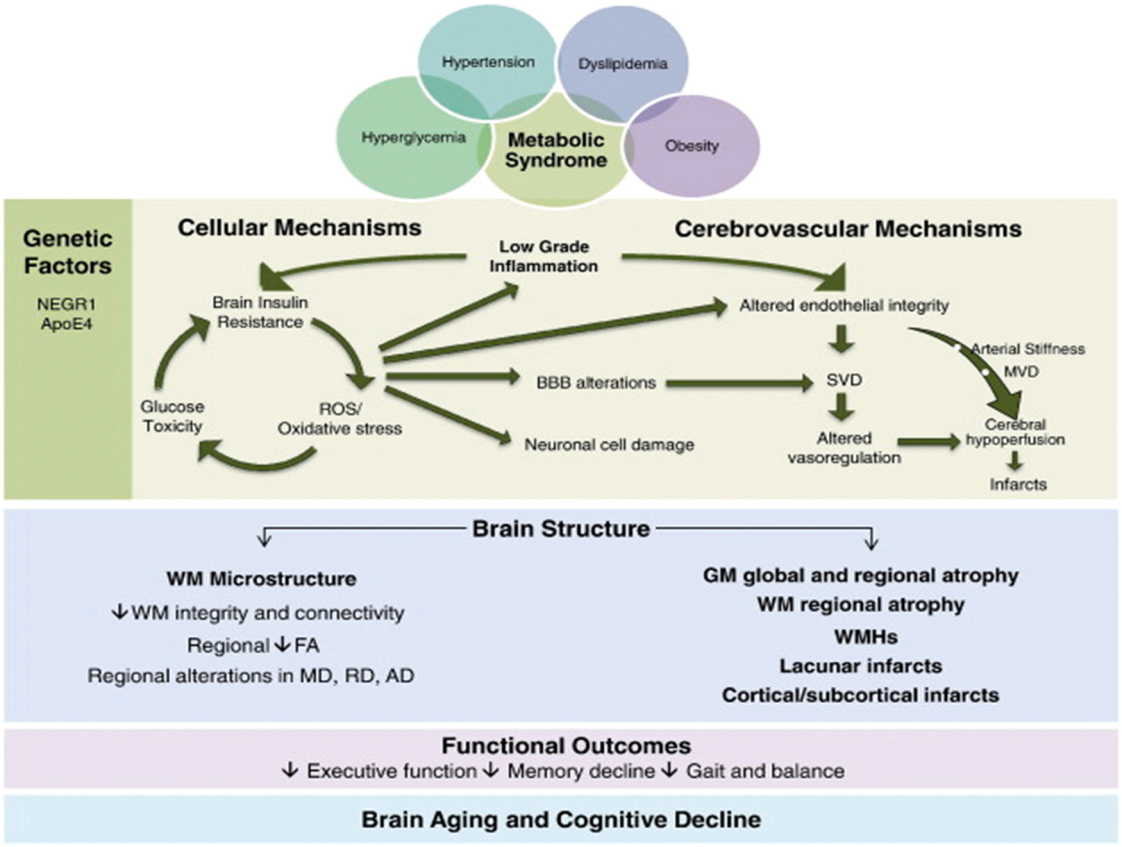

Fig. 11. : Different pathways/mechanism/factors that leads to Dementia.
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3.9. *Vascular cognitive impairment*

Cerebrovascular disease, which is believed to be one of the prevalent causes of cognitive impairment, can be caused by various vascular factors and such related cognitive abnormalities are collectively known as "vascular cognitive impairment" [124]. Vascular dementia results in a

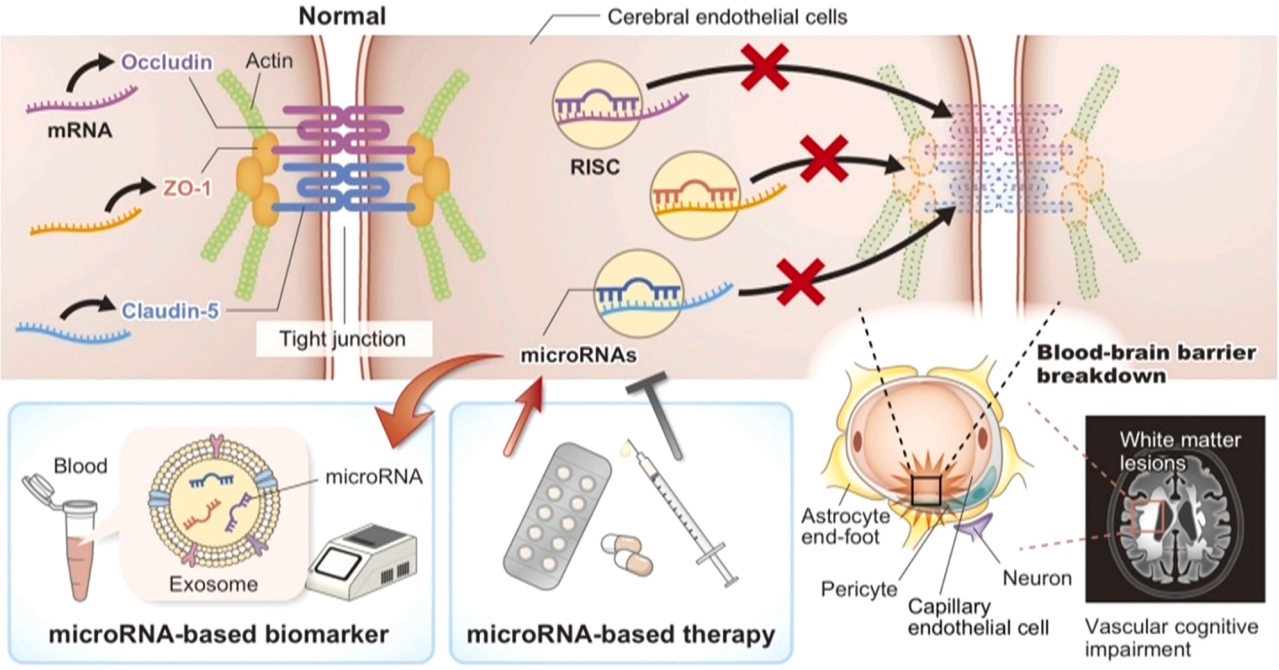

Fig. 12. : Activation of vascular cognitive impairment in Dementia.
Source: Reproduced with permission from [128] Elsevier Masson SAS publishes.

decline of cognitive skills and affects the ability to perform daily activities. Clinically obvious stroke, small-vessel ischemic illness (or Binswanger disease), rare genetic ailments such as cerebral amyloid angiopathy (CAA) and cerebral autosomal dominant arteriopathy with subcortical infarctsare just a few of the etiologies [125]. Vascular cognitive impairment is thought to be responsible for 15–35% of all dementia cases, making it the second most common cause after Alzheimer's disease [126,127] (Fig. 12).

When all "mixed-type" dementias are included, the prevalence of VCI occurring with Alzheimer's disease (AD) or any further disorder is significantly greater. Hypertension [129,130], diabetes, smoking [131] and hypercholesterolemia are all substantial and systemic risk factors, whereas; Atherosclerosis, myocardial infarction and atrial fibrillation are all independent risk factors for VCI [132,133]. Post-stroke vascular cognitive impairment is a prominent cause because cognitive deficits might occur suddenly or gradually after a stroke and they usually plateau after a few weeks or months. Re-occurring silent or clinical strokes deteriorate the impairment process even more. Sensory motor symptoms, such as visual field impairment or lateralized weakness, can help to determine the cause of multiple infarcts. Small arterioles within deep-white matter obstruct over time in small vessel ischemic illness, as evidenced by confluent hyperintense lesions on MRI [134]. Subtle abnormalities in speech (or Dysarthria), slow cognitive tempo, recollection trouble, and sometimes psychomotor slowness or lethargy are some of the symptoms that appear insidiously without overt neurologic disturbances [135]. Involuntary urination, Parkinsonism predominant in the lower extremity, and considerable functional deterioration can all result from severe small artery ischemia disease [136]. Microbleeds and lobar haemorrhages are caused when cerebral arteries are affected by the pathologic accumulation of amyloid protein, which is known as cerebral amyloid angiopathy [137]. MRI is frequently used to make this diagnosis, and it can also be made after a brain haemorrhage develops focal neurologic signs or symptoms. Persistent, momentary ischemia attack-like indications, such as numbness, weakness, or paresthesias, can also be caused by cerebral amyloid angiopathy and are commonly felt as traveling through contiguous body parts [138]. The frequency and pattern of bleeds in cerebral amyloid angiopathy are strongly associated with cognitive impairment; individuals with over one microbleed have an almost 70% chance of acquiring vascular dementia in no more than 5 years. With autopsy investigations demonstrating mild to recurrent senile plaques in many individuals with cerebral amyloid angiopathy, the chances of cerebral amyloid angiopathy and AD could be as high as 90% or higher [139]. The foundation of vascular cognitive impairment care is caution in addressing systemic vascular associated conditions and employing neuropharmaceuticals such cholinesterase inhibitors.

3.10. Management and treatment

Disease-modifying treatments, or those that has been demonstrated to alter the fundamental pathology or track of the disease, are now unavailable. The best management is individualized to each patient and their unique conditions, and it must adjust as the ailment develops. Both the patient and the caregivers should be allowed to make the decision and all practical steps should be taken to permit patient's involvement even when cognition drops; also, it is quite essential to follow a multidisciplinary approach that involves doctors, nurses and other medical professionals along with social services/charities and other support services. Driving, with the caveat that if AD is diagnosed, it does not rule out if indications be insignificant and executive and parietal functions are somewhat intact; finances; home support and future development, particularly as the person retains decision-making capacity, are all important factors to consider. Referring to hospice for end-of-life arrangements can be especially effective if done before the development of end-stage dementia.

Acetylcholinesterase inhibitors (AChEI) (galantamine, rivastigmine and donepezil) are the most common symptomatic management, boosting availability of acetylcholine neurotransmitter by decreasing synapse disintegration. Gastrointestinal distress and leg cramps are quite peripheral cholinergic side effects, but these are normally well endured, especially when the medication is started at a low dose and titration is done carefully. Because of the danger of bradyarrhythmias, AChE inhibitors should either be avoided or taken with caution by people who have cardiac conduction abnormalities. AChE inhibitors have been shown to be advantageous in mild to severe AD, with the majority of evidence focusing on the mild to the moderate stage [16]. Limited data is available on behavioral disturbance and daily actions; however, there is some evidence of help. The advantage found in clinical studies is minor at best in all domains. No evidence is available to support the fact that one medicine in a class is more effective than the other; nevertheless, variations of dosage frequency, variation of dose, escalation time frame, and delivery (transdermal and oral) provide alternatives that can be administered as per requirements of specific patients. The DOMINO-AD trial found that stopping donepezil therapy amplified the chances of nursing home settlement of moderate-to-severe AD patients over the next 12 months but not for the next three years. Authors speculated that stopping treatment possibly will have dangers, even if the advantages of continuing are unclear [140].

A symptomatic treatment for moderate-to-severe Alzheimer's disease is Memantine. This low affinity NMDA receptor antagonist lessens L- glutamate neurotoxicity (excitatory) without meddling with the receptor's physiological functions. Constipation and headache are two common side effects. Memantine also been demonstrated to cause a minor but clinically significant effect on thought and practical decline in people with moderate to severe Alzheimer's disease, with several indications that it lessens the risk of anxiety [141]. Therapy with a combination of AChE inhibitors and memantine now has some proof. A recent meta-analysis showed little indication of enhanced cognition with dual-therapy, although there was proof of better behavioral symptoms in moderate to severe type Alzheimer's disease [142].

Concurrent mental disorders are frequent and can be challenging to treat. Anxiety and depression are common in Alzheimer's disease, and they have a big effect on the quality of life, caregiver burden, and institutionalization risk [143]. Antidepressant treatment for depression has only minimal evidence of effectiveness [144]. There is some evidence that psychological therapy can help dementia patients with depression and, to a minor extent, anxiety. Tricyclic antidepressants should be avoided since they can exacerbate confusion.

Later-stage dementia can lead to agitation, aggressiveness, and psychosis. Atypical antipsychotics are frequently preferred over traditional antipsychotics, but benefits are modest regardless of medication [145], and no therapies for behavioral symptoms in dementia are currently approved. Chest infection, stroke, and death are all serious side effects. As a result, antipsychotics should be avoided wherever feasible and used only when neuropsychiatric symptoms, mainly psychosis, are severe, disabling, or pose a safety concern, and their usage should be monitored on a frequent basis. The best data support the use of low-dose risperidone [146]. Person-centered care training. Music therapy and communication skills training are non-pharmacological therapies that have some evidence of efficacy [147].

3.11. Future perspectives

In recent years, our knowledge of Alzheimer's disease has vastly improved however, a lot more is still to be learnt about it. Next-generation genomic investigations have identified numerous critical pathways in the development of Alzheimer's disease, which is presently being investigated in animal models as well as cellular models and are contributing to the discovery of potential therapeutic targets. A more detailed and thorough understanding of the preclinical period of AD, which views β-amyloid, tau, and inflammation as part of the cellular phase of AD pathogenesis rather than as stagesin a sequential process

[148], will lead to more complex approach to therapy and anticipation.

The collapse of several important Phase 3 treatment studies involving monoclonal antibodies targeting cerebral β-amyloid have raised doubts about the amyloid hypothesis and the possibility for disease variation in AD in general. However, it's worth noting that plenty of these trials has been limited by issues with targeting engagement and patient selections [149]. Not only did a fraction of people included in several of these clinical trials show no signs of AD pathology [150], but the majority of the research focused on people with late-stage AD, when -amyloid may no longer be the best target. Plenty of clinical trials, including promising initial results from trial of Aducanumab, which targets AD at initial stages and shows a drop in amyloid burden and a one-year suspension in disease development in prodromal as well as mild AD patients [45], also numerous further studies in MCI and minor AD patients, are being conducted whose results would be reported in the coming years. In the preclinical period, efforts are being made to employ techniques to either decrease amyloid utilizing immunotherapy or else avert the production of pathogenic forms. The DIAN-TU and API-ADAD studies use genetic screening to identify at-risk people in fAD cohorts [151,152]. The Generation project is looking for ApoE4 people, while A4 study is looking for healthy older people with the asymptomatic amyloidosis [153]. Tau pathology and other alternative targets are garnering attention, with a number of therapeutic trials currently underway. Although there have been no effective trials to date [154], targeting neuroinflammation offers potential.

If disease-modifying treatments do show efficiency in individuals with advanced disease, it would be critical to guarantee that they would both be inexpensive and that they could be distributed rapidly and fairly to everybody who would benefit, which would be a big problem for current healthcare systems. It would be necessary to correctly determine which persons are in danger in order to prevent sickness. The use of PET, CSF, and, eventually, blood to identify new disease-specific biomarkers has already yielded vital understandings of the mechanisms leading to the progress of AD. The ability to detect persons at risk of acquiring Alzheimer's disease will increase as these technologies are used to larger and larger cohorts, especially when paired with the genetic data. A long-term follow-up would facilitate the improvement of risk models and the biomarkers that could predict whether a person is at risk of Alzheimer's disease and when they are – knowledge that will be useful in clinical trials and, eventually, personalized medication. When this data is combined with epidemiological techniques, a coherent indication foundation for the degree to which AD can and cannot be averted through initial or mid-life therapies will emerge [155].

Finally, we anticipate a day when the polygenic risk score and other well-known risk factors may be combined together to generate a personalized risk score. At the appropriate age, individuals with high risk able to be referred for further intrusive testing of Alzheimer's disease pathology, such as amyloid imaging, and other, presumably blood-based biomarkers to forecast disease propinquity, as well as customized therapy with a variety of medications tailored to an individual's point of illness. While this paradigm of individualized illness prevention may still be a ways off, developments on a variety of fronts are bringing this idea closer.

4. Conclusion

This review focused on the introduction and pathophysiology of dementia, highlighting the scope of the differential diagnosis and the importance of an organized approach based on all clinical characteristics. Finally, a few major topics are highlighted in this evaluation report of dementia. First, the review focuses on the introduction of disease with its different types and sub-types. Second, it tells about the pathophysiology of dementia and especially concern with the Alzheimer's disease. Third, diagnosis methods and the evaluation of dementia are classified. Furthermore, when disease-modifying medicines become accessible, proper diagnosis will become even more important as the molecular pathophysiology of degenerative forms of dementia is dissected. Finally, the article focuses on managing and treating disease with their future perspectives.

CRediT authorship contribution statement

Rohit Malik: Conceptualization, Writing – original draft. **Sunishtha Kalra:** Conceptualization. **Saurabh Bhatia:** Writing – original draft. **Ahmed Al Harrasi:** Writing – original draft. **Govind Singh:** Literature Review. **Syam Mohan:** Literature Review. **Hafiz A. Makeen:** Literature Review. **Mohammed Albratty:** Literature Review. Rohit Malik, Sunishtha Kalra, Saurabh Bhatia, Ahmed Al Harrasi, Govind Sing, Syam Mohan, Hafiz A. Makeen, Abdulkarim M. Meraya, Mohammed Albratty, Bojlul Bahar and Murtaza M. Tambuwala – contributed towards the writing the initial draft and preparing the revision.

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Consent to participate

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Consent to publish

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Competing Interests

None.

Conflict of interest statement

All authors declare no conflict of interest.

Data Availability

Information/data collected from Open source..

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