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AN OVERVIEW: ROLE OF B-AMYLOID PRECURSOR PROTEIN IN THE PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

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ABSTRACT

This article discussed the diagnosis and treatment of Alzheimer's disease. In recent years, significant advancements have been developed in the diagnosis and treatment of Alzheimer's disease. Recent studies and research developed in the genetic field which is helpful in the treatment and diagnosis of Alzheimer's disease. The newly revised criteria for the diagnosis of Alzheimer's disease are biomarkers for supportive evidence for the pathology. The identification of new susceptibility genes has opened new avenues for exploration of the underlying disease mechanism. In addition to detecting novel risk factors in large samples, next-generation sequencing approaches can deliver novel insights with even small numbers of patients. This common and devastating cerebral degeneration occurs throughout the world and accounts for one-half to two-thirds of all cases of late-life intellectual failure in many developed countries that have achieved high-life expectations. Because the etiology of Alzheimer's disease remains unclear, fasting hyperinsulinemia has been incriminated in several human diseases, we examined the relationship between Alzheimer's disease, fasting plasma insulin, glucose, body mass index and waist.

KEYWORD; Alzheimer's disease, Amyloid precursor protein, Cognitive, Non-Cognitive, Periodic Acid-Schiff.

INTRODUCTION

Alzheimer's disease, first introduced by Alois Alzheimer's in 1907.it is a neurodegenerative disease characterized by impairment of memory and eventually by disturbances in reasoning, planning language, and perception [1]. By 2030, a projected 66 million people worldwide will be living with dementia a figure set to rise to 155 million by 2050 [2]. Most people's memory declines with age, so the line between normal age-related forgetfulness and the earliest signs of Alzheimer's disease can be fine so fine that a category of mild cognitive impairment, or MCI, has been created, in part to avoid diagnosing Alzheimer's disease in people with more benign

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memory impairments [3]. Studies of carbohydrate metabolism in Alzheimer's disease have been few and inconsistent showing both normal and raised plasma glucose and insulin. However, because several glucose utilization is reduced in ad as measured by positron emission tomography and hyperinsulinemia [4]. Alzheimer's disease is a progressive neurodegenerative disorder that targets neuron communication and can result in loss of cell function or cell death [5]. The Food and Drug Administration, the first putative disease-modifying therapy (DMT) approved for the treatment of Alzheimer's disease (AD) [6]. Our understanding of AD has developed in 3 stages. Although the 1907 description by Alois Alzheimer clearly identified the salient clinical and pathological features of the condition.it was not until the seminal work of Blessed and col- leagues7 that the disease was recognized, not as a rare neurological disorder, but asthe most common cause of dementia [7]. Plaques can be subdivided into 'classical' and 'diffuse' types. In both cases amyloid in the form of fibrils of the Aβ peptide is the primary deposit. In the 'classical' plaque, a dense central core of amyloid is surrounded by diseased neurons that project neurites, towards and around the core [1]. There are two major neuropathological hallmarks of AD in the brain: extracellular senile plaques composed of deposits of Aβ peptides and intraneuronal neurofibrillary tangles (NFTs) formed by hyper-phosphorylated tau protein.[8] Perhaps no disorder of the human brain has arousedmore interest among neuroscientists in recent yearsthan Alzheimer'sdisease (AD) [9]. Cell loss, senile plaques, and neurofibrillary tangles appear regu- larly in the neocortex, hippocampus (including the ento-rhinal cortex), amygdala, and basal nucleus of Meynert in Alzheimer's disease[10].

ETIOLOGY

The etiology is combination of genetic, life style and environmental factors. Major risk factor is age, with the prevalence approximately doubling every 5 years after the ages of 65 and more. Other major risk factors including inherited genes, there are two categories of genes that influence whether a person develops a the first risk genes and other is deterministic gene [11]. However, the relevance of tau dysfunction and related disorders had remained unclear[12]. It is not clear how the etiology of these patients relates to the etiology of the autosomal dominant case [1]. Studies have indicated that medial temporal and subcortical tau pathology precedes Ab pathology in the majority of patients. Genome-wide association studies (GWAS) in LOAD have implicated a number of different genes involved in innate immunity, cholesterol metabolism, and endocytosis, suggesting greater etiological heterogeneity [13]. Titration during the silent incubation period of sporadic, late onset AD (SAD), occurring in more than 99% of AD cases. SAD has a very complex etiology that is difficult to precisely define [8]. VBI usually is characterized as infarcts or hemorrhages. Infarcts often are classified by size: territorial infarcts (larger than 1 cm in greatest dimension) in the region supplied by a large basal artery or one of its branches, lacunar infarcts (smaller than 1 cm in greatest dimension but grossly visible), and microinfarcts. The last appear to have various etiologies, including emboli, small vessel disease, and CAA. Other forms of ischemic injury occur, such as diffuse white matter injury; however, these are more difficult to judge objectively than infarcts [14].

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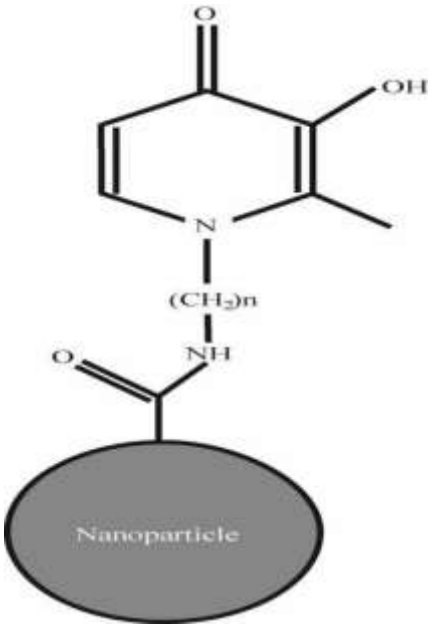
Mercury is a well-known neuro toxin and also has been reported to be a risk factor for the development of Alzheimer's disease. Animal and invitro studies have a demonstrated that mercury cause tau protein hyperphosphorylation, and the increased formation of amyloid-beta protein. Hg ion increased membrane structural integrity of neurites and neuron growth cones and also inhibit binding of guanosine triphosphate to β-tubulin reducing the biological activity [15].

Copper toxicity results in the pooling of copper in different tissues of the body. Prominent areas of copper pooling include the liver, brain, and eyes. A 2013 study of male Wistar rats conducted by pal et al. found copper toxicity effects on the brain include swelling and increased number of astrocytes, star shaped glial cell, and copper deposition in the choroid plexus, which is located in close contact with the cerebral cortex [5].

The ability of chelators to remove iron from paraffin sections of brain tissue was examined histochemical as previously described to detect redox-active iron. Brain sections from four AD patients (80–84 years) were either untreated or subjected to treatment with iron chelators and the degree of iron chelation in the treated sections compared, using differential interference microscopy, with the iron deposition in paired untreated sections. Briefly, hippocampal tissue from AD patients was fixed overnight in methiocarb. After dehydration in ascending concentrations of alcohol, the tissues were embedded in paraffin and 6m sections placed on silane-coated slides [16].



The underlying mechanism of AD is not clear, but there is evidence and a relatively wide agreement that the so-called amyloid cascade is a key early event in the development of AD. This hypothesis suggests that the mis-metabolism of the amyloid- (A), a 39–43 residue peptide, is the initiating event in AD pathogenesis. The amyloid cascade contains several aggregation stages: oligomers, protofibrils and fibrils that are found in the senile plaques, a hallmark of AD. Aggregation intermediates have been proposed to instigate further pathological events, including

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formation of intracellular neurofibrillary tangles, another hallmark of AD, and disruption of synaptic connections, which would lead ultimately to neuronal cells death and dementia [17].

A question is generally asked if PE has been clinically recognized for centuries, why we do not know much about its etiological causes, prediction and treatment [18]. Its diagnosis is based on new-onset hypertension and proteinuria at ≥20 weeks of gestation. In the absence of proteinuria, diagnosis requires the onset of hypertension together with other systemic disorders such as thrombocytopenia, elevated levels of liver significant androgen dysfunction and HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) [19]. Besides these maternal multi-systemic injuries, PE can cause adverse perinatal outcomes including pre-term birth, intrauterine growth restriction, and fetal death [20].

to repair of the damaged area of the brain, but chronic inflammatory reactions, which are usually of low grade and persistent in time, result in a response that supports the neurorestorative processes. Moreover, chronic inflammation impairs the mechanism for clearing abnormal proteins in aging brains that lead to tau-associated impairments of axonal integrity and transport, accumulation of amyloid precursor protein (APP), formation of paired helical filaments, and synaptic dysfunction. All these events precede and cause prominent neurodegeneration and result in cognitive decline [21].

SYMPTOMS:

There are two type of symptoms:

- **COGNITIVE**
- **NON GONGENITIVE**

COGNITIVE: Loss of memory, aphasia, apraxia, agnosia, and disorientation (disturbed perception of time and incapable to recognize familiar people) and impaired decision-making function. ; Mental decline, confusion in evening hours, delusion, forgetfulness, mental confusion, inability to do simple math. symptoms of AD most commonly include deficits in short-term memory, executive and visuospatial dysfunction, and praxis. Several rarer variants of AD wither lative preservation of memory have been recognized [22]. AD is a late-onset, progressive, age-dependent neurodegenerative disease, characterized by the progressive decline of cognitive functions and memory as well as marked differences in brain including the entorhinal cortex, and spreads to the hippocampus, temporal cortex, frontoparietal cortex, and finally to the subcortical nuclei (raphe). Loss of synapses and synaptic damage in the brain sites affected by AD are the best correlates of cognitive decline in patients diagnosed with AD [23]. There is clinical evidence that neuroinflammation is already present in the mild cognitive impairment (MCI) stage, before the onset of dementia Cerebrovascular diseases, such as cerebral small vessel disease, increase the risk of cognitive impairment and dementia, and constitute a potential preventive and therapeutic target for AD [24]. Limitations in NP highlight a significant clinical and research gap in cognitive assessment across the full spectrum of individuals from healthy cognitive function to dementia [25]. Technological advances offer solutions to the challenges of

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early identification of impairment in cognitive and functional abilities, and estimation of the risk of developing AD [26]. Brain regions related to memory are affected early in AD, but the progression neurodegenerative process gradually compromises regions related to other cognitive abilities, such as language and motor control [27]. Cumulative evidence indicates that AD neuropathological process is initiated several years, if not decades, before clinical signs are evident in patients, and diagnosis made. While several imaging, cognitive, CSF and blood-based biomarkers have been proposed for the early detection of AD; their sensitivity and specificity in the symptomatic stages is highly variable and it is difficult to justify their use in even earlier, pre-clinical stages of the disease [9]. Here, we generate knock-in mice that express wildtype human Aβ under control of the mouse APP locus. Remarkably, changing 3 amino acids in the mouse Aβ sequence to its wild-type human counterpart leads to age-dependent impairments in cognition and synaptic plasticity, brain volumetric changes, inflammatory alterations, the appearance of Periodic Acid-Schiff (PAS) granules and changes in gene expression. In addition, when exon 14 encoding the Aβ sequence was flanked by loxP sites we show that Cre-mediated excision of exon 14 ablates hAβ expression, rescues cognition and reduces the formation of PAS granules [28].

NON-COGNITIVE: Depression, psychotics symptoms (hallucination and delusion), behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities, and combativeness) [29] Although AD is most commonly regarded as a disease of the memory, the entire brain is eventually affected by neuronal dysfunction or neurodegeneration, which brings about a host of other behavioral disturbances. AD patients often present with apathy, depression, eating and sleeping disorders, aggressive behavior, and other non-cognitive symptoms, which deeply affect not only the patient but also the caregiver's health [30] . Yet, a collection of findings offers biochemical insight into mechanisms underlying non-cognitive symptoms in AD, and indicate that, at the molecular level, such symptoms share common mechanisms. Here, we review evidence indicating mechanistic links between memory loss and non-cognitive [31]. Despite their obvious social and clinical relevance, and in contrast with the investigation of mechanisms underlying cognitive symptoms and memory loss, few studies to date have addressed molecular mech-anisms underlying non-cognitive symptoms of AD [27] [32] In contrast to the non specificity of available scales, the rating scale presented here is designed specifically for the evaluation of severity of major dysfunctions in cognitive and noncognitive behaviors characteristic of persons with Alzheimer's disease [29]. From a qualitative perspective, the present results should be similar to those obtained in other studies in which different evaluation tools are used. In fact, although other tools probably assess noncognitive symptoms in greater detail, ADAS-Noncog scale include the main behavioral symptoms for assess dementia [19].

BEHAVIOURAL; The high prevalence of BPSD in patients suffering from AD implies that the assessment of behavioral symptoms is of great importance in clinical practice [19]. Most patients with Alzheimer's disease present with amnestic problems; however, a substantial proportion,

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over- represented in young-onset cases, have atypical phenotypes including predominant visual, language, executive, behavioral, or motor dysfunction [33]. we analyzed plasma samples, obtained from patients aged 18–99 years old who had been diagnosed with Alzheimer's disease syndromes (Alzheimer's disease dementia, logopenic variant primary progressive aphasia, or posterior cortical atrophy), FTLD syndromes (corticobasal syndrome, progressive supranuclear palsy, behavioral variant frontotemporal dementia, non-fluent variant primary progressive aphasia, or semantic variant primary progressive aphasia), or mild cognitive impairment [34]. Moreover, the gut–brain axis influences CNS development and behavioral performances in both normal and pathological conditions [35]. Although improvements in cognition are usually no greater than five points on the ADAS-cog scale, more obvious improvements are noted by careers in behavioral and functional aspects such as attention and social engagement, which can be maintained for four to five years [22]. Importantly, LoNA administered mice display severe LTP deficits, and behavioral, these mice exhibit impaired cognitive functions as demonstrated by the Morris water maze task [36]. Murine neonates exposed to brominated flame retardants, which are readily absorbed by body fat, showed behavioral changes, while adult mice displayed impaired learning and memory Broad spectrum antimicrobials, which are active ingredients of consumer products like soaps and toothpastes, are known to cause neurodevelopmental disturbances and behavioral changes; however, evidence directly linking these to AD is lacking [37].

PATHOPHYSIOLOGY

Ab peptide was first identified as the primary constituent of meningovascular amyloid in 1984 and subsequently as the main constituent in amyloid neurotic plaques [38]. Over the ensuing decades, enormous research efforts were expended to clarify the underlying biology of this peptide and its role in AD pathophysiology. Ab is produced by sequential cleavage of β-amyloid precursor protein (APP) by b-secretase. Random effects meta-analysis was used in all analyses [39]. Publication bias was adopted to check up if the pooled effect values were impacted by part of studies' positive results and assessed by Egger's test and was assessed with funnel plots. Sensitivity analyses were employed to inspect if the pooled effect estimates were influenced by removing a single study or were influenced by characteristics of the study design or population, of which one study was deleted per time to discover the effect of this study for the result. Meta-regression was employed to exam if the pooled effect values was influenced by a particular factor, and for those which were high heterogeneity or moderate heterogeneity, univariate regression analyses were adopted to find the source of heterogeneity [9].

CONCLUSION

Alzheimer's disease is a progressive neurodegenerative condition characterized by memory loss and cognitive decline. In the brain, two primary pathological features are observed: the formation of extracellular senile plaques containing Aβ peptides and the presence of intraneuronal neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. This disease

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typically manifests in later stages of life and leads to a gradual deterioration of cognitive functions and memory. The neuropathological changes associated with Alzheimer's disease begin in regions such as the entorhinal cortex and then extend to other areas including the hippocampus, temporal cortex, frontoparietal cortex, and subcortical nuclei. While many rating scales exist for assessing Alzheimer's disease, a specific scale has been developed to evaluate the severity of cognitive and noncognitive impairments characteristic of this condition. While memory deficits are common, some cases, particularly in younger individuals, may present with atypical symptoms such as visual, language, executive, behavioral, or motor dysfunction. The Aβ peptide, identified as a key component of amyloid deposits in the brain, is derived from the sequential cleavage of β-amyloid precursor protein (APP) by β-secretase. This discovery highlighting the role of Aβ in the pathogenesis of Alzheimer's disease and its association with the formation of amyloid plaques.

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