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Alzheimer's Disease: Criteria for Dental Treatments

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Abstract

Among manifestations of neurodegenerative diseases, Alzheimer Disease (AD) contributes for 60-70% to elderly dementia. AD patients suffer from impaired cognitive function and from a compromised capacity to perform activities of daily living. Neurodegenerative diseases are characterized by neuronal loss, dystrophic neurites, and cerebrovascular amyloid. AD occurs more often in woman (2/3 of AD cases) compared with men. The presence of extracellular β -amyloid peptide and hyper phosphorylated tau protein are typical of the physiopathology of the AD brain. Developed under the age of 65 years, the PSEN1 gene is located on chromosome 14q24.3. In the elderly over 65 years, the late-onset of AD, the gene coding for PSEN2 is located on chromosome 1q31-q42. For the late onset AD, the apolipoprotein E was associated to the main risk factors of developing the disease (including molecules such as clusterin, complement receptor, phosphatidylinositol binding clathrin assembly protein and sortilin). Four genes have been identified on chromosome 11. The Amyloid P Protein precursor (APP) encoded by the gene (APP) is located on chromosome 21q. Altered APP processing and A β accumulation shed light on the AD pathogenesis. TNF α may act as a diagnostic marker with high sensitivity and specificity in patients with AD. Studies have identified altered oral health conditions (periodontitis, caries, gingival bleeding, probing depth >4 mm). Poor gingival health and oral hygiene increase with the severity of dementia. Dental professionals should use behaviour management techniques for developing preventive strategies in order to stabilize the lesions.

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Keywords

Alzheimer Disease; Neurodegenerative Disease; Impaired Cognitive Functions; B-Amyloid Peptide; Hyper Phosphorylated Tau Protein; Parodontitis; PSEN1; PSEN2; Chromosome 14; Chromosome 1; Chromosome 21; TNF α ; A β Accumulation

Introduction

Alzheimer Disease (AD) is a complex and heterogeneous neurodegenerative disorder manifesting late in life, with loss of memory, declining cognitive function, and, ultimately, decreasing physical functions [1,2]. The group of neurodegenerative disorders includes Alzheimer's, Parkinson's and Huntington's diseases. AD is the most frequent cause of the three pathologies. The gene for the precursor protein failed to provide significant evidence of link-amyloid (i.e., APP). Several studies found oral health conditions (including caries, periodontitis, gingival bleeding, probing depth >4 mm) [3]. The APM analysis found significant linkage to many chromosomal regions. Only the affected individuals demonstrated linkages to many chromosomes 19 and 21. They are classified either as early onset PSEN1 (under 65 years) or as late onset (PSEN2, over 65 years).

Two main genes are involved in the AD early onset (APP and presenilin -1). For the late onset Alzheimer disease, Presenilin 2 (PSEN2) is the other gene involved in the pathophysiology of the disease. The apolipoprotein E was found to be the main risk factor, including clusterin, complement receptor, phosphatidylinositol binding clathrin assembly protein and sortilin related receptor [4].

Four genes have been identified on chromosome 11:

- PSEN1 present on chromosome 14
- Gene APP (Amyloid Precursor Protein) located on gene 21
- Gene PSEN2 located on chromosome 1
- and/or SORL1 (sortilin related receptor) chromosome, located on chromosome 11

Genetic mutations enhance the production of Amyloid Precursor Protein Gene (Apoe4, located on chromosome 19). Initial insidious memory impairment is leading to disorientation, personality and judgment dysfunction, speech abnormalities, and apraxias. Altogether they are typical. "Synapse loss is the most specific pathological feature of Alzheimer's disease," is now an accepted dogma [5].

Two proteins have been identified and they characterize the Alzheimer's disease.

- Tubule Associated Unit (TAU) is a member of Microtubule Associated Proteins (MAP). Tauopathy is a class of diseases associated with accumulated tau proteins. TAU is found in neurodegenerative diseases in human, the MAP1 gene is located on chromosome 17q21. It is a phosphorylated protein.
- A β amyloid plaques are found in the brain of people with Alzheimer disease. This protein is derived from the Amyloid Precursor Protein (APP).

The tau protein, also forms prion-like misfolded oligomers, and there are some evidences that misfolded A β can induce tau to misfold. The gene of the amyloid precursor is located on chromosome 21.

Genes Locations and Clinical Forms of AD

The location of the A β PP gene on Chromosome 21 provides a link and that is seen in AD.

Chromosome 19: Is one of the major risk factors for the development of AD, carrying the ϵ 4 allele of APOE either in heterozygous or homozygous state.

Chromosome 14/Chromosome 1: The two genes are located on chromosome 14 and 1, respectively. PSEN1 is located on chromosome 14q24.3 and PSEN2 on chromosome 1 q31-q42. Oral health of the elderly with Alzheimer's disease is a common phenomenon [5,6].

AD symptoms and treatment strategies: Alzheimer's lesions are irreversible. They can be slow down by some drugs:

A: Cholinergics or acetylcholinesterase inhibitors

B: Neurotropins

C: Antioxydants. The A β vaccine trials and Secretase effectors [7]

AD is implicated in 20% of a population older than 80 years. Characterized by the loss of memory and autonomic functions, a shorter life expectancy, AD is more frequent in females than males and concern mostly old persons, with neuropsychiatric and functional impairments. Depression is often encountered, together with anxiety and exposure to an important stress. Hearing is reduced, as well as enhanced constipation. Cervical spondylarthrose, spontaneous falls, and loss of weight are the other symptoms. Alzheimer is also characterized by: language deterioration, impaired visual-spatial skills, poor judgement, indifferent attitude, but preserved motor function. First memory decline and over several years, destroyed cognition and ability

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to function, ending with severe brain damage are observed in a period of 8-10 years from initial diagnostic. Dementia is the cause of 60,000 deaths per year [8-10]. Short-term memory loss, forgetting recent events, such as appointments, names and face, difficulties in understanding what is said; confused by routine activities, agitated, irritable becoming apathetic and non-responsive, hearing, visual, and smelling hallucinations are linked to ageing dementia [11].

Molecular and Genetics Aspects of Alzheimer Disease

Genes implicated in Alzheimer Disease onset beyond the age of 65, may appear earlier (40-50 years). Chromosome 21 became the first target of genetic linkage. The amyloid β protein precursor (APP) is encoded by a gene (APP) located on chromosome 21q. The APP717 substitution could be envisioned to disrupt membrane integrity resulting in the release of unprocessed APP. Consequently, the β A4 domain would not undergo “normal” cleavage, and become potentially amenable to amyloid formation. The putative iron-responsive element in APP is situated precisely at residues 40-42 of the β A4 domain.

This implies several possibilities:

- 1) APP is not the site of the defect in this familial Alzheimer disease pedigree for which there is suggestive but not significant evidence for linkage to chromosome 21.
- 2) APP is the site of the defect, and the apparent crossover event. It is due either to intragenic recombination within the relatively large APP gene or to the introduction into this pedigree of a second familial Alzheimer disease gene. The complete sequencing of all exons and the promotor of APP in affected individuals of this pedigree should resolve whether APP is the site of the gene defect in this family [3,8-10,12]. Altered APP processing and A β accumulation seem to be key factors in the AD pathogenesis (Table 1).

Pathogenesis

A. Multiple cognitive deficits are manifested by
1. Memory impairment (impaired ability to learn new information and to recall previously learned information)
2. Aphasia (language disturbance)
3. Paraxial impairment (impaired ability to carry out motor activities)
4. Agnosia (failure to recognize or identify objects)
5. Disturbance to executive function
B. Impairment in social or occupational functioning represents a significant decline
C. The course is characterized by gradual onset and continuing cognitive decline

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D. The aforementioned cognitive deficits are not the result of :
1. Central nervous system conditions that cause progressive deficits in memory (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, brain tumor, hydrocephalus)
2. Systemic conditions that are known to cause dementia (e.g., HIV infection, hypercalcemia); or neurosyphilis, vitamin B or folic acid deficiency, or hypothyroidism

Table 1: Pathogenesis report.

Oral Pathologies Linked to AD

Chronic oral and dental periodontitis are the most frequent pathologies of neuropathologies and namely for AD [13]. Gum disease and tooth decay can cause discomfort or pain and lead to infection.

Drugs such as antidepressants, antipsychotics and sedatives are producing side effects such as dry mouth [14]. The dental problems associated with these conditions (Alzheimer's, Parkinson's and Huntington's diseases) include a decrease in oral hygiene, difficulty in controlling and retaining dentures, and purposeless chewing. Medications can result in xerostomia and consequently to root caries and recurrent decay [15].

Amyloid- β and tau protein are components of the plaque and tangles. Potential anti-tau the stabilization of microtubules, but most of these approaches have been discontinued because of toxicity and/or lack of efficacy. Tau contributes the intracellular trafficking.

Tumor necrosis factor- α was 749.1 ng/ μ L in the case group and 286 ng/ μ L in the control group. The Growth Factor expression is elevated in the AD group (three-fold higher) in the AD group and is involved in AD. This difference was statistically significant and may act as a diagnostic marker of periodontal disease in patients with Alzheimer disease. TNF α is neurotoxic related to endothelial dysfunctions and apoptosis. It was concluded that the TNF α may act as a diagnostic marker with high sensitivity and specificity in patients with AD [2,13]. These findings were denied by Cacabelos, et al., however the previous results were confirmed by Ide, et al., and an increase in serum CRP, TNF β and TNF β /IL 10 ratio was detected in AD patients [2,16].

Poor gingival health and oral hygiene have been found to increase with the severity of dementia [17,18]. Therefore, dental professionals and care-givers should use behaviour management techniques for preventive oral care. Older adults with cognitive impairment have significantly older dentures that are significantly less clean compared with persons who do not have AD. Another problem is that AD patients' perception of pain may be distorted, and localization of dental pain is generally very poor [19,20].

In Summary

Therapies for Alzheimer disease are gradually shifting from amyloid- β ($A\beta$)-targeting to tau-targeting approaches. Early anti-tau therapies were based on inhibition of kinases or tau aggregation, or on stabilization of microtubules. Most of these approaches have been discontinued because of toxicity and/or lack of efficacy. For the present time, most of the tau-targeting approaches are immunotherapies. Tau is likely to be a better target than $A\beta$, because the tau burden correlates better with clinical impairments than does the $A\beta$ burden. Both $A\beta$ and tau are likely to be targeted prophylactically for clearance [21].

A possible comorbidity between oral chronic inflammatory condition (periodontitis) and neuroinflammation (neurodegenerative disease such as AD) has been suggested [22]. But the question is still open.

Conclusion

Although there is no healing for most neurodegenerative diseases, some drugs are acting on the speed of brain degradation, namely when the disease is at the beginning of the disease. Brain degradation that occurs may takes some years (8-10 years). Some drugs make slower the degradative process and therefore the life of Alzheimer's patients is more acceptable. However, it is clear that severe deterioration of late onset is not reversible.

The cholesterol-lowering medication atorvastatin calcium was evaluated. The other drug treatment for AD imply that, (1) Inhibitors of acetylcholinesterase (donepezil, galantamine and rivastigmine), antiglutamates (antagonists of NMDA receptors (memantine) are used with stabilizing effects, and (2) It is interesting to know that the FDA have recently accepted that aducanumab may be put in the market. This drug is a monoclonal antibodies anti-amyloide.

Up to now, there is no healing for Alzheimer's disease, but a decrease of clinical signs may be observed by using these medications.

Conflict of Interest

The author declares no conflict of interest.

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