Clinical Biochemistry 72 (2019) 3–6

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

# Clinical aspects of Alzheimer's disease

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ARTICLE INFO

*Keywords:*
Alzheimer's disease
Dementia
Plaques
Tangles
Beta amyloid
Tau protein
Clinical aspects

ABSTRACT

Alzheimer's disease is a progressive, irreversible, incurable, neurodegenerative illness and the most common of the dementing disorders. It starts usually after 60 years of age and may span 8 to 12 years. The continuous and slow decline caused by this disease, is characterized by cognitive deterioration, loss of functional independence, changes in behaviour, and expanding needs for care. In the last three decades, the proteins predominating neuritic plaques and neurofibrillary tangles have been detected and researched: amyloid-beta protein in the plaques and hyperphosphorylated tau in the tangles. Alzheimer's disease is now considered a long-term process with a slow progress and with a prolonged development of pathological changes that precedes symptoms by years. AD is becoming one of the most problematic and expensive illness for the civilization, also known as "silent threat".

## 1. Introduction

### 1.1. History of Alzheimer 'disease

At the beginning of the 20th century (1906), Alois Alzheimer presented his pathological findings of a 55 years old demented woman, Auguste Deter. She had died after a 5-year history of progressive psychiatric disturbance, continuous memory and language problems. Alzheimer, a German psychiatrist, informed about two pathological changes: neurofibrillary tangles and neuritic plaques. [1] In the same year as Alzheimer, Oskar Fischer described neuritic plaques in 12 cases of senile dementia. In 1907, he published an article reporting his findings. Fischer was a member of the Prague neuropathological school headed at that time by Arnold Pick. During World War II, Fischer was arrested by the Gestapo (1941), and died of a heart attack at the age of 65 in the concentration camp in 1942 in north western Bohemia. [2]

### 1.2. Clinical aspects of Alzheimer's disease

Alzheimer 's disease (AD) is an irreversible and incurable progressive neurodegenerative illness featuring cognitive and functional deficits as well as loss of functional independence and behavioural changes. [3] Cognitive symptoms of AD mainly include deficits in short-term memory, praxis and visuospatial and executive dysfunction [4]. Primary progressive aphasia, posterior cortical atrophy and frontal variant of AD are rarer and atypical variants of Alzheimer's disease with relative preservation of memory.

AD is the most common type of dementia in order of occurrence, accounting for 60–70% of all cases. Its prevalence increasing with age and affects 10% of people over the age of 65 and about 50% of people over the age of 85. We can also see Alzheimer's disease in younger individuals, occasionally in their 20s (more likely to be caused by a genetic abnormality). [3] The amount of people with AD is expected to reach 131 million worldwide by 2050, and the top number of those affected is awaited in middle-income and low-income countries. AD is becoming one of the most problematic and costly illnesses with yearly health care cost related to that of cardiovascular disorders and more than cancer. [5] AD is the 4. – 5. leading cause of death. Till now, there is no efficient cure capable of reducing disease progression. AD is devastating for those who acquire it, and can also be equally devastating for the caregiver, whether that person is a family or a professional member. Only few diseases disrupt patients and their loved ones so completely or for so long a period of time as Alzheimer's and caring is held to be very stressful and emotionally involving. [6]

Medical diagnosis of AD is hard, especially at the early phase of the illness, mainly because symptoms are repeatedly dismissed as normal consequences of aging. For the correct diagnosis and following management of patients, recognizing of the clinical characteristics of the disorder stays crucial.

AD progresses slowly into three identifiable clinical stages – mild

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https://doi.org/10.1016/j.clinbiochem.2019.04.015
Received 4 February 2019; Accepted 25 April 2019
Available online 26 April 2019

(early), moderate and severe (last), which exist together with usual aging processes. AD is characterized by an insidious onset in a state of clear consciousness, and by memory problems. A short-term memory loss is the most typical incipient symptom for Alzheimer's disease. During the course of AD several changes are gradually added to the initial symptoms, e.g. changes in personality and behaviour, deterioration of verbal communication, impairment in visuospatial tasks and motor dysfunction.

It's necessary to stress that the symptoms of Alzheimer's disease are not belonging to the aging process. To identify Alzheimer's disease, extensive tests are required to eliminate all other possible dementia or other cases [7].

A clinical diagnosis of AD is usually based on medical records, neuroimaging, physical and neurological examination, neuropsychological evaluation, collateral history from family and laboratory tests (e.g. rule out metabolic problems, thyroid and kidney disorders, assessment of vitamin B12, levels of heavy metals and anaemia and to rule out syphilis). Widely used neuropsychological tests, such as mini-mental state examination (MMSE) or Addenbrook ACE-R test are not sufficient in early AD and usually provide negative results. The neuroimaging is one of the advanced clinical methods for the confirmation of AD and since 2007, the PET scan combined with a volumetric MRI and an invasive cerebrospinal fluid protein analysis (Aβ, total-tau, phospho-tau) has been accepted by NINCDS–ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) as a suitable procedure for the diagnosis of AD [3,8]. Not all dementias are caused by Alzheimer's disease and can be differentiated by their signs and symptoms. The extrapyramidal symptoms, the presence of focal abnormalities, or gait disorders, most likely points away from a diagnosis of Alzheimer's disease. Definitely, there are another dementia- causing illnesses that may be relevant differential diagnoses.

### 1.3. Risk factors of Alzheimer's disease

The major risk factor for the development of AD is age, but the old age is not enough to evoke this illness. Other risk factors are the existence of one or more apolipoprotein gene E4 alleles (APOE4), family history of AD, low occupational and educational skills, cardiovascular risk factors, and moderate or severe brain traumas in the patient's history.

The pathogenic process of AD probably begins 20–30 years before the first clinical signs become evident; an individual's baseline risk is likely determined by inherited nuclear and mitochondrially-encoded genes. The environmental factors as hypertension, insulin resistance, dyslipidaemia, inflammatory processes, metabolic syndrome and midlife obesity, likely modify this baseline risk. [3].

The prevalence of AD is also gender modulated, it was reported that nearly 2/3 of all AD patients are women. Probably societal factors (e.g.: lower occupational and education attainment among women compared to men), hormonal and genetic factors are likely important as well. In AD prevalence there have also been reported the racial differences: older Hispanics and African Americans have a higher occurrence of Alzheimer's disease relative to older Caucasians in part because of higher prevalence of cardiovascular comorbidities and lower education levels. Great impact may have other societal and genetic factors as well [4].

### 1.4. Biological hypothesis of the disease

The whole aetiology of the illness is still not clear, but available data suggest Alzheimer's disease is more than just a neurodegenerative brain disorder. It is a systemic illness with the signs in blood and the peripheral tissues provoked by inflammatory, metabolic, oxidative, and other biochemical mechanisms. Brain pathologies are seen predominantly in the medial temporal lobe but also elsewhere in the brain and involve neuronal loss, neurogenesis defects and synaptic damage, which in turn contribute to cognitive impairment [3].

Several hypotheses trying to explain the origin of AD have been postulated; e.g.: amyloid beta overproduction and clearance, acetylcholine deficiency, tau hypothesis, brain-derived neurotrophic factor (BDNF) deficit, mitochondrial dysfunction and neuroenergetic hypothesis, nerve growth factor (NGF) deficit and others. The pathology specific for AD includes extracellular neuritic plaques (composed of various amyloid beta (Aβ) peptides, including the 40 and 42 amino acid cleavage products ($A\beta_{40}$ and $A\beta_{42}$) of the amyloid precursor protein), the intracellular structure of neurofibrillary tangles (containing an abnormally phosphorylated form of tau protein), the loss of neuronal synapses, microglial activation, and the loss of pyramidal neurons in brain.

To date, a definitive diagnosis of AD can only be made with both a clinical diagnosis and a post-mortem histopathological examination of the brain. [3].

AD is in the most cases sporadic, with no clear aetiology or causative factors identified. Only 1–5% of cases have genetic ground where a clear transmission of the disorder in an autosomal dominant fashion across multiple generations has been detected – known as familial AD. Up to now, abnormalities in three genes responsible for majority of AD cases have been reported: APP (amyloid precursor protein) found on chromosome (Chr) 21, PSEN1 (presenilin 1) found on Chr 14, PSEN2 (presenilin 2) found on Chr 1. All mentioned genes influenced the production of the amyloid-beta peptides that accumulate in plaques in the brain.

Genetic abnormalities in PSEN1 are the most current, with nearly 200 different abnormalities being reported, and together, these mutations are responsible for ~50% of all familial cases. The APP gene abnormalities are relatively common as well, with over 30 mutations described. Mutations on PSEN2 are rare (~12 reported in 20 families). [1] The AD will develop in 100% of affected persons, because (with several exceptions in PSEN2 families), these mutations are fully penetrant. Autosomal dominant genetic forms of AD usually start earlier (in their 50s–60s) and progress faster in comparison to the sporadic form of the disease. The disease onset is variable within families, as well as across families harbouring the same mutation. AD risk genes just modify the risk for the illness over the lifespan. [10] There are also other genes that alter the risk of AD, the most important is ApoE (apolipoprotein) located on Chr 21. It comes in three allelic forms, e2, e3 and e4 and the presence of the e4 allele confers a threefold risk increase for AD, the presence of two e4 alleles leads to a tenfold increase. [11,12] In the last years, scientists have provided lot of genome wide association studies and have identified over 20 genetic loci where variants add to a low risk of AD, including major histocompatibility complex class II (HLA), ATP -binding cassette, subfamily A, member 7 (ABCA7), bridging integrator 1 (BIN1) and complement component receptor 1 (CR1). These genes and ApoE indicate that lipid metabolism, immune/inflammatory mechanisms, endocytosis and lipid transport are eminent processes for disease changes in an aging brain. Notably, many other protective genes (in addition to the ApoE e2 allele) affecting these pathways have also been established: sortilin-related receptor 1, clusterin, and PICALM (phosphatidylinositol binding clathrin assembly protein) [1].

### 1.5. Typical (Memory) Phenotype of AD

Patients with AD typically present marked episodic memory deficits, together with mild anomia, executive and visuospatial disturbances. To meet criteria for AD, progressive decline in at least two cognitive domains must be presented: impaired memory together with language difficulties, executive, and visuospatial dysfunction. Impairment in functioning or activities of daily living must be also evident. Functional disturbance is an important sign to distinguish AD from the prodromal state of mild cognitive impairment [4].

For the memory deficits observed in Alzheimer's disease is typical rapid forgetting due to a pervasive loss in anterograde episodic memory. We can see deficits on both visual and verbal episodic memory tasks, executive dysfunction, visuospatial and/or language problems [1,9].

### 1.6. Stages of AD

Usually, we recognize three stages of Alzheimer's disease: mild (early), moderate and severe stage. In the mild stage, individuals with AD have difficulties with recent episodic memories, while difficulties with memories from the distant past have they minimal or none. A common early symptom in AD – language disturbance is in general mild. The slow decline in visuospatial skills similarly occurs in the initial dementia stages, executive dysfunction begins in the predementia stages. These impairments worsen throughout the course of the illness. Working and semantic memory are kept until later in the disease process. In the early stage of AD a person may live autonomously, may still work and be active in society. People close to the affected person notice increasing problems in speech and memory, trouble with misplacing or losing objects, planning or organizing [13]. In the mild stage of AD neuropsychiatric symptoms like anxiety, apathy, irritability and depressive symptoms may be found. Anosognosia often manifests early on and brings another complication in daily care. Neurologic examination is mostly normal in this phase.

Moderate Alzheimer's stage is usually the longest period of the disorder and can last for years. Patients have problems with episodic memory, but they may still remember essential details about their life. All aspects of cognitive functions are affected. Individuals with AD often need more care. Other people can notice symptoms like forgetfulness of events or about one's own private history, mood and behavioural changes especially in challenging situations (eg. massive anxiety, suspiciousness and delusions, compulsive, repetitive behaviour, wandering) [14]. Patients can't recall their own address or telephone number and are often mistaken about situation and the date. Caretakers must help them with daily and personal activities like choosing proper clothing, bathing or preparing meal. In this stage a variety of neuropsychiatric symptoms and changes in sleep patterns may exhibit.

In severe Alzheimer's disease (late) stage patients commonly need extensive help with their daily activities and personal care. All previous skills continue to worsen. Individuals lose the ability to manage their environment and movement, including the ability to walk and sit. Patients usually become mute, incontinent, and bedridden. Multiple complications arise during this disease period like immobility, deep venous thrombosis, malnutrition, risk of meal aspiration and infections, which often turn in the direct cause of death. Pathologic reflexes are also found in the severe disease phase like root, suck and grasp reflexes. [4]

### 1.7. Neuropsychiatric symptoms

A variety of neuropsychiatric symptoms, e.g. behavioural symptoms are often seen in AD sufferers. The most severe of them are irritability, diminished insight, and sundowning. About 50% of AD patients are also often agitated. They can be aggressive, combative, can shouting, or be hyperactive. Nearly 30–50% of persons with AD have psychotic symptoms, mainly visual hallucinations and delusions of persecution. These symptoms often fluctuate and once manifest tend to worsen over the course of the disease. Neuropsychiatric symptoms are stressful for the patient, family members and caregivers and require prompt therapeutic help. The higher is the psychological stress of family caregiving, the more adversely it is felt this role by and considerations of institutionalizing the demented individuals are more intensive. [15].

### 1.8. Atypical Alzheimer's disease variants

According to the original diagnostic criteria (NINCDS-ADRDA, published in 1984), memory impairment was the main cognitive deficit observed in association with pathology typical of Alzheimer's disease. In addition to the classic AD presentation, several less common AD variants should be recognized. Some individuals with typical AD brain pathology observed at autopsy, do not always present with memory disturbances as the main clinical sign. The diagnostic criteria were then updated to describe these atypical, non-amnestic clinical presentations of AD pathology that include a visuospatial and language presentation, and an executive/frontal presentation. [1] Patients with the frontal variant of AD are often impulsive, impatient, irritable, and disinhibited and they constantly show significant executive disturbances. The early progressive language involvement is (most often in the form of logopenic aphasia) characterized with pronounced anomic deficits and impaired repetition but preserved syntax and grammar. The posterior cortical atrophy presents with visuospatial dysfunction (e.g. ocular apraxia, acalculia, agraphia, right/left disorientation, and finger agnosia), apperceptive visual agnosia, and environmental disorientation. Patients often develop ideomotor and constructional apraxia early on in the presence of quite preserved memory and insight [1,9].

## 2. Conclusions

For Alzheimer's disease is typical a high amount of heterogeneity in its evidence, development, susceptibility to risk factors, as well as response to therapy. Diagnosis is difficult, especially at the beginning of the disorder, mostly because symptoms are frequently dismissed as normal results of elderly. [16] Progress in the field of AD research has been especially pronounced in the past decades with technological improvements in neuroimaging, animal models of the disease, gene investigations and biomarkers. The impact of AD on individual sufferers, their families and caregivers is terrifying. As the number of patients with AD is on the rise, families, carers, the medical system, and society as a whole will have to bear the burden of this illness unless a therapy will be found. It is necessary to identify individuals who are at risk of AD well before symptoms become evident. Till now we have no preventative or disease modifying medications that can reduce the risk or delay the onset of developing the illness. To discover disease-altering treatments in the near future will be for AD research an important goal. [3]

## Acknowledgments

This research was supported by project Novel blood-based biomarkers for early diagnosis, prognosis and progress of Alzheimer's disease (GA ČR no. 17-05292S, Czech Republic) and by project Neuropsychiatric aspects of neurodegenerative disorders (Progres Q27/LF1) provided by Charles University in Prague.

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