J Neurol (2013) 260:1936–1941
DOI 10.1007/s00415-013-6921-3

Progress in Alzheimer's disease research in the last year

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Received: 4 March 2013 / Revised: 6 April 2013 / Accepted: 6 April 2013 / Published online: 18 April 2013

Abstract Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with a prevalence of 5 % after 65 years of age, increasing to about 30 % in people aged 85 years or older. It is characterized by progressive cognitive impairment, including impaired judgment, decision-making and orientation, and in some cases accompanied by psycho behavioral disturbances or language impairment. Herein, we summarize and discuss the main articles describing novel findings in AD published over the last year, including clinical, therapeutic, and research issues.

Keywords Alzheimer's disease · Biomarkers · Genetics · Risk factors · Imaging · Cerebrospinal fluid · Therapy · Disease-modifying drugs

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with a prevalence of 5 % after 65 years of age, increasing to about 30 % in people aged 85 years or older. It is characterized by progressive cognitive impairment, including impaired judgment, decision-making, and orientation is some cases accompanied by psycho behavioral disturbances or language impairment. Mutations in genes encoding for amyloid precursors protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) account for about 3 % of cases, characterized by an early onset (even in the third or fourth decade of life), whereas the majority of cases is sporadic, likely caused by the interaction of genetic and environmental factors.

The two major neuropathology hallmarks of AD are extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). The production of Aβ, which represents a crucial step in AD pathogenesis, is the result of cleavage of the APP, which is over-expressed in AD [1]. Aβ forms highly insoluble and proteolysis resistant fibrils known as senile plaques (SP). NFTs are instead composed of the tau protein. In healthy subjects, tau is a component of microtubules, which represent the internal support structures for the transport of nutrients, vesicles, and mitochondria within the cell. Microtubules stabilize growing axons, which are necessary for the development and growth of neurites [1]. In AD, tau protein is abnormally hyperphosphorylated and forms insoluble fibrils, originating NFTs into the cell.

In the last few years, biomarkers for an early diagnosis and treatment have been discovered and validated, including cerebrospinal fluid (CSF) Aβ, tau, and phosphorylated tau (Ptau), structural and functional imaging. These new discoveries have been incorporated in novel criteria for the diagnosis of AD [2, 3].

Herein, we summarize and discuss the main articles describing novel findings in AD published over the last year, including clinical, therapeutic, and research issues.

Clinical aspects and biomarkers

Epidemiology, diagnosis, and biomarkers

Among risk factors for dementia, it was shown that delirium is a strong risk factor in a large oldest-old population

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[4]. Fixed- and random-effects regression models were used to assess the association between delirium and incident dementia and decline in mini mental state examination (MMSE) scores. Results showed that delirium increased the risk of incident dementia (OR = 8.7) and was associated with the worsening of dementia severity (OR = 3.1) as well as with the deterioration in global function score (OR = 2.8) [4].

Prioni et al. [5] investigated stereotypy frequency and type in patients with AD, behavioral variant frontotemporal dementia (bvFTD), progressive supranuclear palsy, and Parkinson's disease dementia, demonstrating that AD patients have fewer stereotypes than the other groups.

Buchhave et al. [6] assessed the ability of the CSF biomarkers Aβ, Ptau to predict the development of AD by analyzing these proteins in a cohort of subjects with mild cognitive impairment (MCI) followed-up clinically for 5–10 years. Baseline CSF Aβ levels were reduced in both patients who converted to AD in 0–5 years (early converters) and in those who converted in 5–10 years (late converters), whereas tau and Ptau levels were altered in early, but not in late, converters. Overall, 90 % of patients with MCI and pathologic biomarker values at baseline develop AD within 10 years [6]. Implications coming from this study include that (1) studies with a shorter follow-up will underestimate the positive predictive value and the specificity of CSF biomarkers, (2) patients with pathologic biomarkers should be selected for clinical trials with novel disease-modifying drugs, (3) Patients diagnosed with MCI with normal CSF biomarkers would most likely not need extensive and costly follow-up.

Regarding CSF biomarkers for AD diagnosis, Mattsson et al. [7] demonstrated that, although the diagnostic accuracies for AD decrease with age, the predictive value for a combination of biomarkers remain stable, whereas the negative predictive value decreases slightly in old subjects, due to the high AD prevalence in older ages. To predict instead time to dementia in patients with MCI and evidence of amyloid pathology, injury markers, including abnormal CSF tau, abnormal CSF Ptau, and hippocampal atrophy, are likely more useful than other biomarkers [8].

In an attempt to identify peripheral biomarkers for AD, Llano et al. [9] performed a multivariate analysis of 146 plasma analytes in a large cohort of patients with AD or MCI as compared with elderly controls. They identified four different proteomic signatures, each composed of 5–14 analytes that differentiate AD from controls with sensitivity and specificity ranging from 74 to 85 %. Five analytes, including apolipoprotein A-II, apolipoprotein E, serum glutamic oxaloacetic transaminase, α-1-microglobulin, and natriuretic peptide, were common to all signatures. Unfortunately, none of these predicted the conversion from MCI to AD [9]. A similar approach was carried out by Soares et al. [10], who showed increased plasma levels of eotaxin 3, pancreatic polypeptide, and N-terminal protein B-type brain natriuretic peptide in patients with AD, in line with previous observations in CSF. In addition, increases in tenascin C levels and decreases in IgM and apolipoprotein (Apo)E levels were also observed. Notably, patients carrying an ApoE ε4 allele showed a distinct profile, characterized by low C-reactive protein and ApoE levels and high cortisol, interleukin 13, apolipoprotein B, and γ-interferon levels, thus highlighting the importance of genotype on blood protein profiles [10].

Among candidate biomarkers, molecules related to DNA damage and telomere dysfunction, including chitinase activity, *N*-acetyl-glucosaminidase activity, stathmin and EF-1a, were studied in CSF from AD patients as compared with controls and patients with non-AD dementia. Watabe-Rudolph et al. [11] showed that enzymatic activity of chitinase and stathmin protein levels were significantly increased in CSF from patients, both with AD or non-AD dementia, compared with controls. As single marker, chitinase distinguished patients with dementia from no dementia with an accuracy of 85.8 %. In another study [12], CSF proteomic changes were analyzed in familial and sporadic AD as compared with non-demented subjects. The authors found overlap between familial cases, both presymptomatic and symptomatic, and sporadic ones. Fourteen proteins altered were previously reported in other studies, including amyloid precursor protein, transferrin, α(1)β-glycoprotein, complement components, afamin precursor, spondin 1, plasminogen, hemopexin, and neuronal pentraxin receptor, whereas others were unique to this study, including calsyntenin 3, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) 4 glutamate receptor, CD99 antigen, di- *N*-acetyl-chitobiase, and secreted phosphoprotein 1.

Familial Alzheimer's disease

Familial AD (FAD) is considered the best study model for understanding the pathogenesis of the disease, particularly to elucidate mechanisms occurring before the appearance of symptoms. In line with this, Bateman et al. [13] studied 128 subjects of families with a FAD autosomal dominant mutation in amyloid precursor protein or presenilin genes, including symptomatic and asymptomatic carriers as well as non-carriers, on the basis that results obtained in FAD could be translated to sporadic AD. They demonstrated that biomarkers known so far change very early during the pathogenesis. In particular, variations occur as follows:

– CSF Aβ levels start dropping 25 years before occurrence of symptoms.

- Aβ deposition, measured by positron-emission tomography (PET) with the use of Pittsburgh compound B, was detected 15 years before expected symptom onset.
- Increased concentrations of CSF tau levels and an increase in brain atrophy at magnetic resonance imaging (MRI) were detected 15 years before expected symptom onset.
- Cerebral hypometabolism on PET and impaired episodic memory were observed 10 years before expected symptom onset.
- Global cognitive impairment, measured by the MMSE and the Clinical dementia rating scale (CDR), was detected 5 years before expected symptom onset.

These findings imply that the targeting of Aβ earlier in the course of the disease may provide better clinical outcomes than the treatment of mild to moderate dementia (phases in which the neuronal and synaptic loss has already occurred). Moreover, they suggest that secondary prevention trials, which are designed to prevent or delay cognitive and clinical impairment, may ultimately test the Aβ hypothesis, just as the cholesterol hypothesis of heart disease was tested three decades ago. Nevertheless, the current analyses are based on cross-sectional data, and thus need to be confirmed by studying individual longitudinal changes.

On the basis of the previous considerations, Reiman et al. [14] followed-up 44 young adults from the Colombian Alzheimer's Prevention Initiative Registry in Medellín Antioquia (Colombia), including 20 PSEN1 E280A mutation carriers and 24 non-carriers. They underwent neuropsychological testing, lumbar puncture and venous puncture, and structural and functional MRI. Young adults at genetic risk for autosomal dominant FAD had functional and structural MRI findings, as well as CSF and plasma biomarkers consistent with Aβ(1–42) overproduction. Therefore, this study demonstrates that more than two decades before the estimated age at MCI onset (44 years) and at full-blown dementia (49 years), functional and structural MRI changes are detectable in young adult PSEN1 E280A mutation carriers, along with CSF and plasma biomarker findings that suggest Aβ(1–42) increased production.

Joshi et al. [15] compared clinical characteristics between FAD and non-familial early onset AD (NF-EAD), aiming to identify clinical features that suggest a genetic origin of the disease and that thus suggest to go on with the genetic counseling. Patients carrying a PSEN1 mutation had an earlier age at disease onset as compared with non-carriers (41.8 versus 55.9 years), and, at initial assessment, longer disease duration and lower MMSE scores. Patients with NF-EAD were more likely to present with non-memory deficit. FAD patients were instead more likely to have headaches, myoclonus, and gait abnormalities.

Therapeutic aspects

In the last few years, a number of claimed "disease-modifying" compounds, mainly aimed to prevent or remove Aβ, have been developed and tested in double-blind, placebo-controlled clinical trials.

In this framework, Winblad et al. [16] reported results of a phase I, double-blind, placebo-controlled, 52-week study with CAD106 (Novartis), carried out in two centers in Sweden. CAD106 is the first second-generation vaccine. It presents multiple copies of Aβ1-6 peptide derived from the N-terminal B cell epitope of Aβ that avoids T cell activation, coupled to the Qβ virus-like particle. In animals, CAD106 induced Aβ-antibody titers without activating Aβ-reactive T-cells. In this trial, 58 patients with mild to moderate AD, aged 50–80 years, were entered into one of two cohorts according to time of study entry, and then randomly allocated to receive either CAD 106 or placebo (ratio 4:1; the first cohort, consisting of 31 patients, received CAD106 50 μg or placebo; the second, consisting of 27 patients, received CAD106 150 μg or placebo). Each patient received three subcutaneous injections. Primary objectives were to assess safety and tolerability of CAD106 and to identify Aβ-antibody response (patients with Aβ-IgG serum titers >16 units at least once during the study were considered responders). Almost all patients (56/58) reported adverse events. The most common side effect in cohort 1 was nasopharyngitis, whereas is in cohort 2 was injection site erythema. No cases of clinical or subclinical cases of meningoencephalitis were observed. Sixty-seven percent of CAD106-treated patients in cohort I and 82 % in cohort 2 developed Aβ antibody response. However, also one placebo-treated patient out of 12 had Aβ-IgG concentrations that qualified them as responder. In conclusion, results of these trials suggest that CAD106 has a favorable safety profile and acceptable antibody response in patients with AD [17]. Additional vaccines are under testing (see [17] for review).

A randomized, double-blind, placebo-controlled, clinical trial with antioxidants has recently been carried out in AD [18]. Patients with mild to moderate AD were randomly assigned to treatment for 16 weeks with 800 IU/day of vitamin E (α-tocopherol) plus 500 mg/day of vitamin C plus 900 mg/day of α-lipoic acid (E/C/ALA); 400 mg of coenzyme Q 3 times/day; or placebo. Outcomes included changes in CSF biomarkers and cognition. Results showed that antioxidant treatments did not alter CSF biomarker and did not influence cognition.

Jeppsson et al. [19] identified, using fragment-based screening and structure-based design, a potent and selective inhibitor of human BACE1, named AZD3839 potentially useful for treating AD. They studied its effect, together with pharmacokinetic/pharmacodynamic analyses, in mouse and guinea pig. Results suggest that this compound has disease-modifying potential in the treatment of AD and it has been progressed into phase I clinical trials in men.

Research aspects

Tartaglia et al. [20] assessed the relative contribution of white matter (WM) and gray matter (GM) abnormalities to cognitive dysfunction in patients with AD and bvFTD, demonstrating that reduced integrity of specific WM tracts contribute to cognitive deficits observed in bvFTD patients, after accounting for GM atrophy. In AD instead, memory impairment was related to WM tract injury, but this relationship was no longer observed when GM volumes were included.

Regarding brain changes occurring during AD pathogenesis, La Joie et al. [21] demonstrated, by using structural MRI, (18)F-fluorodeoxyglucose PET, and (18)F-florbetapir PET (an amyloid tracer) that there is a region-specific hierarchy between atrophy, hypometabolism and Aβ load in AD. In particular, in the hippocampus, atrophy exceeded hypometabolism, whereas Aβ load was minimal; in posterior association areas, Aβ deposition was predominant, together with marked hypometabolism and lower but still significant atrophy; in frontal regions, Aβ deposition was maximal, whereas structural and metabolic alterations were low.

Regarding in vivo models, Lee et al. [22] analyzed micro(mi)RNA-206 expression in Tg2576 transgenic mice and human AD brain samples. They demonstrated that mouse brains and the temporal cortex of human AD brains had increased levels of miR-206, which targets brain-derived neurotrophic factor (BDNF) transcripts.

New findings on the role of tau protein have been described by Tai et al. [23], who demonstrated that, in addition to its well-described axonal localization, tau is present at both presynaptic and postsynaptic terminals in normal human brains. In AD, tau becomes hyperphosphorylated and misfolded at both terminals, and the accumulation of hyperphosphorylated oligomers at synapses is associated with increased ubiquitinated substrates and increased proteasome components, consistent with dysfunction of the ubiquitin–proteasome system. In addition, Saman et al. [24] demonstrated that exosome-associated tau is present in human CSF, and is phosphorylated at Thr-181, suggesting that exosome-mediated secretion of phosphorylated tau may play a role in the abnormal processing of tau and in the genesis of elevated tau levels in CSF in early AD.

Regarding basic research, Israel et al. [25] developed a new model for studying AD by reprogramming primary cells from patients into induced pluripotent stem cells (iPSCs). In particular, they reprogrammed fibroblasts from two patients with familial AD, two with sporadic AD and two non-demented controls into iPSCs lines and obtained purified cultures with more than 90 % neurons. Relative to controls, iPSC-derived neurons from patients exhibited significantly higher levels of the pathological markers Aβ(1–40), Ptau(Thr231) and active glycogen synthase kinase-3β (aGSK-3β).

Another field of research possibly explaining the complexity of AD concerns the role of epigenetic alterations. In this regard, Marques et al. [26] demonstrated that BACE1 mRNA levels are increased in the aged triple transgenic animal model of AD (3xTg-AD) as well as in peripheral blood mononuclear cells (PMBC) from AD patients, along with an increase in promoter accessibility and histone H3 acetylation, while BACE1 promoter region was less accessible in PBMC from MCI individuals.

Final remarks

AD is the most common and the most studied neurodegenerative disorder. Results of the last year, as well as previous findings, lead to an increased knowledge of pathogenic events at the basis of the disease, with potential implications for future treatments. In this regard, a crucial point that emerged is that disease-modifying treatments for AD could be effective only in certain phases of the disease, particularly in mild stages. Therefore, an early diagnosis is advisable, even before symptoms occur. To do so, validated biomarkers have been included in the clinical workup, including CSF and imaging analysis, as well as genetics. Concerning genetically determined AD, it has become clearer and clearer that such cases represent the best model for testing the efficacy of new drugs, and clinical trials on a large Colombian population of mutation carriers is already ongoing, hopefully opening the way to early preventive treatments.

Conflicts of interest None.

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