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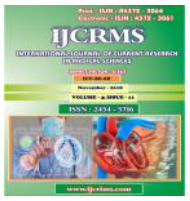

Review Article

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Alzheimer Disease Research

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Abstract

Alzheimer disease is the most common cause of dementia and represents a major public health problem. The neuropathologic findings of amyloid-β plaques and tau containing neurofibrillary tangles represent important molecular clues to the underlying pathogenesis. Genetic factors are well recognized, but complicated. In addition to research techniques, we also consider related pitfalls and flaws in the current research funding system. Conversely, we identify encouraging new trends in research and government policy. In light of these new research directions, we provide recommendations regarding prioritization of research funding. The goal of this document is to stimulate scientific and public discussion on the need to explore new avenues in AD research, considering outcome and ethics as core principles to reliably judge traditional research efforts and eventually undertake new research strategies.

Keywords: Alzheimer disease, animal models, human methods, induced pluripotent stem cells, computational models, Gerotarget.

Introduction

On April 17th 2015 the Physicians Committee for Responsible Medicine (http://www.pcrm.org/) held a roundtable with expert researchers on Alzheimer disease (AD) and human-based research approaches from the United Stated and the United Kingdom, to discuss why and how the AD research community should adopt human-based research strategies to overcome the increasing prevalence of AD in the 21st century. The major goals of the roundtable were: (1) to discuss the relevance of human-based models and tools for investigating AD pathophysiology at multiple levels of biological complexity, taking human relevance into account; (2) to formulate strategic recommendations as potential guidelines for determining research funding priorities in the field of AD research. In the present document we describe the major discussion outcomes of that meeting. We also reflect on how these recommendations fit in with current, quickly evolving, scientific and public policy efforts.

It is important to note that roundtable participants sometimes expressed different opinions regarding the discussed topics. While some felt that the first step should be to reduce animal models, others felt that current techniques already offer vast, powerful and unexplored pathways to study AD, and that sufficient alternatives already exist to fully proceed with human-based research.

However, all participants agreed that there is now a range of new techniques and research directions that have been under-explored and need to be supported through changes in public funding and research priorities. The clinical manifestation of Alzheimer disease (AD) is dementia that typically begins with subtle and poorly recognized failure of memory and slowly becomes more severe and, eventually, incapacitating. Other common findings include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Occasionally, seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism occur.1

Differential diagnosis of Alzheimer disease: Differential diagnosis of AD includes other causes of dementia, especially treatable forms of cognitive decline, such as depression, chronic drug intoxication, chronic central nervous system infection, thyroid disease, vitamin deficiencies (especially B12 and thiamine), central nervous system angitis, and normal-pressure hydrocephalus.1

Other degenerative disorders associated with dementia, such as frontotemporal dementia, including frontotemporal dementia with parkinsonism-17, Picks disease, Parkinson disease, diffuse Lewy body disease, Creutzfeldt-Jakob disease, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), may also be confused with AD.7

Computerized tomography and magnetic resonance imaging are valuable for identifying some of these other causes of dementia, including neoplasms, normal-pressure hydrocephalus, frontotemporal dementia, and cerebral vascular disease.

Prevalence of Alzheimer disease:- AD is the most common cause of dementia in North America and Europe, with an estimate of 4 million affected individuals in the United States.

The prevalence of AD increases with age. Mild memory loss is often called mild cognitive impairment. In many persons mild cognitive impairment is considered an early stage of AD.

Evaluation strategy:- Family history

A three-generation family history with close attention to the history of individuals with dementia should be obtained. For each affected individual, the age of onset of dementia should be noted. Generally, individuals with onset before age 65 years are considered to have early-onset AD and those with onset after age 65 years are considered to have late-onset AD. Medical records of affected family members, including reports of neuroimaging studies and autopsy examinations, should be obtained.

- The diagnosis of EOFAD is made in families with multiple cases of AD in which the mean age of onset is before age 60–65 years.
- The diagnosis of late-onset FAD is made in families with multiple cases of AD in which the mean age of onset is after age 60–65 years.

Genetic counseling:- Mode of inheritance

Because AD is genetically heterogeneous, genetic counseling of persons with AD and their family members must be tailored to the information available for that family. AD is usually considered polygenic and multifactorial. EOFAD is inherited in an autosomal-dominant manner.

Risk to family members—late-onset nonfamilial Alzheimer disease

Genetic counseling for people with nonfamilial AD and their family members must be empiric and relatively nonspecific. It should be pointed out that AD is common and that the overall lifetime risk to any individual of developing dementia is approximately 10–12%.

First-degree relatives of a person with AD have a cumulative lifetime risk of developing AD of about 15–30%, which is typically reported as a 20–25% risk.77,78 This risk is about 2.5 times that of the background risk (~27% vs. 10.4%).79,80

Disagreement exists as to whether the age of onset of the affected person changes the risk to first-degree relatives. One study found that early-onset AD increased the risk,78 whereas another study did not.77

The number of additional affected family members probably increases the risk to close relatives, but the magnitude of that increase is unclear unless the pattern in the family is characteristic of autosomal-dominant inheritance. Having two, three, or more affected family members probably raises the risk to other first-degree relatives in excess of that noted above for nonfamilial cases, although the exact magnitude of the risk is not clear. Heston et al.81 found a 35–45% risk of dementia in individuals who had a parent with AD and a sib with onset of AD before age 70 years. Jayadev et al.82 also report data suggesting that offspring of parents with conjugal AD (i.e., both parents affected) had an increased risk of dementia.

Risk to family members—early-onset familial Alzheimer disease

Many individuals diagnosed as having early-onset AD have another affected family member, although family history is negative 40% of the time.10 Family history may be "negative" because of early death of a parent, failure to recognize the disorder in family members, or, rarely, a de novo mutation. The risk to sibs depends upon the genetic status of the affected proband's parent. If one of the proband's parents has a mutant allele, then the risk to the sibs of inheriting the mutant allele is 50%. Individuals with EOFAD (and a mutation in *APP*, *PS1*, or *PS2*) have a 50% chance of transmitting the mutant allele to each child. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related genetic counseling issues:- Use of APOE genotyping for predictive testing

In contrast to the use of *APOE* testing as an adjunct diagnostic test in individuals with dementia, there is general agreement that *APOE* testing has limited value used for predictive testing for AD in asymptomatic persons. Data suggest that a young asymptomatic person with the *APOE* e4/e4 genotype may have an approximately 30% lifetime risk of developing AD.83 Further refinement of this risk reveals that women with an *APOE* e4/e4 genotype have a 45% probability of developing AD by age 73 years, whereas men have a 25% risk.71 These risks are lower—and the likely age of onset later—for persons with only one *APOE* e4 allele (peak age 87 years) or no *APOE* e4 allele (peak age 95 years). These estimates are not generally considered clinically useful; however, a research study to assess the potential use of *APOE* testing in relatives of individuals with late-onset AD is under way.

Prenatal testing

Prenatal diagnosis for pregnancies at increased risk for mutations in the *PSEN1* gene is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15–18 weeks' gestation or chorionic villus sampling at about 10 to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

No laboratories offering molecular genetic testing for prenatal diagnosis of EOFAD caused by *APP* or *PSEN2* mutations are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified.

Requests for prenatal diagnosis of adult-onset diseases are uncommon. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified. Preimplantation diagnosis has been reported in a mother with an *APP* mutation

Management

Treatment of manifestations

The mainstay of treatment for AD is necessarily supportive and each symptom is managed on an individual basis.[1] In general, affected individuals eventually require assisted living arrangements or care in a nursing home.

Although the exact biochemical basis of AD is not well understood, it is known that deficiencies of the brain cholinergic system and of other neurotransmitters are present. Drugs that increase cholinergic activity by inhibiting acetylcholinesterase produce a modest but useful behavioral or cognitive benefit in some affected individuals. The first such drug was tacrine; however, this agent is also hepatotoxic. Newer such drugs with similar pharmacologic action, such as Aricept® (donepezil),[89–91] Exelon® (rivastigmine),[92] and galantamine,[93–95] are not hepatotoxic.

Memantine, an NMDA receptor antagonist, has shown some effectiveness in the treatment of moderate to severe AD.[96–99]

Antidepressant medication may improve associated depression.

Therapies under investigation

Treatment trials evaluating use of anti-inflammatory agents (NSAIDs), estrogens, nerve growth factors, ginkgo biloba, statins, beta-site cleaving enzyme (BACE) inhibitors, and antioxidants are under way or recently reviewed.[100–102]

Other

Vitamins and other over-the-counter medications have been used in the treatment of AD.[103]

Some, but not all, reports suggest that affected individuals taking 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A reductase inhibitors for hypercholesteralemia have a reduced incidence of dementia.[104–106]

Immunization of an AD mouse model with β-amyloid has attenuated the AD pathology and stimulated the search for a possible vaccination approach to the treatment of human AD.[107] A human trial of this approach was halted because of encephalitis in a few subjects.[108–110]Alternative approaches to immunization therapy have been proposed.[111]

Thus far, treatment of symptomatic AD with estrogens has not proven beneficial.[112,113]

Genetics clinics

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources.

Support groups

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

The implementation of the proposed strategies would necessarily require additional efforts to increase general public awareness regarding AD pathology and recognition of current failures in research efforts, and ways to prevention. In particular, public initiatives and national campaigns addressing the relevance of nutrition, cognitive training, and physical activity as preventive strategies to reduce the risk of AD and ameliorate AD symptoms, as the ones recently undertaken should be encouraged and supported.

Summary:- Disease characteristics

AD is characterized by dementia that typically begins with subtle and poorly recognized failure of memory and slowly becomes more severe and, eventually, incapacitating. Other common findings include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Occasionally, seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism occur. Death usually results from general inanition, malnutrition, and pneumonia. The typical clinical duration of the disease is 8 to 10 years, with a range from 1 to 25 years. About 25% of all AD is familial (i.e., two or more persons in a family have AD) of which about 95% is late-onset (after age 60–65 years) and 5% is early-onset (before age 65 years).

Diagnosis/testing:- Establishing the diagnosis of AD relies upon clinical-neuropathologic assessment. Neuropathologic findings of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles remain the gold standard for diagnosis. The clinical diagnosis of AD, based on signs of slowly progressive dementia and findings of gross cerebral cortical atrophy on neuroimaging, is correct about 80–90% of the time. The association of the *APOE* e4 allele with AD is significant; however, *APOE*genotyping is neither fully specific nor sensitive. *APOE* genotyping may have an adjunct role in the diagnosis of AD in symptomatic individuals and a limited role at this time in predictive testing of asymptomatic individuals. Three forms of EOFAD caused by mutations in one of three genes (*APP*, *PSEN1*, and *PSEN2*) are recognized. Molecular genetic testing of the three genes is available in clinical laboratories. Management.

Treatment is supportive. Each symptom is managed on an individual basis. Assisted living arrangements or care in a nursing home is usually necessary. Drugs that increase cholinergic activity by inhibiting acetylcholinesterase produce a modest but useful behavioral or cognitive benefit in some affected individuals. Antidepressant medication may improve associated depression. An NMDA receptor antagonist is also FDA approved.

Genetic counselling

Because AD is genetically heterogeneous, genetic counseling of persons with AD and their family members must be tailored to the information available for that family. It should be pointed out that AD is common and that the overall lifetime risk for any individual of developing dementia is approximately 10–12%. Genetic counseling for people with nonfamilial AD and their family members must be empiric and relatively nonspecific. First-degree relatives of a simplex case of AD (i.e., single occurrence in a family) have a cumulative lifetime risk of developing AD of about 15–30%, which is typically reported as a 20–25% risk. This risk is about 2.5 times that of the background risk (~27% vs. 10.4%). In contrast, EOFAD with mutations in *APP*, *PS1* or *PS2* is inherited in an autosomal-dominant manner.

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