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Alzheimer's disease: An alternative approach

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Alzheimer's disease (AD) is the most common neurodegenerative cortical dementia. It starts with memory loss, spatial disorientation in people above the age of 65 yr with a preference to females. Its incidence is expected to increase threefold by 2050. It affects almost one out of ten persons above the age of 65 years. Majority of patients are sporadic, but a very small percentage is autosomal dominant. The pathomechanisms postulated include amyloid cascade hypothesis according to which mutation in amyloid precursor protein causes Aβ aggregation. The next hypothesis is signal transducer and activation of transcription 3 (STAT3) causing aberration in intracellular signalling pathways. Senile plaques and neurofibrillary tangles are other important pathological changes reported. It is observed that dementia research has not yielded the expected result world over, and therefore, the pitfalls with reference to known facts about diagnosis, clinical features, pathogenic mechanisms, assessment of progression, biomarkers, treatment and prevention, as well as brief information on our experiments with relatively inexpensive methods of differentiating the most common types of dementia AD and frontotemporal dementia are discussed.

Key words Alzheimer's disease - newer concepts - pathogenesis - prevention - treatment

Introduction

Alzheimer's disease (AD) represents the most common neurodegenerative dementia amounting to 50-75 per cent of all dementias and is expected to become threefold more by 2050, and about 36 million people have dementia all over the world[1,2]. However, despite sincere research efforts, AD-based research has suffered major setbacks as no new drugs have been discovered in the past one decade and pathological mechanisms are not clearly understood[3]. Transgenic animal models show Aβ-amyloid, neuritic plaques, neurofibrillary tangles (NFTs) as well as synaptic and degenerative changes but do not show the typical phenotypic features[4]. Therefore, the treatment that works in these models fails in humans[5]. As per amyloid cascade hypothesis, amyloid precursor protein (APP) is processed by three proteases α, β and γ secretase. Breakdown by β-secretase is pathogenic as it generates Aβ and by α-secretase is non-pathogenic. Several other mutations in APP are reported including the ones which cause amyloid angiopathy[6]. Presenilin 1 and 2 (PS1 & PS2) are involved in familial AD (FAD) which is believed to cause neuronal death by independent mechanisms[6]. Insoluble Aβ leads to senile plaques. NFTs result from hyperphosphorylation of tau. The role of excitotoxicity, Aβ oligomers enriching the postsynaptic tau and simultaneous interactions of apoE4, Aβ, α synuclein are all postulated[7]. Signal

transducer and activator of transcription 3 (STAT3) is a mediator of cell survival. This is reduced in hippocampus of AD patients. *APOE* gene on chromosome 19 is also considered a risk for late-onset AD[8]. Ubiquilin 1 (*UBQLN1*) on chromosome 9 and sortilin-related receptor 1 (*SORL1*) are also involved in recycling of APP[9]. However, research in these areas have not yielded a satisfactory result.

Human-based models using induced pluripotent stem cells (iPSCs), imaging and computational models have been tried. Whether lifestyle-related factors, connectomics, proteomics, lipidomics, metabolomics, nutrigenomics and epigenomics correlate with the pathogenesis of AD is another question. Disease-related adverse outcome pathways seem to be multifactorial with probable role for age; physical and mental activity; socio-economic, educational and environmental factors; pollutants; pesticides and insecticides and metabolic insults[10]. Therefore, there is a need to think and rethink about the causal role of the traditional pathology postulated. New directions in basic research using non-mammalian models such as *Dictyostelium discoideum*[11] have also been attempted. The problems faced by the scientific community are inability to determine causality due to multiple confounders, body fluid-based parameters vulnerable for change with techniques, transport, storage as well as factors related to postmortem/antemortem status and *in vivo*/*in vitro* experiments. iPSC-based study needs expertise, expense and time apart from not being fully representative of AD pathology. Biobanking to preserve AD patients-derived fibroblasts is also being done[3]. Imaging techniques are increasingly being used to analyze AD-associated neural network modifications. Normal or abnormal by visual rating of atrophy does not indicate disease and depends on clinical suspicion[12]. Structural imaging narrows down the differential diagnosis partly. Medial temporal atrophy helps differentiate other dementias from AD[13]. Asymmetric frontotemporoparietal atrophy suggests progranulin mutation[13]. AD is generally characterized by early medial temporal atrophy, however, DLBD (diffuse Lewy body disease) does not show this feature. This particular radiological differentiation is applicable only in the early stage of the disease. When the disease advances dopamine transporter imaging is needed where significant abnormality is seen in DLBD as against AD[14].

Focal atrophy of anterior temporal lobe is seen tau mutation macrotubule-associated protein tau with loss of hippocampus, parahippocampus and amygdala bilaterally. Behavioural variant frontotemporal dementia (FTD) may also show medial temporal atrophy bilaterally and therefore show some resemblance to AD. Hence, clinical association is needed for diagnosis[15]. However, the returns are very limited compared to the investment in dementia research and these negative results should make one explore newer avenues and treatment probably has to be patient tailored. Currently, there is a lot of mismatch between the postulated pathomechanism, clinical features and treatment-oriented research.

Clinical classification of AD and postulated pathogenetic mechanisms

AD is clinically classified into early-onset AD when it occurs in persons below the age of 65 . This is also called as familial AD (FAD β) and late-onset or sporadic AD (SAD) when it occurs after the age of 65. The two key biochemical features postulated are extracellular Aβ plaques and intracellular NFTs. APP is normally cleaved by α and β secretase to sAPPα or sAPPβ, which promote neuronal growth[16]. In patients with AD, the APP is sequentially cut by α and γ secretase and converted to insoluble product which circulates in blood and promotes the same in more cells[17]. There is abundance in β sheets as against alpha helices normally. This is called as amyloidal cascade. Atypical hyperphosphorylation of tau protein, a microtubule-associated protein that supports the cytoskeleton structures and regulates functions, causes the NFTs[16]. This leads to the activation of protein kinases and cellular apoptosis[18]. The genes thought to be associated with FAD are *Aβ-APP*, *PS1* on chromosome 1 and *PS2* on chromosome 21[18]. With reference to SAD-APOE, triggering receptor expressed in myeloid cell 2 (TREM2) and CD33 which are related to tau modification and microglial phagocytosis of Aβ are considered responsible[19]. There is also abnormality in the metabolism of proteins, glucose, cholesterol and proteostasis failure in ubiquitin protease pathway which triggers cell death and increases NFT formation[20]. Inability to process gangliosides causes conversion of APP precursor to insoluble toxic Aβ. Aberrant synthesis of tau occurs due to abnormal glucose metabolism as well as increase in cytokines, reactive oxygen and neuroinflammation. It is clear that brain also shares immunological defences such as any other system[21]. The tangles and β-pleated fibrillar Aβ and tau containing NFTs directly activate the classical complement pathway[22]. This in turn results in molecules of cytopathic relevance, resulting

in clustering of microglia and astrocytes. There are also membrane attack complex, upregulation of complex defence proteins and probably opsonization. The believed cascade of mechanism is amyloid which leads to inflammation, phosphorylation of tau, oxidative stress, altered calcium homoeostasis, loss of synapses, cholinergic dysfunction, apoptosis with additional disturbance, other neurotransmitters such as serotonin and norepinephrine[16].

Clinical features

Diagnosis of dementia and its cause largely is Clinical Grade A, Level-2[23]. This is all the more relevant with more controversies and no universally accepted biological, radiological or pathological marker. However, history from a caregiver is most essential. The order of appearance of symptoms is important starting from minor changes in 24 h routine. Description of cognitive memory and behaviour-related symptoms, features of amnesic onset clubbed with visuospatial problems, dressing and praxis-related abnormalities should be elicited[24]. NINCDS-ADRDA Alzheimer's criteria (proposed by National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association) are commonly used for clinical diagnosis[24]. However, non-amnesic onset, rapid progression, acute and age <40 yr are not uncommon[25]. Pathology as a definite indicator of diagnosis needs to be dropped. However, the reported decline in incidence is a welcome information[26]. Patients typically repeat questions for which answers have been given, forget appointments, messages to be conveyed, recently read information, word finding and naming difficulties, visuospatial disorientation resulting in getting lost in unfamiliar and later familiar environment, dressing and using familiar objects become difficult. Behavioural changes are seen as the disease advances. Depressive symptoms, apathy, loss of sleep and appetite are not uncommon. Patients can manifest with features of anxiety, paranoia, delusions, visual hallucinations and misidentification, and toward the advanced stage sexual disinhibition and socially inappropriate behaviours can occur[27]. All patients need thorough clinical examination to look for correctable factors and neuropsychological examination to document cognitive deficits. Mental status assessment should include levels of attention, orientation, short- and long-term memory, language, visuospatial functioning, calculation and executive functioning[28]. Hindi mental status examination[29], clock drawing test[30], everyday activity assessment questionnaire[31], geriatric depression scale[32] and Zarits caregiver burden assessment scales[33] are simple tools used in the assessment of disability. Clinical stages recognized are pre-clinical with no impairment.

Our observations with early diagnosis and quantification of progression

Most of the available tools lack sensitivity and specificity. This causes considerable delay in diagnosis. Most therapeutic options are useful only if started very early in a multidisciplinary way. Anterior dementias alter the various frontal sub-cortical circuits while posterior dementias are less likely to do that in early stages, and hence, default mode networks are likely to show different patterns of involvement in these two conditions[34]. With this hypothesis, we analyzed resting motor threshold (RMT), central motor conduction (CMCT), and silent period (SP) in both these groups of disorders. The results showed reduced RMT in majority of our patients with AD[34]. CMCT was in the upper limit of normal in the patients with FTD[35]. There was significantly reduced SP in both groups *i.e.* AD and FTD, suggesting increased cortical excitability and reduced cortical inhibitions[35]. This observation could mean early changes in the neurotransmitters, specially gamma aminobutyric acid (GABA) and acetyl choline (ACh). This if confirmed in a larger population, may serve as a biomarker in AD patients and also will open new therapeutic options such as GABA agonist[35]. CMCT is prolonged in FTD and SP is reduced in AD and FTD. RMT is reduced in patients with AD. Thus, the patterns are distinguishable in both conditions[36]. Another study was taken up to know the pattern of involvement of autonomic functions in these two groups of patients. The rationale was the degenerative process which involves the central autonomic network, and ACh, which gets depleted in AD, is important in autonomic system. With this rationale, we studied patients with AD and FTD and found sympathetic dominance in both groups, but parasympathetic suppression was found only in AD. This observation might serve as an early marker to differentially diagnose these two conditions. It might also explain some of the symptoms such as sudden unexplained death[37]. In our attempt to look for inexpensive and easily available additional biomarkers, a pilot study on long loop reflex 2 (LLR2) was done in these two types of cortical dementias. The absence of LLR2 was consistently seen in FTD which could be explained by early breakdown of frontal subcortical circuits in this condition as against AD[38]. This is likely to serve as an

inexpensive and very early biomarker to differentiate the two common types of cortical dementias[34]. In a study on differential involvement of balance and gait in these two categories of dementia, it was found that both FTD and AD had balance and gait deficits in single as well as dual-tasks[34]. Dual-task testing will be useful in bringing out subtle abnormalities in these domains. AD has limits of stability issues of balance; hence, postural stability training might be useful in preventing and managing falls in this population. Dual-task gait assessments may be included as an add-on diagnostic tool for early differentiation of these two conditions[34]. We also described a unique phenomenon of misidentifying self-image as another person resulting in severe caregiver problem, and termed as mirror image agnosia[39,40]. For assessing progression and quantifying loss in rural regions, a study was conducted comparing quantitative voxel-based volumetric assessment of brain for visual quantification of electroencephalography (EEG). There was a significant correlation between grand total EEG score (GTES) and dementia severity and global grey matter volume, but the proportional correlation with GTES and volumetric scores was not significant[41].

Assessment of course

Clinically Mini Mental Status Assessment, Clock Drawing Test, Function Activities Questionnaire and Geriatric Depression Scales are commonly used to assess neuropsychological efficiencies and deficiencies. Serial assessment of hippocampus and whole-brain volume assessment is reported to correlate with clinical deterioration[42]. Therefore, this parameter can be used in assessing therapeutic responses for research purpose. Magnetic Resonance Imaging (MRI) spectroscopy and Positron Emission Tomography (PET) show changes but lack of longitudinal data and prohibitory cost interfere with its regular use. Cerebrospinal fluid (CSF) Aβ and tau are also abnormal in other neurodegenerative disorders[43] and therefore, lack specificity. Proteomic studies in the blood and plasma might give some answer in this area.

Therapeutic options

Currently available treatments modify symptoms for some time but do not change the course of disease. Benefits in activities of daily living, behaviour and global functioning are seen in a minority of cases[44]. Commonly available drugs are acetyl cholinesterase inhibitors (AchE), butyryl cholinesterase (ChE) inhibitors, and N-methyl-D-aspartate (NMDA) inhibitors. In transgenic animals, vaccination against β-amyloid protein as well as β and γ secretase inhibitors 3 was tried, but adverse effects were observed[45]. Agitation, depression and anxiety seen are treated with atypical neuroleptics, anticonvulsants and benzodiazepines if no causes such as infection, pain, faecal impaction, fractures and drugs are identified. Galantamine inhibits ChE, induces release of Ach, stimulates AchR and is used in mild AD. Rivastigmine inhibits AchE and butyryl ChE and is useful in mild cases. Donepezil trial in AD2000 failed to prove benefits[46]. Memantine is a non-competitive NMDA receptor antagonist which reduces Aβ production, tau hyperphosphorylation and synaptic dysfunction[47]. Selective serotonin reuptake inhibitor is used to treat depression, benzodiazepines for anxiety, and neuroleptics for aggression.

Other research strategies

The drugs tried in the treatment of AD are as follows: Beta- and gamma-secretase inhibitors to remove amyloid plaques, immunotherapy to remove amyloid deposit, passive immunization with monoclonal antibody against amyloid, bapineuzumab, solanezumab, ponezumab, IVIg, *etc*. Drugs which prevent Aβ aggregation are tramiprosate, clioquinol, epigallocatechin 3-gallate, *etc*. Drugs which enhance Aβ degradation by insulin degrading enzyme, non-amyloid pathway drugs such as glycogen synthase kinase 3 β inhibitors, leptin, humanin, statins, thiazolidinediones such as pioglitazone, rosiglitazone, *etc*. Lithium is believed to reduce NFT, caspase inhibitors, activity-dependent neurotrophic factors, non-steroidal anti-inflammatory agents, antioxidants, neuroregenerative agents such as stem cells are also being tried.

Role of stem cells

The principle involved is using the neurogenesis capacity of stem cells. There are four types of stem cells viz. neural stem cells, mesenchymal stem cells, embryonic stem cells and iPSCs. Self-renewal and differentiation to all kinds of nerve cells are demonstrated in neural stem cells and are likely to emerge as a potential treatment option[48]. Plasma exchange studied in some patients showed decreased Aβ1-42 levels in plasma and increased Aβ1-42 levels in CSF. There were behavioural problems during the exchange, but cognitive functions such as memory and language showed sustained improvement[49].

Prevention

Prevention by vaccines has not been successful. Factors promoting AD pathology such as sleep disordered breathing, head injury, vascular risk factors, substance abuse and sedentary lifestyle should be properly addressed. Physical and mental activity is encouraged. Diet containing neuroprotective antioxidants should be used, and artificial taste makers should be avoided. Slow wave sleep is concerned with clearing of metabolic waste and activity during this phase increases amyloid accumulation[50]. Therefore, proper sleep hygiene is to be encouraged. Cognitive engagement is important. However, a definitive way to prevent AD is not yet available.

Conclusion

AD increases with increasing life expectancy in the community. There is no definite way for prevention. Effective early diagnostic tools and efficient treatment options are not available, except perhaps reducing caregiver burden by educating them regarding the symptomatology associated with the disease and educating ways to address the problem symptoms non-pharmacologically as well as pharmacologically. Despite, availability of advanced neuroimaging techniques and neuropsychological evaluation tools early diagnosis of AD still remains in enigma. At the time of diagnosis most patients are fairly into moderate to severe degree of impairment. Several neuropathological targets have been identified for pharmacotherapy based trials, but the *in vitro* experience with these agents has not been satisfactory. Therefore, there is a need for simple, easily available, sensitive, multimodal biomarkers for the early diagnosis, as well as effective disease modifying pharmacological agents which are possible only if drug trails are based on targeting the correct pathomechanisms. Therefore, a new look is needed from both diagnostic and therapeutic point of view.

***Conflicts of Interest*:** None.

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