

Review

Overview and Current Status of Alzheimer's Disease in Bangladesh

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Abstract. Alzheimer's disease (AD) is a complex neurological disorder with economic, social, and medical burdens which is acknowledged as leading cause of dementia marked by the accumulation and aggregation of amyloid- β peptide and phosphorylated tau (p-tau) protein and concomitant dementia, neuron loss and brain atrophy. AD is the most prevalent neurodegenerative brain disorder with sporadic etiology, except for a small fraction of cases with familial inheritance where familial forms of AD are correlated to mutations in three functionally related genes: the amyloid- β protein precursor and presenilins 1 and 2, two key γ -secretase components. The common clinical features of AD are memory impairment that interrupts daily life, difficulty in accomplishing usual tasks, confusion with time or place, trouble understanding visual images and spatial relationships. Age is the most significant risk factor for AD, whereas other risk factors correlated with AD are hypercholesterolemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, and diabetes. Despite decades of research, there is no satisfying therapy which will terminate the advancement of AD by acting on the origin of the disease process, whereas currently available therapeutics only provide symptomatic relief but fail to attain a definite cure and prevention. This review also represents the current status of AD in Bangladesh.

Keywords: Alzheimer's disease, age, risk factors, diagnosis, genes

INTRODUCTION

Alzheimer's disease (AD) is a multifactorial neurodegenerative brain disorder in which approximately 5.3 million people in the United States, including almost half of the population at 85 years and older have affected and it has become a devastating condition with a huge societal impact, both in terms of financial cost and the progression of number of older people [1, 2]. It has become the only one of the top ten causes-of-death with unknown genetic causes as well as no specified diagnosis and disease-altering treatments [3]. Neuritic plaques containing amyloid- β peptide (A β ₄₂) and neurofibrillary tangles

composed of hyperphosphorylated tau are considered as microscopic hallmarks of AD [4]. AD results from a combination of genetic, environmental and lifestyle factors [5]. Although, at present there is no permanent known cure of AD, current treatment advances are designed for assisting people to maintain mental function, manage behavioral symptoms, and slow or delay the symptoms of disease by targeting specific genetic, molecular, and cellular mechanisms so that the actual underlying cause of the disease can be prevented [1]. The clinical presentation of AD is heterogeneous and insidious, whereas the psychological and financial effects of AD on caregivers and family members are significant. In this review, we study clinical features of AD, various risk factors; several genes associated with AD, available diagnosis process, pathophysiology of AD, treatment of AD. We also emphasize on the recent advances on the

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molecular pathogenesis and the implications for the development of treatment and of new methods for early diagnosis, taking into account existing observations.

CLINICAL FEATURE

AD is an irreversible, progressive brain disorder which slowly demolishes memory and thinking skills and, eventually, the power of accomplishing the simplest tasks [1]. Being a neurodegenerative disease [6], AD slowly and progressively declines brain cells. As it is the most common form of dementia, it affects 60–65% percent of people with dementia worldwide [7–9]. It is named after German neurologist Alois Alzheimer, who in 1907 first recognized the symptoms as well as the neuropathological characteristics of the disease, such as amyloid plaques as well as tangles in the brain [6]. AD declines memory and cognitive function resulting confusion, alteration of mood and disorientation in time and space. In most people with AD, symptoms first come along in their mid-60s [8–10] though it is neither infectious nor contagious. Again, AD can be either sporadic or familial [8] where sporadic AD can affect adults at any age usually showing effects after age 65 and is well-known as the most common form of AD [8–13]. The reason of occurring very uncommon form of AD named familial AD is mutation in one of several genes [7, 14, 15].

Dementia is a syndrome which is characterized as the progressive deterioration of cortical functioning including language, judgment, comprehension, memory, thinking and learning [16–18]. The course of dementia will differ from person to person and is associated with a range of factors including the subtype of dementia, physical health, lifestyle factors and the social supports of the person with the disease [8]. When AD progresses, the person's ability to accomplish roles of daily living such as shopping or managing finances will be hampered, which suggests the need of personal assistance to undertake even simple activities for that person. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for AD require the presence of progressive deficits in at least two cognitive domains, one of which should be memory, which are not related to any other disease process [10]. The cognitive deficits must represent a change from a previous state of normal functioning. These changes must be distinguished from acute or subacute confusional states

or delirium (emetabolic encephalopathy). The recent National Institute on Aging/Alzheimer's Association criteria for dementia requires impairments in two cognitive domains for the diagnosis of dementia, not necessarily in memory functions [8, 11, 12]. The clinical features of AD differ among individuals where the most common initial feature is demonstrated as significant deterioration to recollect new information. This memory impairment occurs because the first neurons to malfunction and die are usually neurons in brain regions engaged in generating new memories [8, 13, 15, 16]. As neurons in other parts of the brain malfunction and die, individuals experience other difficulties.

Overall, the common clinical features of AD are memory impairment that interrupts daily life, challenges in designing or resolving problems, difficulty in accomplishing usual tasks at home, at work or at leisure, confusion with time or place, trouble understanding visual images and spatial relationships, new problems with words in speaking or writing [8].

RISK FACTOR

Age

Age is the most significant risk factor for AD where the incidence of AD in men and women increases robustly with age [19, 20]. The International Alzheimer's Disease Report estimates that 47 million people worldwide are living with AD in 2015, and this is estimated to increase to 131 million people by 2050 [21]. After the age of 65, the lifetime risk of AD is one in six for women (16.7%), whereas it is one in eleven for men (9.1%) [22].

Obesity/metabolic syndrome

Relationship between AD and obesity suggests an up to 40% increased risk for obese individuals in some studies, [23–26] others have observed no correlation [27–29]. Weight loss and low body mass index are significantly correlated with elevated risk of AD in older adults, whereas a higher body mass index may be protective at advanced ages [23, 30–32].

Family history of Alzheimer's disease

Family history of AD may play crucial role in the occurrence and advancement of AD. The persons whose parents or siblings are the patients of AD are

more susceptible to AD than a person do not have family history of AD [33–35]. The exact relationship between the elevated risk of AD and family history of AD is not fully recognized through existing research.

Smoking

Early onset of AD is correlated with smoking which is considered as a modifiable risk factor for AD estimating to account for 4.7 million AD cases worldwide. Numerous studies have observed that smoking has been associated with both increased and decreased risk for AD. But, smoking during lifetime is linked with at least a 1.7 times (70%) greater risk for AD, and the risk markedly elevates with greater cumulative smoking exposure [36].

General anesthesia and AD

Several studies have reported the preclinical manifestation for the possible role of general anesthesia in the advancement of AD processes in cell culture or animal models. Current demonstration suggests the correlation between exposure to volatile general anesthesia and AD pathogenesis in transgenic mouse models [37, 38], whereas the evolution of tauopathy [37] and A β processes linked with AD have also been detected in animals exposed to general anesthesia [37].

Diet

Numerous research studies have been demonstrated that dietary components may play crucial role in the progression of AD risk observing in both human and animal models. Cognitive impairment in humans, elevated levels of A β and tau pathology in rodents which are the predictors of AD pathogenesis are correlated with the high sucrose and fructose contents of Western diets [39–42] whereas trans and saturated fatty acids are linked with higher risk of AD and mild cognitive impairment [43, 44]. Trans and saturated fatty acids are shown to exhibit high levels of A β by another rodent experiment [45, 46]. Again, diet with induced oleic acid and reduced fat was found to decrease A β levels and pathology in transgenic mice [47]. Various observations have been suggested that A β levels decreases significantly with diets containing high omega 3 polyunsaturated fatty acids [48–51].

Others

Cardiovascular disease, social and cognitive engagement, traumatic brain injury, down syndrome etc. are also suspected as risk factors of AD but no significant research has been established to demonstrate their relationship with AD [52–64].

GENETIC FACTOR

Apolipoprotein E (APOE)

Apolipoprotein E (APOE) is one of the strongest heritable risk factor for late onset of AD which is located on the proximal long arm of 19th chromosome i.e., at chromosome 19q13.2 which encodes a pleiotropic glycoprotein [8–10, 65–67]. It is well-known essential brain apolipoprotein which is secreted by astrocytes [68–71]. In 1991, the relationship between APOE and AD was first introduced [65] and later it was affirmed in 1993 through studies of an association between the APOE ϵ 4 allele and AD risk [6, 7, 66, 72]. Being distributed in liver, brain, and macrophages [11, 73], the APOE gene exists as three polymorphic alleles (ϵ 2, ϵ 3, and ϵ 4), where the APOE ϵ 3 allele is the most common (77%), ϵ 2 allele is the least common (8%) [74, 75]. Individuals having the ϵ 4 allele have higher risk of AD in comparison with subjects carrying the more common ϵ 3 allele, whereas the ϵ 2 allele decreases risk [76, 77]. APOE ϵ 4 elevates risk in familial and sporadic early and late-onset AD [18] with dose-dependent effect on age at onset [66, 78].

A β PP

Amyloid- β protein precursor (A β PP) is a type-1 transmembrane neuronal protein which is situated at chromosome 21q21 [79–82]. It acts like a signal-transduction receptor and is distributed in many tissues and intensified in the synapses of neurons [83, 84]. Firstly, A β PP is made in the endoplasmic reticulum, then post transcriptionally modulation occurs in the Golgi (N- and O-linked glycosylation, sulfation, and phosphorylation), and finally, released to the cell surface via the secretory pathway and endocytosed and processed in the endosomal-lysosomal pathway from the cell surface [85, 86]. Approximately 14% of early-onset autosomal dominant cases of AD are occurred by dominant mutations in A β PP, whereas

two recessive A β PP mutations (A673V and E693D) generate early-onset AD [78].

Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2)

Presenilins are major components of the atypical aspartyl protease complexes which are involved in the γ -secretase cleavage of A β PP [87]. PSEN1 and PSEN2 belong to integral membrane proteins which is composed of nine transmembrane domains with a hydrophilic intracellular loop region and located on chromosome 14q24.3 and on chromosome 1q31-q42 respectively [79, 88]. It is distributed in the cell surface, Golgi, endoplasmic reticulum, and mitochondria [89, 90].

ATP Binding Cassette Transporter 7 (ABCA7)

Being a member of ABC transporter superfamily, ABCA7 was first reported in macrophages whose location of ABCA7 is on chromosome 19p13.3. It exhibits significant roles in lipid metabolism and the phagocytosis of apoptotic cells [91–93]. Through the C1q complement pathway, ABCA7 has suspected function to modulate phagocytosis of apoptotic cells by macrophages [94]. Again, it manifests in the efflux of lipids from cells into lipoprotein particles with stimulating cholesterol efflux by inhibiting A β secretion *in vitro* [95].

AKAP9: a kinase (PRKA) anchor protein 9

Being expressed in the hippocampus, cerebellum and the cerebral cortex and encoding with a scaffold protein with physical attachment of type I protein phosphatase and cAMP-dependent protein kinase to the N-methyl-D-aspartate receptors for stimulating channel activity, AKAP9 is located on chromosome 7q21.2 [96, 97].

Bridging Integrator 1 (BIN1)

The location of BIN1 (Bridge Integrator 1 or Amphiphysin 2) is on chromosome 2 (2q14.3) which was recognized as Myc box-dependent-interacting protein 1 by interacting with Myc-box region of the MYC oncoprotein encodes several splice variants [98–100]. The SNPs in BIN1 modulating risk for late onset AD were identified by genome-wide association study [101, 102], whereas in aging mice, in transgenic mouse models of AD, and in persons with schizophrenia, the variation

of the nature of BIN1 has been demonstrated [103, 104]. The role of BIN1 is in enhancing Clathrin-mediated endocytosis, intracellular endosome trafficking, senescence, immune response, calcium homeostasis, and caspase-independent apoptosis [105–108], whereas BIN1 has been observed to involve in phagocytosis by macrophages and attaches α -integrins to modulate the immune response [109].

CD2 Associated Protein (CD2AP)

The composition of scaffolding protein named CD2AP is 639 amino acids with molecular mass of approximately 70 kDa [110] which exhibit its activities in cytoskeletal reorganization and intracellular trafficking [111]. Being distributed in adult and fetal human tissues as an approximately 5.4kb transcript [112], it is located on chromosome 6p12 which encodes CD2 associated protein [112]. CD2AP is related in mediating vesicular trafficking to the lysosome and it is attached with proteins involved in cytoskeletal organization [113] resulting endocytosis [114, 115] and cell-cell interactions [116]. Ligand binding of CD2AP improves protein segregation, CD2 clustering, and cytoskeletal polarization [111].

Clusterin (CLU)

A stress-activated chaperone protein encoding three alternative transcripts named Clusterin (CLU) is a 75 kDa apolipoprotein which is located on chromosome 8p21.1 [117, 118]. Being distributed throughout the body, especially in the brain for exhibiting its activities in apoptosis, complement regulation, lipid transport, membrane protection, and cell-cell interactions [117], clusterin alters A β clearance, amyloid deposition, and neuritic toxicity and purified clusterin interacts with A β affecting fibril formation *in vitro* [119, 120]. By modulating the membrane attack complex, clusterin inhibits the inflammatory response associated with complement activation [117].

CD33

CD33 may mediate A β clearance and other neuroinflammatory pathways which are controlled by microglia in the brain whereas high CD33 brain expression has been associated with AD status [121].

Ephrin Type-A Receptor 1 (EPHA1)

In transgenic mouse models of AD, it was demonstrated that ephrin receptors were minimized in the hippocampus prior to the development of impaired object recognition and spatial memory, while low levels of Eph receptor have been recognized in postmortem hippocampal tissue from patients with incipient AD [122].

SORL1

Being originally recognized as an AD risk gene in candidate-based approaches [123, 124], SORL1 mediates the processing of A β PP by presenilins and the production of A β [125]. Recent meta-analysis of one observation has been demonstrated a significant association between clusters of polymorphisms in SORL1 and AD in both Caucasians and Asians [126].

TREM2

One type of transmembrane receptor protein called TREM2 is located on chromosome 6q21.1 which is expressed on myeloid cells to regulate phagocytosis and suppress inflammation reactivity [127] including microglia, monocyte-derived dendritic cells, osteoclasts, and bone-marrow-derived macrophages [128].

Tau

Tau is a cardinal constituent of neurofibrillary tangles which is located on chromosome 17 of the human genome expressing six isoforms of the tau protein in adult human brain [129, 130]. Tau has been found to be associated with induced oxidative stress, impaired protein-folding function in the endoplasmic reticulum, and deficient proteasome-mediated which is also linked with autophagy-mediated clearance of damaged proteins in AD [131, 132].

Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM)

The location of the PICALM gene is on chromosome 11 (11q14.2) which is distributed in acute myeloid leukemia, acute lymphoblastic leukemia, and malignant lymphoma [133], whereas the levels of PICALM were modulated in the brain of an amyloid mouse model of AD in contrast to wild-type mice [134].

DIAGNOSIS

The diagnosis of AD depends on clinical features, medical history, family discussions and contemporary diagnostic tests including clinical, neurological, and psychiatric examination whereas neuropsychological testing can be recognized as a tool for getting objective signs of memory disturbances in early stages and laboratory studies, such as thyroid-function tests and serum vitamin B12, are used to explain the secondary causes of AD. But, the 2011 criteria and guidelines recommend biomarker tests for the recognition of two biomarker categories: (1) bio-markers demonstrating the level of A β accumulation in the brain and (2) biomarkers exhibiting that neurons in the brain are declined or actually degenerating. The proper application of these biomarkers helps researchers to enroll individuals with the brain changes for providing treatments target [135, 136]. Various stage of the disease with various factors, like environmental factor, genetic factors, age, sex, etc., should be considered carefully to get significant results from biomarker test or combination of test [58]. For the diagnosis of AD, the elevated levels of cerebrospinal fluid (CSF) biomarkers have been detected in the combination magnetic resonance imaging (MRI) and CSF biomarkers as the diagnostic accuracy. All these are measured significantly through MRI to predict future clinical decline [135–138]. Again, these are demonstrated significantly by a multimodal classifier which firstly chooses MRI and fluorodeoxyglucose positron emission tomography (PET) regions of interest, then combines them with CSF biomarker data accurately [139]. Some methods used as diagnostic tools for the disease are MRI measurements of medial temporal lobe atrophy, PET imaging of glucose metabolism and A β deposits, and CSF biomarkers, but recently none of these are recommended in any consensus guidelines for diagnosis of the disease [139, 140]. To get validated diagnosis techniques, further research is needed in large prospective studies.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

The pathophysiology of AD is depended on numerous hypotheses because of its multifactorial characteristics [141]. Various causative factors make the pathophysiology of AD more complex involving a number of processes. Numerous hypotheses

are associated with AD pathophysiology including cholinergic hypothesis, A β hypothesis, tau hypothesis and inflammation hypothesis [142, 143]. Two major hypotheses are correlated with AD: accumulation of protein plaques which is consisted of A β [144] as well as, the generation of neurofibrillary tangles linked to hyperphosphorylation of tau proteins [145]. These protein abnormalities and oxidative stress and inflammation, failure of synaptic function, depletion of neurotransmitters and eventual cell death [145] are associated with the pathophysiology of AD. Recently it has been recognized that the most commonly employed A β hypotheses which is considered as triumph for the last two decades, does not account for the complicated pathophysiology of this crippling disorder [146]. The function of A β oligomers in synaptic impairment has been reported significantly in current observations which indicates that these are primarily the only one among several other signals declining the integrity of brain functions [143, 147, 148]. Again, the generation of amyloid plaques arising in the later age which becomes prominent to be rather late event [149].

TREATMENT

Anti-amyloid therapies

Acting on A β aggregates which are well-known as amyloid plaques is the main focus of anti-amyloid therapies for the treatment of AD.

Drugs to reduce A β production

β -secretase inhibitors: The outcome of BACE inhibitor is in significant reduced levels of A β_{40} and A β_{42} in brain of A β PP transgenic mice and elevated levels of soluble A β PP β , soluble A β PP α secretion whereas β -secretase inhibitors betterment in cognition can be attained which in future may worsen with the advancing age [150–152].

γ secretase inhibitors: Semagacestat (LY-450139), MK-0752, E-2012BMS-708163, PF-3084014, Begacestat (GSI-953), and NIC5-15 are found in various clinical trials to provide γ -secretase inhibiting activity, whereas Semagacestat has been observed to minimize A β concentrations in plasma and A β production in the central nervous system [153–155]. Ibuprofen, Indomethacin, and Sulindac sulfide which are popular subsets of non-steroidal anti-inflammatory drugs firstly attach to A β PP, then reduce A β_{1-40} and A β_{1-42} production with increased

generation of A β_{1-38} fragments for exhibiting their activity as γ -secretase modulators [156].

α -secretase modulators: Agonists of muscarinic, glutamate, statins, serotonin, oestrogens, and testosterone and protein kinase C activators are popular α -secretase modulator but their application in the treatment of AD is not well-understood [157].

Drugs interfering with A β aggregation

Stemazole, curcumin, SK-PC-B70M, T-817 MA etc. have been demonstrated to provide possess therapeutic potential for the treatment of AD [158–162].

Metal chelators

In the pathogenesis of AD, metals have been assumed to act as key-regulator in the treatment of AD, among them that Zn/Cu-selective chelators significantly elevate the solubilization of A β deposits in AD brains. [163–165].

Enzyme mediated A β degradation

Neprilysin, insulin degrading enzyme, plasmin, endothelin converting enzyme 1 and 2, and angiotensin-converting enzyme, etc. have been shown to possess their abilities of degrading A β peptide [166].

Therapeutic clearance of A β

Immunotherapy-mediated A β clearance

Immunotherapy mediated A β clearance can be attained through active and passive immunization [167], whereas active and passive A β immunotherapy in AD Tg mice has been observed to minimize cerebral A β by ameliorating cognition [168]. Active immunization with anti-A β has been shown to elevate amyloid plaque clearance reducing plaque-associated pathology, CSF tau level and slowing patient's cognitive decline [169–172]. Again, withdrawal of amyloid plaques and elevation of behavioral performance in AD mice can be accomplished by its vaccination with HSV amplicons showing A β and interleukin-4 expression [173].

Targeting tau phosphorylation

Targeting hyperphosphorylated tau is an attractive approach because various phospho-tau epitopes are selectively and specifically correlated with AD pathology. Tau phosphorylation has gained importance in AD leading to microtubule instability.

Inhibition of glycogen synthase kinase 3 (GSK3) and cyclin dependent kinase 5 (CDK5), primary enzymes affecting tau phosphorylation enzymes may prevent tau phosphorylation. Both lithium and roscovitine have been reported to inhibit the actions on these kinases, whereas both lithium and valproate which are active against GSK3 β can diminish tau pathology in transgenic mice [174–177]. Recently, an irreversible inhibitor of GSK3 β called Tideglusib (NP031112) and other small molecule inhibitors of GSK3 like SB216763, SRN-003-556 [178] and CHIR-98014 [179] are being studied to observe their supposed prominent role in the treatment of AD.

Herbal supplements

Herbal supplements which can be used in the treatment of AD are *Panax ginseng*, *Ginkgo biloba* (EGb761), *Withania somnifera*, *Curcuma longa* [180–188].

Other miscellaneous therapies

Statins

Treatment with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) has been suggested to promote the prevention of AD [189]. A prospective cohort study named the Sacramento Area Latino Study on Aging (SALSA) was conducted among 1789 older (≥ 60 years of age) Mexican American individuals from the Sacramento, CA, area without a previous diagnosis of dementia. Here, Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin were used and statin users were reported about half as likely as those who did not take statins to treat dementia/cognitive impairment (hazard ratio (HR)=0.52; 95% CI 0.34, 0.80) during a 5-year follow-up period [190]. Another prospective observational study called the AD Anti-inflammatory Prevention Trial (ADAPT) was observed among 2,233 participants. Here, elective statin use was reported to be correlated with significantly decreased risk of incident AD that remained unchanged after adjustment for age, gender, education, and APOE genotype [191]. The application of statins was been shown to be correlated with a reduced risk of AD (HR = 0.57; 95% CI 0.37 to 0.90) in comparison with those that did not take cholesterol-lowering drugs, whereas the use of non-statin cholesterol-lowering drugs was not reported to exert the same correlation. These observations are reported in the largest population-based observational study of this kind

which was known as the Rotterdam Study involving 6,992 participants for a mean of 9 years [192]. In a systemic review and meta-analysis of 16 studies in qualitative synthesis and 11 in quantitative synthesis using statins named simvastatin, lovastatin, pravastatin, the researchers demonstrated that long-term data may support beneficial role for statins in the prevention of dementia [193]. Finally, a Cochrane Database systematic review and analysis of double-blind randomized placebo-controlled trials of statins in people at risk of AD and dementia conducted two trials with 26,340 participants using simvastatin, pravastatin and demonstrated that statins given to older patients at risk for vascular disease were not beneficial in preventing dementia [194]. Based on the conflicting results of these studies and insufficient evidence, statins cannot be recommended for the purpose of AD-related dementia treatment.

Melatonin

In experimental models of AD, it was demonstrated that melatonin is detected to exert free radical scavenging, anti-oxidative properties, anti-amyloidogenic effects, whereas it weakens tau hyperphosphorylation. All of these properties are supposed to be beneficial in the treatment of AD [195–197]. Again, serotonin which is well-known precursor of melatonin has depleted bit-by-bit and it is reported during the course of AD [198]. Numerous studies have suggested that gold nanoparticles can be beneficial for the early detection and treatment of AD [199]. Music can be a good enhancer in patients with AD and numerous studies have been conducted to demonstrate its use as an alternative non-pharmacological treatment of AD [200–202].

CURRENT STATUS OF ALZHEIMER'S DISEASE IN BANGLADESH

A few data are available about the number of AD patient in Bangladesh. There is no precise epidemiological data of AD in this country [203]. Here, the awareness about AD is now in primary stage. Therefore, affected patient and their family members are facing different problems continuously. The fund for conducting research on AD is limited. A lower middle income country like Bangladesh is not yet prepared for the management of AD. At present, most of the people of the country are in the young group. However, within 20–30 years there will be huge elder group people in this country. Therefore, there will

be more chances of occurrences of AD. So, it is high time to think about the disease and its management as a proactive manner and take necessary action in this regard. The policy makers, health professional and allied groups should come forward to make national priority for AD in Bangladesh.

Smoking rate in Bangladesh

Bangladesh is one of the largest tobacco consuming countries in the world [204]. It is one of the top ten countries with high current smoking occurrence of 44.7 % among men [205]. It was found that 43.3% of adults aged 15 years or above use some form of tobacco in Bangladesh. [206].

Obesity levels in Bangladesh

Almost one-fifth of the Bangladeshi adult population is overweight, according to a global study [207]. This study also said that over the last 33 years, rates of either being overweight or obese doubled among Bangladeshi adults but remained low among children. Another study found that young age obesity is alarmingly high and on rise amongst urban children from wealthy families [208].

CONCLUSION

In this paper, we assess clinical features of AD, risk and genetic factors, available diagnosis process, the different expressions of pathophysiological mechanisms behind AD and its management through conventional drug therapy, including modern investigational therapeutic strategies, currently introduced and ongoing new insights into the potential therapeutic targets elaborately to figure out complicated AD puzzle. Though numerous clinical trials are designed to open a new door for demystifying the exact reasons of AD, structural and functional influence of various genes associated with AD, fistful information are available in this case. There is no therapy which will terminate the advancement of AD by affecting the origin of disease process, whereas some available non-targeted pharmacological treatment such as anti-inflammatory therapy, metal chelation, antioxidant supplementation, epigenetic modifications can be deleterious due to their improper usage. Choice of inappropriate experimental design, limited population, population heterogeneity, improper use of biomarker in clinical trial, incomplete reporting of

data, failure to find suitable compound and significant treatment procedure, failure to use appropriate dosage, etc., can be the major reasons of failure of understanding the neuropathological features of AD and achieving a definite therapeutic approach.

Future direction

The number of AD patient is growing day by day. The high occurrence of AD patient is co related with increasing rate of the life expectancy. AD is a disease causing great sufferings to the patient and their relatives and is also a growing healthcare problem with economical as well as social consequences. There is so far not possible to cure AD but some symptomatic treatment is available. Risk factors can help to identify high-risk individuals who might benefit from different therapeutic outcomes. The focus of dementia research is developing strategy to prevent or delay the onset of dementia [209]. Much of the evidence suggests that the accumulation of A β and the abnormal phosphorylation of tau is a reasonable target [210]. However, more targeted treatment approaches are needed to be proposed.

DISCLOSURE STATEMENT

The authors have no conflicts of interest to disclose.

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