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A neurological disorder that destroys vital brain functions: Alzheimer's disease

Jutishna Bora[1*], Aayesha A Qureshi[2], Saqueib Imam[3]
[1-3] Department of Biotechnology, Amity University Kolkata, Kolkata, West Bengal, India

Abstract
Robert M Sapolsky, a famous neurologist who saw the world from a much different perspective, helped the neuroscience to strip the mind like never before. Neurology is a vast field of science where the knowledge to handling a person's brain's ill state dwells in, since the neurosciences first discovery in the 1930 by the Egyptians, it has helped in understanding the human mind, manipulate it, and most importantly helping us to know how the incurable brain diseases can be cured or at least prevented. One of the brain diseases that would be further discussed is called the Alzheimer's disease under the family of other brain diseases-dementia. Alzheimer's is a rare brain disease increasingly becoming common in the entire world, has a lot of mysteries attached to it regarding its root cause and then finally, can a cure for Alzheimer's be devised?

Keywords: mild cognitive impairment (mcr), anomia, hypothyroidism, attention deficit hyperactivity disorder (adhd), neurodegeneration, aceylcholinesterase

1. Introduction
Alive but brain dead? This is the usual phrase a person associates or has been associating since ages with any form of brain disease or the brain disorders as it has been said. Alzheimer's disease also called as senile dementia in other parts of the world, is a slowly progressive disease, whose root cause is due to the extensive damage to the brain cells, in short there is a deterioration in the brain cells and as we know brain cells are responsible for transmitting impulses to carry out various actions performed by our body, that is, brain overall monitors the whole body function. There is a defense mechanism in the body to defend against the deterioration of the brain cells, by producing a protein amyloid, but due to excess formation of the amyloid protein, its deposits cause a great deal of damage to the brain leading to increased condition of dementia and finally causing Alzheimer's. Researches on how it is caused are still being carried out and Alzheimer's has generated a lot of hypothesis but still remains a mystery on how it is caused, but why is it still a mystery? Even with the advancement of technology, over these advancing years, scientists are still in trouble with the question that what actually causes Alzheimer's disease, for example if we consider the amyloid protein hypothesis, then it has not yet been determined, that, the formation of protein leads to Alzheimer's or it is because the person is already suffering from Alzheimer's which leads to excess deposits of amyloid protein in the brain leading Alzheimer's disease [17, 22]. The damage done by Alzheimer's starts with an increased decline in thinking, decision making, a person's ability to function independently is also affected.

1.1 Signs and SYMPTOMS
The signs and symptoms that point towards Alzheimer's are exclusive and pretty evident hence detecting becomes easier, some of them occur at a very slow rate:

- Memory loss: Start of Alzheimer's disease is marked by the most important evident symptom, which is short term memory loss, it starts mildly, such as forgetting which day it is or forgetting about the little conversation had, loosing track of time are the signs of mild memory loss.
- Frequent mood swings: Increased irritability, anxiety driven thoughts, loss of temper on small situations, short-lived happy moments, such signs indicate early development of Alzheimer's disease. Sometimes these mood swings could lead to major problems such as depression or bipolar nature.
- Confusion about time and place: Alzheimer's causes a person to become rather estranged from their family, friends and they become increasingly unpredictable in performing certain interactions. They often forget what time it is and get lost in a place which is quite familiar to them.
- Restlessness and loosing attention: Major-effect of progressing Alzheimer's is becoming restless and sense of losing attention. Short attention span or also called as the attention deficit hyperactivity disorder (ADHD), often developed in a person suffering from Alzheimer's which leads to loss of acute focus on tasks [17, 18, 19].

2. Causes
Scientists have so far researched and among those researches, many hypothesis have come forward towards their theory for supporting the cause for Alzheimer's disease, some of the important or rather relevant hypothesis/ theories for the cause of Alzheimer's are-

2.1. Amyloid Hypothesis
This is one of the oldest, and the first hypothesis given by the scientists. It was Glenner who first put forward the concept that, amyloid-β protein might be the cause of Alzheimer's disease. It wasn't until the late 90s when a team led by hardy uncovered the first mutation in the gene APP, then in 1996, two more mutations was discovered in the genes that were responsible for encoding the γ-secretase proteins- presenilin 1 (PSEN1) and presenilin 2 (PSEN2) [16]. Mutations in these proteins affect the position where the

γ-secretase cuts the APP gene, this favors the formation of longer improper amyloid-β, and they aggregate with each other forming clumps leading to the formation of amyloid deposits in the brain famously called plaques, leading to severe brain damage or rather called as tangles in the brain [16]. As per to the amyloid hypothesis, aggregation of Aβ in the brain is the main impact driving Alzheimer's pathogenesis. The rest of the disease process, containing development neurofibrillary tangles including tau protein, is suggested to result from a disproportion between Aβ production and Aβ clearance [1]. An experimental vaccine was found to clear the amyloid plaques in human trials but it was not effective on dementia [2]. The amyloid hypothesis has been the mainstream concept underlying in the Alzheimer's research. It basically states that the accumulation and deposition of oligomeric or fibrillar amyloid β (Aβ) peptide is the main cause of Alzheimer's disease. Normally, Aβ is extirpated from APP (Amyloid β protein precursor a membrane-spanning glycoprotein of unknown function) by β- and γ-secretase and released outside the cell, where it is rapidly degraded. But in the aged subjects, the metabolic capability to degrade Aβ is reduced and Aβ peptides may start to accumulate. Aβ 40 and Aβ 42 consisting of 40 and 42 amino acid residues respectively, are the primary components of the accumulation of Aβ. Aβ amyloid fibrils are induced by an increase in the level of Aβ 42 and the accumulated Aβ amyloid fibrils develop into senile plaques which then causes neurotoxicity leading to neurodegeneration [3].

2.2. Tau hypothesis

In 1968, Kosik discovered that NFTs (Neurofibrillary Tangle) were composed of phosphorylated tau proteins. When tau is hyperphosphorylated, it segregates from microtubules and accumulates into paired helical filaments (PHFs) and NFTs. The tau hypothesis puts forward that tau tangle pathology precedes Aβ plaque formation and that tau phosphorylation and accumulation is the major cause of neurodegeneration in Alzheimer's disease [4]. Tau phosphorylation decreases its capability to promote microtubule assembly which then causes neurodegeneration via synaptic dysfunction and neuronal loss. Neurofibrillary tangles can cause neuronal dysfunction and death. While the amyloid hypothesis proposes that tau accumulation happens downward of Aβ accumulation, tau tangles can be found in the brains of patients with very light dementia and no Aβ pathology. Tau pathology also coordinates more closely with AD succession and intensity than Aβ plaque load does [5]. Aβ plaques can occur in people who do not undergo neurodegeneration, the same cannot be said for NFTs, which are seen in frontotemporal dementia and other tauopathies. This may be because amyloid plaques are situated in the extracellular space whereas tau tangles occur within neurons where they can intensely impair axonal transport [6]. Tau-based approaches have shown some great results and there are currently seven anti-tau therapies in phase II trials. Unfortunately, the number of anti-tau therapies put forward, have also proved to fail when it came down to clinical trials. Glycogen synthase kinase 3 beta (GSK-3β) is a protein kinase that enables tau phosphorylation, and is therefore a striking target for anti-tau therapies. However, Tideglusib, a GSK-3β inhibitor, did not show noteworthy clinical benefit in a phase II trial [7]. Methylene blue dye derivatives Trx0014 and LMTM inhibit tau accumulation and appeared to slow cognitive decline in phase III trials [5].

2.3. Cholinergic Hypothesis

Twenty years ago, the cholinergic hypothesis was presented and suggested that a dysfunction of acetylcholine consisting of neurons in the brain contributes to the cognitive decline observed in people with advanced age and Alzheimer's disease. Cholinergic abnormalities might also contribute to noncognitive abnormalities and accumulation of toxic neurotic plaques in Alzheimer's disease. This hypothesis has served as a basis for most of the drug and development and treatment strategies in Alzheimer's disease. The analysis of post mortem enzyme activity should be taken into account and should be assessed within the wide range of cholinergic abnormalities which are known to occur in both aging and Alzheimer's disease. The results of post mortem in both aged humans and Alzheimer's patients propose that a host of cholinergic abnormalities including modifications in choline transport, nicotinic and muscarinic receptor expression, neurotrophin support, acetylcholine release and also axonal transport may all contribute to cognitive abnormalities in aging and Alzheimer's. But some recent studies has shown that choline acetyl transferase/ acetylcholinesterase activity was not affected in the brain of patients with mild cognitive impairment and early stage Alzheimer's disease, which creates a challenge for this hypothesis [8].

2.4. Osaka Mutation

This theory is considered to be the modern, most supported and relevant theory put forward by two scientist Takami Tomiyama and Hiroyuki Shimada from the department of translational neuroscience, Osaka city university graduate school of medicine. In the early stages of diagnosis for Alzheimer's disease, it was found that the start or the onset of this disease was marked by a synaptic dysfunction taking place in the brain due to the clumping of mutated long oligomers of Amyloid-β protein, this was called the amyloid-β protein hypothesis, but this theory or hypothesis didn't have any direct evidence to support this concept of synaptic dysfunction causing cognitive brain impairment in humans. The human affected brain, had both the soluble and insoluble amyloid-β protein (Aβ) coexisted, so it became difficult to determine which pathologies are caused by Aβ oligomers and which are caused by amyloid fibrils. Then with the discovery of Osaka mutation, which was first detected in a Japanese pedigree of familial Alzheimer's disease, amyloid-β protein hypothesis became much clearer [20, 21, 22]. Osaka mutation was caused by the deletion of codon 693 of the APP gene, which resulted in a mutated APP gene lacking the 22nd glutamate [21, 22]. To study this mutation a model of mice was used and the Osaka mutation was not the first mutation to be discovered, in fact, in a Swedish family, studies were carried on the model mice and another mutation called the Arctic mutation in the APP was discovered, which showed signs for the early onset of Alzheimer's disease. After the discovery of arctic mutation, in 2001, an unusual case of hereditary dementia came across, after the examination, the novel APP mutation took place at the same position on the gene as the arctic mutation. This mutation soon came to be called as Osaka mutation (E693Δ) [22]. Osaka mutation showed a unique characteristic that it does not form amyloid fibrils, but showed accelerated

Aβ oligomerization. In 2001, this mutation was discovered in a 57 year old Japanese woman, she was received for diagnosis in the Osaka city university, where she was said to be suffering from mild cognitive impairment (MCI). Her APP, presenilin 1, and presenilin 2 genes were diagnosed and hence this new mutation was discovered on the APP gene. This was considered rather the first deletion-mutation found on the APP gene, where the mutation deleted the codon GAA coding for the 693rd glutamate which corresponded to the 22nd amino acid in the sequence of Aβ protein. Osaka mutational theory was considered as the solid proof for the cause of Alzheimer's disease uniting and supporting all the different hypothesis put forward, thus we can say Osaka mutation is a single explanation for all the other theories and hypothesis put forward.

3. Diagnosis

Breaking the stereotypes with the diagnosis of Alzheimer's disease has been quite a difficult task for scientists over the years, as spoken before science has indeed shown advancement with breakthrough research and discoveries over the ages, but has always lacked when it came to showcasing brain disorders their root cause and diagnosis. Scientists do have made some attempts to diagnose the human brain for Alzheimer's disease, which includes a full assessment of medical and psychiatric history to rule in the possible causes for this disease to occur. Hence, a diagnosis for this disease would include some lab and image-testing, and by the following the methods:

- **Mental status and neuropsychological testing:** The major effects that Alzheimer's disease has on the brain include the disruption of normal ongoing life by affecting the mental status of a sufferer on a devastating level. Neuropsychological tests are carried out for additional insight of a human brain's mental functionality, to check if there is normal functioning and thinking power still enabled or not and then results are compared with the brain of a normal person about similar age and educational level [20, 22].
- **Brain scans/imaging:** This is one of the most important diagnosis method to determine if a person is suffering from Alzheimer's disease or not. Images of brains are taken through MRI scans to study the various abnormal developments such as the shape of the brain taking place due to brain disorders, hence doctors are able to distinguish that if the changes in the brain has taken place due to Alzheimer's or due to some other reason such as stroke or tumors [20].

Now since, under brain scans we have talked about MRI which is used to rule out other brain disorders, the real imaging tool for diagnosing brain diseases or specifically Alzheimer's disease is called the positron emission tomography (PET). This scan involves the injection of a radioactive tracer which is maintained at a low level, into our blood stream, to test for a particular feature or trait of the brain [22, 23]. Now PET has been segregated into the following tests:-

Fluorodeoxyglucose (FDG) PET: These scans are meant to highlight the areas of brain showing low level metabolized nutrients. Now, patterns of degeneration are identified which gives a possible solid hint on Alzheimer's disease as well as other types of dementia.

Amyloid PET imaging: This diagnosing method aims at the measurement of the level of amyloid deposits in the brain. This imaging tool is usually used in the research, but is recommended to be used for a patient suffering from unusual or early onset of dementia symptoms.

Tau Pet imaging: This method helps to determine the level of production of neurofibrillary tangles in the brain which are the clear cause for Alzheimer's disease in the patient. Unfortunately, this testing method is preferred only in the research department and not available for the common masses since it is a very expensive method to carry out.

3. Researches

Researchers are still on it! It has been no hidden truth that brain diseases such as Alzheimer's disease and dementia are 35 years old now and ever since their discovery, scientists and researchers are still researching upon this disease to find the perfect cure or a solid reason for the cause of the dementia and Alzheimer's disease because the age old myth that only people above 60 years of age are suffering from this disease was proven false when a patient named Auguste Deter showed the symptoms of dementia who was aged 40 years at the time and was first diagnosed with dementia at the age 51, early showing of the signs for dementia was described under the name early onset of Alzheimer's disease (EOAD) [23]. Hence researches are still being performed on Alzheimer's and dementia but due to the failure in understanding certain facts such as the actual cause leading to this family of brain diseases under dementia has given the perfect tagline to this disease "Dementia- The Mysterious disease ".Scientists have devised certain models to study Alzheimer's disease, to perfectly strip down the actual affected brain and study the disease on a close perspective. We will also take a look at the breakthrough drugs and the drugs that are still in trial.

4. Model

4.1. 5XFAD (B6SJL)

This is one of the most famous and widely used model, in this model of Alzheimer's disease-

Species Used: Mouse was used as the model to study Alzheimer's disease.

Human Genes to be Examined: APP, PSEN1 were the genes injected in the mutated form in the mouse to study Alzheimer's disease.

Types of Mutations: Following mutations took place in the human genes: APP KM670/671NL (Swedish), APP I716V (Florida), APP V717I (London), PSEN1 M146L (A> C), PSEN1 L286V.

Modifications performed: APP: transgenic, PSEN1: transgenic.

Genetic background of the mouse: C57BL/6 x SJL

Observation

While studying the 5XFAD mouse, it was observed that the human genes inserted in the mouse APP and PSEN1 transgenes, expressed themselves perfectly while showing a total of five mutations directly linked to the cause of Alzheimer's disease. These mutations were described or given the names according to the origin of the place they were first discovered: APP had mutation named the Swedish (K670N/M671L), Florida (I716V), and London (V717I) mutations in APP, whereas mutation in the PSEN1 was named the M146L and L286V mutations. These mutations led to the formation of three lines of mutated transgenic

APP called Tg6799, Tg7031, and Tg7092, out of which TG6799 expressed the highest level of APP gene mutation. Hence TG6799 mice was picked for observation of the APP gene, and it showed many Alzheimer's disease (AD) related phenotypes in the model with the evidence of relative early signs of onset of AD are considered very aggressive [23, 24]. In the beginning of 6 months of its age, the mouse showed neuronal loss in various regions of the brain, accompanied by various cognitive and motor deficits. The aggressive display of the symptoms in females compared to males is due to the fact that APP gene is expressed more in females than in males, which in turn is attributed to the estrogen response element in the thy promoter that drives the overall expression of the transgenes and is also responsible for generating higher levels of Aβ. The intracellular immuno-reactivity observed for Aβ42, co-localized with the cathespin-D, which is responsible for the making of lysosomes and other acidic organelles [24].

Behavior

When put through a test assessing their mental skills such as fear-conditioning test, mental or the memory function was reported to deteriorate at the beginning of 4-5 months of age. To conduct this test, mice were put to training by placing them in a special kind of environment called the novel environment, where they underwent foot-shocks, and to check their memory for this particular event, the mice were returned back to the same environment where they were administered with foot-shocks and the time period for which these mice remained immobilized with fear was recorded. The tests were carried out two times, first was one day after the original administration of the foot-shocks in the novel environment and the next 30 days after, this test was believed to assess the dependent processes of hippocampus and frontal cortex region, respectively [24]. The tests showed that one day after the training the 4 month old 5XFAD mice behaved similarly to non-transgenic mice, however in tests performed after 30 days, 5XFAD mice spent less time being immobilized with fear than did controls. These tests proved that a 4 month old mice had a somewhat normal dependent hippocampal-short term memory function, but memory functions related to the cortex-dependent memory stabilization was found impaired after one month interval between the training procedure and the tests. Whereas, the 6 month old 5XFAD mice showed memory deficits in both the 24 hours and 30 day tests.

Olfactory controlled behaviors was found normal at the beginning of the 4 months of age of the mice but was found impaired by 6 months.

Biomarkers

Biomarkers are usually used in our body to indicate a particular biological process to study or for investigating of any anomalies or unwanted entry of any foreign particle or toxin which is usually difficult to find out. In the 5XFAD mice model of mice, decreased glucose uptake in the olfactory bulb of mice, reported by the end of 3 months with the help of a biomarker ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET). And by the help of this biomarker, hyper-metabolism was observed in various regions of the brain: basal forebrain, basal ganglia, cerebellum, hippocampus, hypothalamus, neocortex, and thalamus, taking place by 6-13 months of age. MRI revealed the 10 percent decrease that took place in the hippocampal volume, by the end of 13 months.

Phenotypic Characteristic changes

Plaques: Around 2 months, reports suggested the formation of extracellular amyloid deposition, slowly progressing first in the subiculum leading all the way to the V of the cortex. Accumulation of aggregates of Aβ42 intra-neuronally within the soma and neuritis starting at 1.5months of age.

Tangles: Tangles are reportedly absent in this model of mice.

Neuronal loss: Around the places in cortical layer V and subiculum.

Gliosis: Onset of gliosis at the beginning of 2 months mark.

Synaptic loss: Reported levels of decline in the presynaptic marker synaptophysin at the end of 4 months, this decline was accompanied by the decline of another presynaptic marker syntaxin as well as the postsynaptic marker PSD-95 by the end of 9 months.

Changes in the LTP/LTD: Deterioration begins in the basal synaptic transmission and LTP in the hippocampal region of the brain, in between the 4 and 6 months mark.

Cognitive impairment: When the mice went through the Y-maze test, showed signs of impaired spatial working memory as well as impaired remote memory stabilization in the contextual fear conditioning test, by the age of 4-5 months.

4.2. Breakthrough drugs

4.2.1. Flurizan

Flurizan is the R-enantiomer of the nonsteroidal anti-inflammatory flurbiprofen, an NSAID that is structurally and pharmacologically related to ibuprofen and is used to treat various inflammatory conditions. As a selective Aβ42-lowering agent, Flurizan would have been the first in its category to treat Alzheimer's disease. The principle for testing Flurizan in Alzheimer's is that it can regulate γ-secretase, the enzyme complex that cleaves the Aβ peptide off its precursor protein, to critically decrease generation of long, aggregation-prone forms of Aβ without influencing γ-secretase cleavage of other substrates, such as Notch. Epidemiological research has depicted that long-term use of NSAIDs is related with a decreased possibility for growth of Alzheimer disease. In disparity to S-fluriprofen, the R-enantiomer is not active toward the cyclooxygenase enzyme, and therefore causes lesser gastrointestinal side effects. In cell-based and animal studies, Flurizan has been depicted to lower Aβ42, likely through a direct consequence on y-secretase [10]. The presenilin constituent of the y-secretase intramembrane complex is thought to be the aim of Flurizan's pursuit [11].

4.2.2. Adacanumab

BIIB037 is a high-empathy, fully human IgG1 monoclonal antibody against a cooperative embodiment found on Aβ. It was initially obtained by the biotech company Neurimmune in Schlieren, Switzerland, from healthy, aged donors who were cognitively normal. The principle was these donors' immune systems had affluently endured Alzheimer's disease, and that the functioning antibodies could be turned into therapeutics by a procedure called reverse translational medicine. BIIB037 tethers accumulated forms of Aβ, not monomer. In the brain, BIIB037 specially ties up parenchymal over vascular amyloid. Thirteen-week chronic dosing in old APP-transgenic mice decreased plaques of all

sizes; vascular amyloid remained unchanged. Brain-exposure studies in mice propose that micro hemorrhages start at 500 mg/kg, more than 100 times the slightest effectual dose for plaque clearance, 3 mg/kg [12].

4.3. Drug studies ongoing:

4.3.1. BAN2401

BAN2401 is the **humanized IgG1** category of the mouse monoclonal antibody mAb158, which critically coheres to large, soluble Aβ protofibrils. The therapeutic antibody was initially developed at the biotech company BioArctic Neuroscience succeeding the finding of the Arctic mutation in APP, which gives rise to a form of clinically typical Alzheimer's that is marked by specifically high levels of Aβ protofibrils and corresponding deficiency of amyloid plaques [13]. M AB158 was found to decrease Aβ protofibrils in brain and CSF of Tg-ArcSwe mice [14]. A multicenter.

4.3.2 Gatenerumab

Gantenerumab is a fully **human IgG1 antibody** objected to tie up with subnanomolar affinity to a conformational epitope on Aβ fibrils. It encloses both N-terminal and central amino acids of Aβ. The therapeutic principle for this antibody is that it acts centrally to separate and deteriorate amyloid plaques by enlisting microglia and stimulating phagocytosis. Gantenerumab favourably links with accumulated brain Aβ, both parenchymal and vascular. The antibody interdicts phagocytosis of human Aβ deposits in AD brain slices co-cultured with human macrophages. It also counteracts oligomeric Aβ42-mediated inhibitory consequences on long-term potentiation in rat brains. In APP/PS-1 transgenic mice, gantenerumab ties up to cerebral Aβ, decreases small plaques by enlisting microglia, and averts new plaque formation. Gantenerumab does not change plasma Aβ [15]. It has been studied as a capable amalgamation therapy with the Roche BACE inhibitor RG7129 in mouse models of Aβ amyloidosis [16].

5. Conclusion

Alzheimer's disease also dubbed as "The virus of the brain" is a part of a larger family of brain diseases under their main head that is dementia. So far, by what we have researched and seen, Alzheimer's has proven to be the one consistent problem for a human being since its discovery 114 years ago. Alzheimer's has had a rich history, it is named after Dr. Alois Alzheimer in 1906, and since then has been the cause of death for over 5.8 million people in America alone between the year 2000-2018 and has been predicted that the total cases by the end of mid-century is estimated to record a steep increase by 13.8 million patients. Looking back, scientists still haven't drawn a conclusion themselves, regarding the real cause of Alzheimer's and until and unless a real root cause for Alzheimer's has been shown or rather proven to be, Alzheimer's cannot be treated properly or a solid treatment, plan/cure cannot be devised. Till now, the Amyloid-β protein hypothesis prevails all the other hypothesis, but different hypothesis and their concepts have had their own share of contribution, but a solid treatment method is yet to be discovered. All in all, we can conclude that still the research is going on regarding treatment or a permanent cure for the patients suffering from Alzheimer's and dementia, there still remain some unanswered questions to this mysterious disease i.e. Alzheimer's disease:

- It is unclear whether inflammation is a result of having Alzheimer's disease, or whether the inflammatory process plays a role in its development.
- How do brain cells die once amyloid plaque gets deposited?
- What is the relationship between the plaques and the tangles found in the brain?
- Why are certain regions of the brain more vulnerable to Alzheimer's disease? Scientists do not understand why there are different presentations of the disease.
- What exactly causes Alzheimer's? There is not yet a sure way to find out why one develops Alzheimer's.

Scientists have not yet been able to find a cure for this disease. There is no proper medication or diagnosis for Alzheimer's.

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