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Focused ultrasound microbubble therapy in the treatment of Alzheimer's disease

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Abstract: Alzheimer's disease is the leading neurodegenerative disorder. It is notorious for imposing an immense burden on the community and health care system. In this article, we briefly elucidate the pathophysiology of Alzheimer's disease along with its rates. Then we described the current drug treatments for it followed by the obstacle created by the blood-brain barrier to transfer these drugs in an effective concentration to the brain. Finally, we discussed how focused ultrasound microbubble therapy could be the best solution to solve the problem created by the blood-brain barrier.

Index Terms **- Microbubbles, Ultrasound, Blood brain barrier, Alzheimer, Targeted drug delivery.**

I. INTRODUCTION

Alzheimer's disease is a neurodegenerative disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks [1]. Alzheimer's disease is the most common form of dementia and may contribute to 60-70% of cases [2]. In 2019, Alzheimer's disease and other forms of dementia ranked as the 7th leading cause of death by WHO. Globally, 65% of deaths from Alzheimer's and other forms of dementia are women [3]. An estimated 6.5 million Americans age 65 and older are living with Alzheimer today, this number could go to 13.8 million by 2060. More than 11 million family members and other unpaid caregivers provided an estimated 16 billion hours of care to people with Alzheimer's and other dementias in 2021 [4].

II. PATHOPHYSIOLOGY OF ALZHEIMER

The neuropathological hallmarks of Alzheimer disease include "positive" lesions such as amyloid plaques and cerebral amyloid angiopathy, neurofibrillary tangles, and glial responses, and "negative" lesions such as neuronal and synaptic loss [5]. Out of these, two major lesions are amyloid plaques and neurofibrillary tangles. Plaques composed mainly of amyloid-β (Aβ) peptides and tangles caused due to hyperphosphorylated tau [6]. In Alzheimer's disease, plaques and tangles form in cortical and limbic areas of the human brain and disturb the communication between neurons, which may result in the apoptosis of neurons in the brain. Because of this patient starts to show dementia and progressive neurocognitive dysfunction [7]

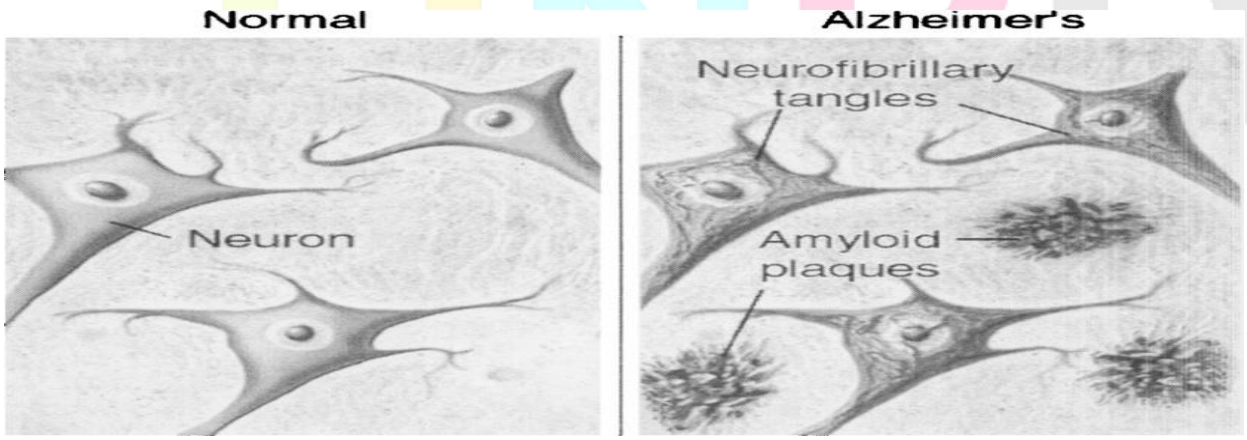


Fig.1. Amyloid plaques and neurofibrillary tangles in the brain of Alzheimer patient [8]

III. CURRENT DRUG THERAPIES ON ALZHIMER.

Despite the vast number of Alzheimer's disease patients, currently there is no cure for Alzheimer. Current medications in the market which are approved by USFDA such as Donepezil, rivastigmine, galantamine, memantine etc. may help to reduce the symptoms but cannot change the underlying disease process [9]. However, Aduhelm (aducanumab) is the first disease-modifying

drug approved by the FDA on 7 June 2021 to treat Alzheimer's disease. The medication helps to reduce amyloid plaque in the brain. It is the first new treatment approved for Alzheimer's since 2003 and is the first therapy that targets the fundamental pathophysiology of the disease. Aducanumab was approved through FDA's 'Accelerated approval pathway' which can be used for a drug on a serious or life-threatening illness that provides a meaningful therapeutic advantage over existing treatments [10]. This pathway requires an additional study after approval to confirm the anticipated clinical benefit. If the follow-up trial fails to verify clinical benefit, the FDA may withdraw approval of this drug. Results of the phase 4 clinical trial for aducanumab are expected to be available by early 2030 [9]. Even though drugs are available, it is still difficult to minimize the Alzheimer's symptom because of the hurdle created by blood brain barrier.

III. BLOOD-BRAIN BARRIER

The blood-brain barrier (BBB) is a continuous endothelial membrane within brain micro vessels that has tight junctions and is covered by mural vascular cells and perivascular astrocyte end-feet. The blood-brain barrier (BBB) has a highly selective semi permeability which is helpful to maintain homeostasis inside the brain and protect neurons from pathogens and toxins present in systemic circulation [11]. But BBB has one downside. Because of the highly selective semi-permeability of the blood-brain barrier, several large molecular drugs cannot reach a therapeutic level in the brain to treat Alzheimer. Thus, administration of the drugs in a higher dose to get effective results becomes inevitable and it may give rise to systemic adverse effects and higher costs for the patient [12]

IV. FOCUSED ULTRASOUND MICROBUBBLE THERAPY [FUS-MB]

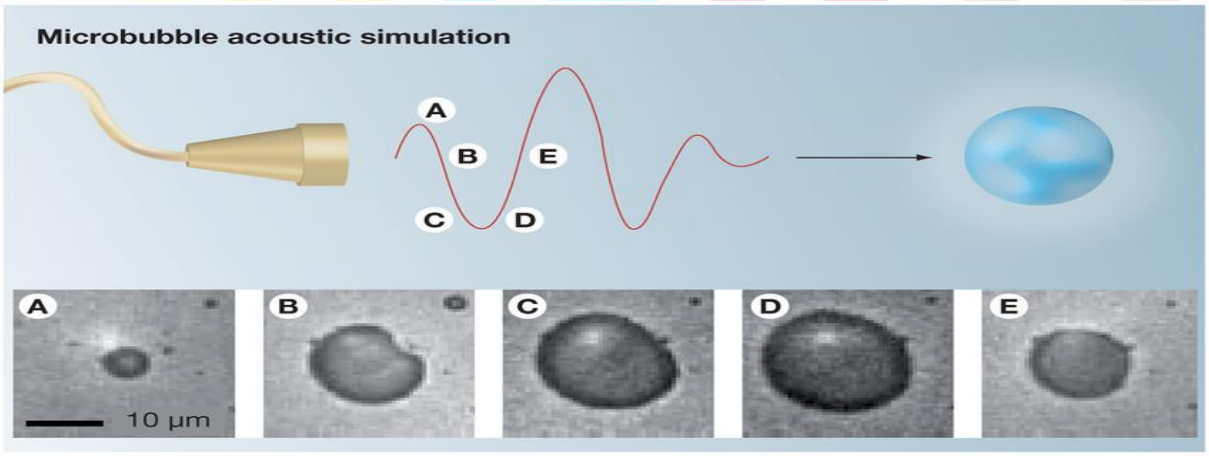
This therapy can be helpful to overcome the obstacle created by BBB while treating Alzheimer's disease using drugs. In this therapy microbubbles coupled with focused ultrasound use to treat the Alzheimer. The diameter of a microbubble is approximately equal to the size of a red blood cell (less than ~10 μm diameter). The shell of the microbubbles is made up of surfactants, lipids, proteins, polymers, or a combination of these materials. This shell provides stability to microbubbles against surface tension. The inside part of microbubbles (MB) is made up of gas. This gas core provides mechanism for ultrasound backscatter and drug delivery [13].

Focused ultrasound microbubble therapy works mainly in two ways.

1] *FUS-MB with drug =*

In this type, the drug is filled within the gas cavity of MB or attached to the shell of MB and then injected intravenously into the Alzheimer's patient. After this injection, the patient gets exposed to the ultrasound waves which are generated by MRI guided transducer array fitted around the head of the patient. Microbubbles get affected by ultrasound and they start to behave depending on the intensity of the ultrasound's acoustic pressure. When the acoustic pressure is low, insonified microbubbles produce a backscattered echo. This echo can be used to detect and locate microbubbles [13]. Once the MB reaches BBB the intensity of the ultrasound increased and the low acoustic pressure gets converted into the Oscillating pressure. At Oscillating pressure, microbubbles undergo stable cavitation (expansion and contraction without bursting) within the blood vessels. Cavitation of microbubbles generates mechanical pressure on the BBB and it opens the tight junctions of the BBB. Cavitation also leads to the bursting of microbubbles and the release of a drug into the brain through the paracellular and transcellular mechanisms [12]. This technique of using ultrasound frequencies to modify the permeability of BBB is known as Sonoporation. Moreover, Microbubbles oscillation near BBB can cause hyperpolarization of the BBB which promotes the endocytosis of large drug molecules [13].

Fig.2. Microbubble acoustic simulation [14]



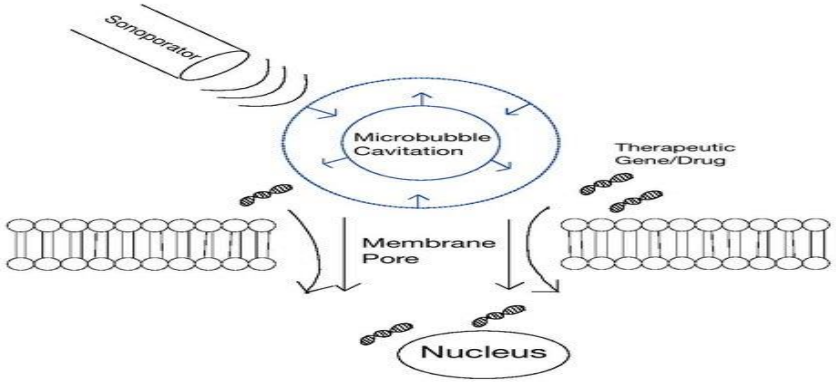


Fig.3. Schematic of Sonoporation mechanism [15]

2] *FUS-MB without drug* =

Focused ultrasound microbubble therapy alone is effective to reduce amyloid plaques and neurofibrillary tangle's pressure even without the administration of drugs along with it. FUS-MB without drug also allow the infiltration of systemic phagocytic immune cells into the brain. Furthermore, it activates astrocytes and microglia surrounding Aβ plaque [12]

Advantages of Focused ultrasound microbubble therapy =

- Reduce amyloid plaques and neurofibrillary tangles
- Non-invasive method
- Local drug delivery
- Reversible BBB opening
- Safe and effective [16]
- Minimize the dose of Drug
- Prevent systemic adverse effects of drug
- Lower the treatment cost
- Induce neurogenesis
- Enhance neural plasticity
- Increase cholinergic function [12]

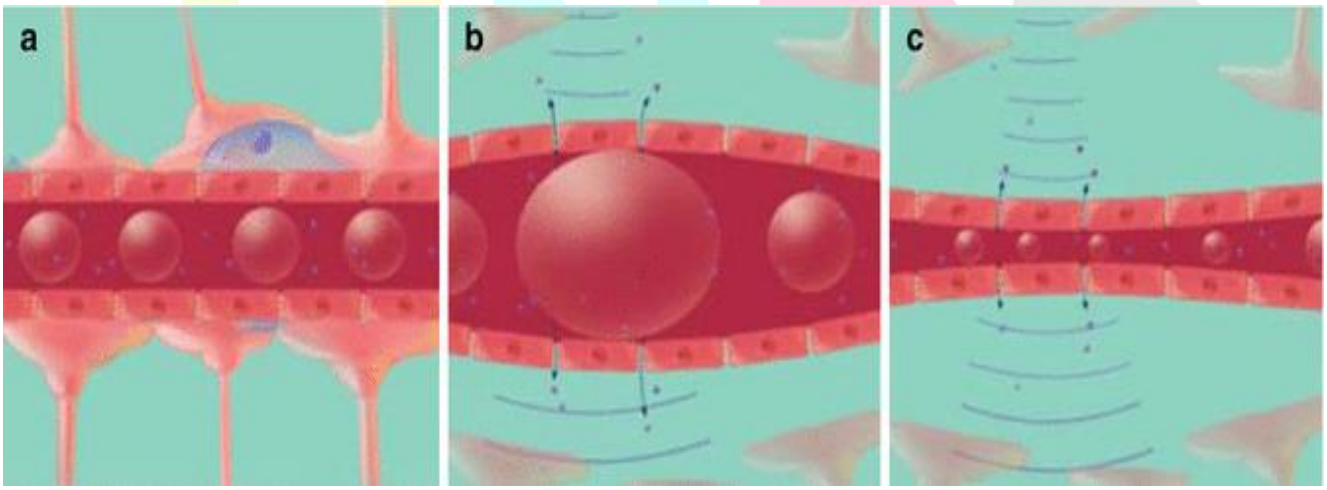


Fig.4. (**a**) Microbubbles flow through the vasculature. (**b**) When ultrasound is applied, the microbubbles expand and (**c**) contract at the frequency of the ultrasound [17]

V. CONCLUSION

Alzheimer's disease is the 7th leading cause of death worldwide. Still, there are no treatments to cure it completely. The blood-brain barrier is the major obstacle to the current therapies which are available for Alzheimer's disease. Focused ultrasound microbubble therapy empowers us to effectively transport the drug to the brain without harming the blood-brain barrier. However, Focused ultrasound microbubble therapy is in its infancy. Although FUS-MB therapy without therapeutic substances has been used on humans in recent years, there are currently no studies using FUS-MB to deliver drugs to patients with Alzheimer's disease. Advancement in the FUS-MB therapy is much required to cure Alzheimer's disease efficiently.

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