



NEURODEGENERATION DUE TO INSULIN RESISTANCE IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's Disease (AD) is a neurodegenerative disorder in which there will be decrease in the memory and cognition impairment. This was 1st described by in 1906. The name Alzheimer's disease is coined by after the name of the scientist Dr. Alois Alzheimer. AD is characterised by the accumulation of Amyloid beta peptides (A β) plaques extracellularly and there will be intracellular aggregation of Neurofibrillary Tangles (NFTS). NFTS are formed due to tau protein hyperphosphorylation. This accumulation of NFTS and plaques leads to necrosis of the brain tissue. There is growing evidence that interlink between Diabetes Mellitus type II (DM type II) and AD. There is almost doubled risk of AD for the patients with type II DM insulin resistance in DM type II is the underlying mechanism for the occurrence of AD in type II DM patients. Insulin is helpful for the dendritic sprouting, cell repair and growth. Hence insulin helps in maintaining the healthy neuronal tissue. With the insulin resistance there will be inhibition of the insulin degrading enzyme. This enzyme is useful for the degradation of the insulin as well as A β s in the brain tissue. As insulin degrading enzyme is inhibited there will be amyloid beta cells in the brain tissue, which ultimately leads to damage of the brain tissue.

KEYWORDS: Alzheimer's Disease (AD), Amyloid beta peptides (A β) plaques, Neurofibrillary tangles (NFTS), Intranasal (NAS) insulin and Diabetes Mellitus type II.

INTRODUCTION

The term AD was named after the German physician "Dr. Alois Alzheimer". There are 2 - forms of AD;

1. Familial form of AD (early stage) – It has symptoms like confusion, lapses of short-term memory loss, mood swings and these subjects are more withdrawn (it is a very rare form of the disease that occurs in people between the age of 30 - 60 years).

2. Sporadic form of AD - Is late onset AD which has symptoms like that of the early onset AD. This usually occurs at the age of 60 years and above.

In this disease there will be accumulation of Amyloid beta peptides (A β) extracellularly and Neurofibrillary Tangles (NFTs) intracellularly in the brain tissue. Accumulation of NFTs occurs due to hyper phosphorylation of tau proteins. Accumulation of NFTs and amyloid beta proteins leads to necrosis of the brain tissue.^[1]

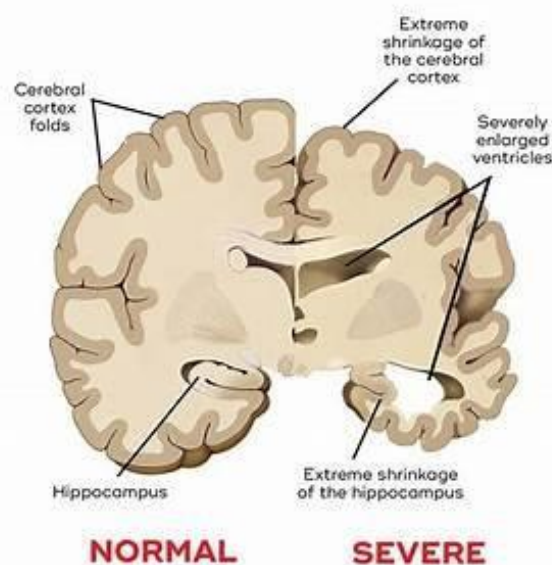


Figure 1: Normal Brain (Vs) Alzheimer'S.

Epidemiology: The prevalence of AD from a pooled data collection from the European countries shown that the prevalence rate of AD in people above the age of 65 years is 6.4 %, whereas in united states the prevalence of AD in people of age above 70 years is 9.7 %. The global prevalence of dementia is 24 million and is predicted that the count may get doubled after 20 years. From the cohort studies since last 9 years, it was revealed that development of AD is 65 % higher in diabetic patients when compared to non-diabetic patients. It was noticed that 46 % of the people with AD has glucose intolerance.^[2]

Causes: The causes that start the process of AD are not exactly known. Scientists concluded that AD starts even before the onset of symptoms. The various risk factors for AD are;

Age: The most significant factor for AD is age. The chances of getting AD doubles with increase in the age of 5 yrs after reaching 65 years. Even underage of 65 years there are chances of getting Alzheimer's (1 out of 20 Alzheimer's patients are under the age 65 years.) this type of Alzheimer's is known as Young onset Alzheimer's.

Family history: There is risk of getting AD if the parents are with AD. But the incidence risk is very small. But in some cases, inheritance of even a single gene can pass the disease to children.

Downs syndrome: People who are at the risk of developing Down's syndrome also have the risk of developing the AD. The reason is when there is downs syndrome it causes accumulation of A β plaques, which leads to brain tissue damage.^[3]

Head injury: Past history of head injury is found to be one of the causes for AD.

Cardio Vascular Diseases (CVD): Although the reasons are unknown CVDs are found to be risk factors for the AD. This includes smoking, obesity, diabetes, high blood pressure, high cholesterol.^[4]

Other risk factors: These factors may not be responsible directly for dementia; researchers found that the risk of getting AD with these factors increases. They are hearing loss, depression, loneliness and sedentary life style.

Symptoms: Although the symptoms of Alzheimer's seem to be mild in the starting of the disease, with time it gets worsen. Symptoms vary with person to person. Any 2 people with AD may not have unique symptoms. There early signs of AD are memory loss. Memory loss increases as the time passes. This occurs as AD 1st affects the hippocampus as the Alzheimer's progresses the memory loss will be in the following ways;

- Loose items or things in a room or in a house (keys, medicine, glasses etc....)
- Forgetting words within a conversation.
- Forgetting the recent conversations/discussions with the family.
- Getting lost in journeys with the families or in family events.
- Forgetting important event

There will be other problems in the aspects of thinking, perception, communication and reasoning. Problems may arise in the areas of;

- **Language** - repeating the words, struggling to follow the instructions.
- **Navigating** - climbing stairs, parking cars, estimation of distance and visualization of things in 3 - dimensions become harder.
- **Concentrating** - difficulty in focusing on things.
- **Planning and organization** - people with AD can't make decisions, can't solve the problems and can't do tasks like cooking etc....
- **Orientation** - forgets days and dates.
- At the early stages Alzheimer's patients also have mood disturbances like depression, anxiety, irritability. Many patients' loose interest in hobbies and activities.

Later changes: As the disease progresses, there will be communication, reasoning and orientation severity. At this condition like Alzheimer's subjects need support from care takers. At this stage there will be; 1. Delusions/hallucinations 2. Agitations (restlessness/pacing). 3. Disturbance in sleep 4. Calling out 5. Repeating the words 6. Person becomes increasingly frail.

Mixed dementia: The Alzheimer's subjects will have more than one type of dementia. It occurs with more than 10 % of subjects having AD.

Atypical AD: In some subjects the primary symptom of AD is not memory loss. But will be one of the following;^[5]

Posterior cortical atrophy: In this condition there will be damage to the back and the upper rare areas of the brain. Therefore, there will be decrease in vision and problem in identifying objects, but eyes seem to be healthy and walk will be staggered.

Logo genic aphasia: There will be damage to the left side of the brain that produces language. Hence, there will be changes in changes in language or speech with long phase.

Frontal variant Alzheimer's: In this there will be frontal lobe damages of the brain which leads to alteration in decision making and planning.

Diagnostic procedures: There are various methods of diagnosing AD. They are;

General examination: Physician will ask the person suffering with AD and his family members about overall health, whether the person following the prescription and OTC medications, diet followed by the patient, past medication history of the patient, observation changes in the behaviour and personality.

Standard scales: There are some standard scales to assess the AD they are;

- Alzheimer's Disease Assessment Scale (ADAS)
- Non-cognitive versus cognitive scale (Cog)
- The Blessed Dementia Scale (BDS)
- Behaviour Rating Scale For Dementia (BRSD)
- Clinical Dementia Rating (CDR)
- Blessed Information Memory Concentration (BIMC)

Alzheimer's Disease Assessment Scale (ADAS): This clinical rating scale consists of 22 questions to measure the changes in daily activities (consists of 8 items out of 22); whereas self-care habits have a total score of 3 and changes in personality, interests and drives has the score of 11. This scale is used to assess the behavioural dysfunction and cognitive characteristics of AD. It has 2 - sub-scales:

Alzheimer's disease assessment scale (ADAS) - Cognitive subscale

Alzheimer's disease assessment scale (ADAS) - Non-cognitive subscale

Behaviour rating scale for dementia (BRSD): It is a standardized clinical instrument that is used to rate the behavioural changes in the dementia and Alzheimer's patient. In this scale the frequency of the psychological behaviour is used to assess the dementia of the patient.

Clinical Dementia Rating (CDR) scale: In this scale the ratings range between 0 – 5. This scale is used to assess the dementia of the patient.

- ✓ 0 = absent
- ✓ 0.5 = questionable
- ✓ 1 = present but mild
- ✓ 2 = moderate
- ✓ 3 = severe
- ✓ 4 = profound
- ✓ 5 = terminal

The Blessed Dementia Scale (BDS): This scale was developed by Blessed and his colleagues in 1968 to measure the intellectual and personality deterioration in the Alzheimer's patient. The total score of this scale is 28 and the score of above 4 is dementia.

Neuroimaging techniques: These are used to know certain changes in the areas of the brain. Among them most widely used techniques are:

CT (computerized tomography) & MRI (magnetic resonance imaging).

The imaging techniques are used to rule out the causes of the dementia (may be due to stroke, tumour, or fluid build-up in the brain).

Fluorodeoxyglucose (FDG) - Positron Emission Tomography (PET) [FDG-PET] scans of brain: This test is done to analyse the intracellular clumps that aggregates in the drug. This test is done using radioactive drug (fluoro-deoxy glucose).

NEUROPATHOPHYSIOLOGY: AD is a form of dementia in which there will be accumulation of neuronal plaques and tangles which leads to neuronal death and there by damage to the brain tissue.^[6]

Several trials have been made to treat the AD using the above pathological mechanisms unfortunately, these have not resulted in successful treatment.⁷ Therefore, and the major risk AD was being focused on the DM is important one. There is Evidence that there is close relationship between the DM type II and the risk of getting AD is double in patients with DM.^[8]

The mechanism is not completely known but Insulin resistance is found to be the main cause due to type II DM there will be Insulin resistance and higher levels of insulin in blood.^[9] Due to hyperinsulinemia brains insulin levels decreases through a compensatory mechanism, as the insulin signalling reduces, there will reduction in the insulin the insulin degrading enzyme. Hence there will be competitive Inhibition of Insulin degradation enzyme that leads to accumulation of Amyloid beta peptides (A β) proteins.^[10]

A total of 130 subjects having Alzheimer's disease were studied to evaluate the effects of Liraglutide in AD. The mean age of the population is 71 $\pm$ 7 years. This study demonstrated that in non-diabetic population of AD, AD has led to decreased glucose metabolisms in brain.^[11] Also, there will be grey matter atrophy. This study also showed that the insulin resistance may precede the AD.

Insulin role in Normal Brain Function: Fast acting insulin analogue - Aspart was given to the healthy participants, Intranasally (NAS) for 8 weeks. A word list was given to the participants and asked to 1 week later. This showed that insulin improved declarative memory, a hippocampus dependent function. Also, after single intranasal application of insulin led to the activation of frontal cortex which further led to improved verbal working memory.^[12]

Working of Intranasal (NAS) insulin in cognitively impaired patients

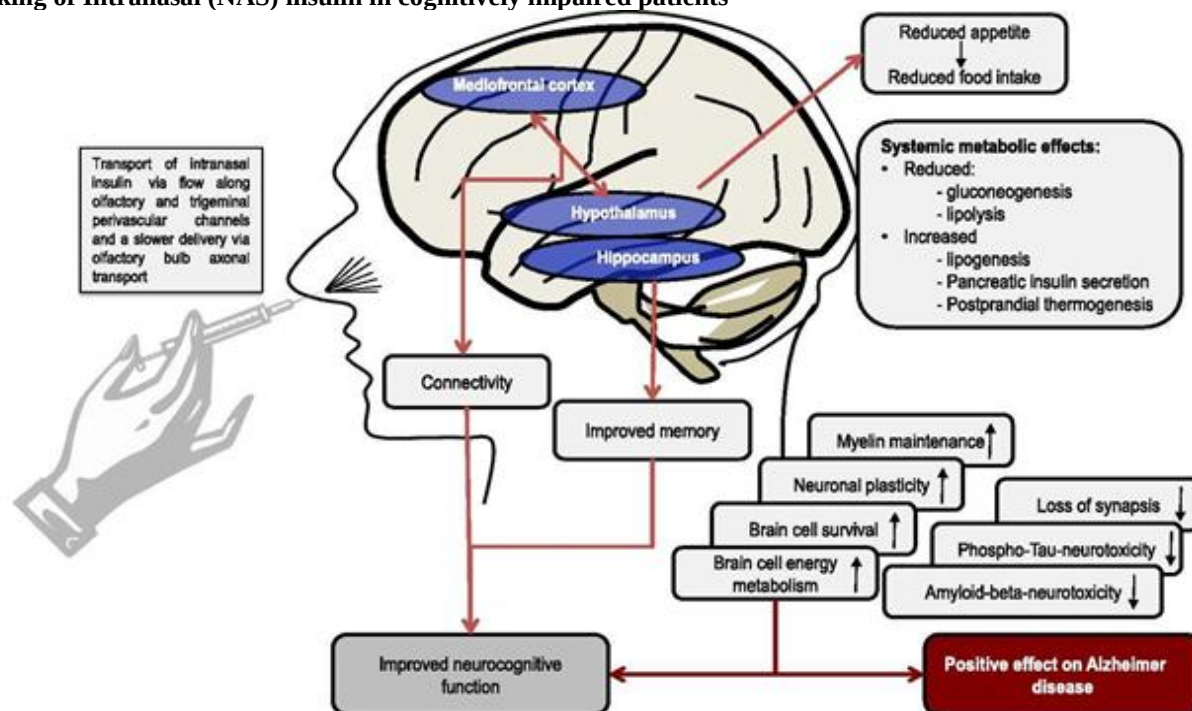


Figure 2: Effect of Insulin In Improving Alzheimers Disease Symptoms.

When AD and mild cognitively impaired patients were given NAS insulin, they improved memory and cognitive function. However, insulin failed to work in patients carrying APOEε4 allele, which is responsible for genetically occurrence of AD. Also, there is development in orientation, social interactions, home activities, speech, personal care, judgement of the patient. The functional ability of the patient is also preserved through intranasal insulin. And these benefits of the insulin were estimated by the caregiver ratings.^[13] With the help of PET imaging techniques, it was found that the uptake of fluorodeoxyglucose in parietotemporal, frontal, praecuneus and cuneus regions of brain is more in patients who took NAS insulin when compared to that of the patients who were given placebo.^[14]

Studies have been conducted to show the central neuro protective action of insulin, which helps in improving the memory (benefitting hippocampus-dependent declarative memory). It showed that direct delivery of the insulin to brain through Blood Brain Barrier (BBB) may modulate the Central Nervous System (CNS).^[15] A randomized, double-blind, placebo-controlled study in which the sample consisted of 104 adults of which 64 are amnesic with mild cognitive impairment and 40 members are having mild to moderate AD for 4 months. Of all the 104 members patients treated with placebo are 30 members, 36 subjects were given 20 IU insulin and 38 subjects

were given 40 IU insulin. The study concluded that the patient receiving the longer trails of NAS insulin has shown improvement in amnesic mild cognitive impairment.

Different dosage forms of insulin used in NAS delivery of insulin in AD: By giving insulin intranasally it transports via the olfactory epithelium and along olfactory and trigeminal nerve pathways from the nasal cavity to the brain. The intranasal administration of insulin improves cognition in humans; hence, acting as a cognition enhancer.¹⁶ Intranasally there will be rapid transport of the drug by passing the BBB. As per the published studies the NAS administration of insulin does not cause any nasal irritation.¹³ Manual nasal pump spray atomiser is used as delivery device to administer NAS insulin.

Table 1: Different dosage forms of insulin used in NAS delivery of insulin in AD.

LIPOSOMES				
Study	Compound	Formulation	Particle Size	Outcome
Preclinical/ Rodents	Galantamine HBr	phosphatidylcholine, cholesterol, propylene glycol	112 ± 8 nm	8 - fold increase of AUC compared to free drug via N2B; 4 - fold increase compared to oral delivery.
Preclinical/ Rodents	Rivastigmine	Cholesterol, soy lecithin	10 ± 2.8 µm	3 - fold increase of AUC compared to free drug via N2B; 5 - fold increase compared to oral delivery.
Preclinical/ Rodents	Ovalbumin as surrogate for protein therapeutics	Dioleoylphosphatidylcholine, cholesterol, stearylamine	299 ± 26.4 nm	> 4 - fold higher AUC brain/AUC blood for the liposomal formulation compared to the PBS preparation.
NANOPARTICLES				
Preclinical/ Rodents	Insulin (for blood glucose management)	Glycopolymer poly (2l actobionamidoethyl methacrylate – r – 3 - acrylamidophenylboronic acid) p (LAMA – r - AAPBA) 2:1	289.4 ± 2.5 nm	80 % decrease of peripheral blood glucose levels with Nanoparticles, 4 - fold increase compared to PBS formulation.
GELS				
Preclinical (Rodents) and clinical (humans) study	Insulin (for blood glucose management)	Carbopol 934P and hydroxypropyl methylcellulose	Prolonged effect on blood glucose levels in rodents; decrease of blood glucose levels by 20 % with nasal gel, no control group for comparison.	
Preclinical/ Rodents	Insulin (for blood glucose management)	tosan and polyvinyl alcohol (PVA)	Prolonged 60 % decrease of peripheral blood glucose levels with gel formulation.	

Note: Area under the Curve (AUC), Phosphate-Buffered Saline (PBS)

CONCLUSION

From various studies it was concluded that in patients having resistance of insulin into the BBB there will be double the risk of neurodegeneration. Insulin is necessary for dendritic sprouting, neuronal cell activation, cell growth and repair. Therefore, usage of insulin in the management of AD disease may be helpful. Hence, there is growing evidence that novel delivery of insulin into the BBB may be effective in the treatment of the AD. From various studies it was found that the longer trails of intranasal (NAS) insulin have shown improvement in amnesic mild cognitive impairment.

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