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Original Research Paper

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INSULIN LIKE GROWTH FACTOR-I LEVEL IN ALZHEIMER'S DISEASE IN RURAL REGION OF VIDARBHA, MAHARASHTRA, INDIA

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ABSTRACT

Alzheimer's disease is a multifarious neurodegenerative disorder which is characterised by deposition of intracellular neurofibrillary tangles and extracellular amyloidal protein which contributes to senile plaques. Our aim is to see serum IGF-I level in the patients of Alzheimer's disease. Total sample size was 100, Age group between 60-80 years, which was divided into 50 study group with the diagnosed Alzheimer's disease cases who attended the Psychiatry OPD of AVBRH Hospital and 50 age and sex matched healthy controls included in the study. The serum IGF-I level was lower in cases as compared to controls. Our study concluded that lower IGF-I levels is the risk factor for the disease progression.

KEYWORDS : Alzheimer's disease, Insulin like growth factor 1, Dementia.

INTRODUCTION

Insulin-like growth factor 1 (IGF-1) is a 7.5kDa peptide hormone produced primarily in the liver and also in smaller quantities in other organs such as the brain.[1] IGF-1 production in the liver is regulated by growth hormone secreted by the pituitary gland. In serum, IGF-1 binds to a family of insulin-like growth factor binding proteins (IGBPs) that extend its serum half-life. The primary target of IGF-1 is the IGF-1 receptor (IGF-1R), but can also activate the insulin receptor.[2] Downstream targets of IGF-1R include activation of the MAPK/ERK and PI3K/AKT pathways, which results in pro-growth and anti-apoptotic signals.[3] IGF-1 levels are high at a young age and then slowly decrease until death.[4] Excess IGF-1 can result in acromegaly, a condition characterized by excessive growth, while lack of IGF-1 can result in dwarfism.[5-6] Increased IGF-1 is also linked to a high risk for certain cancers, likely due to enhancement of cell proliferation.[7] IGF-1 serum levels are reduced in diabetes.[8] IGF-1 plays an important role in neurogenesis and neurodevelopment, and abundant IGF-1 receptors are expressed in the brain.[9]

Hippocampal IGF-1 levels are positively correlated with serum IGF-1 levels and in otherwise healthy rats increasing the level of the latter will result in an increase in the former.[10] Brain IGF-1 is important for cognitive function and may stimulate neurogenesis.[11] Glucose metabolism in the brain is also regulated by IGF-1 and IGF-1R, and a reduction of signaling in this pathway decreases GLUT4 expression and glucose utilization.[12-14] Low serum levels caused by rare mutations in the IGF-1 gene lead to declined cognitive abilities that can be restored by supplementation with recombinant IGF-1.[15] IGF-1 levels also decrease with age[16] and in diabetes[17], both coinciding with declined cognitive abilities. IGF-1 regulates the signaling pathways that are altered in Alzheimer's disease (AD). IGF-1 enhances the survival of neurons that have been exposed to beta amyloid and inhibits tau phosphorylation through the inhibition of GSK-3β.[18-19] Furthermore, the IGF-1 pathway is dysregulated in AD, with alterations in both the levels and phosphorylation state of IGF-1R as well as the levels of IGF-1 and IGF-1R mRNA in the brain.[20] This dysregulation appears to be progressive, becoming more severe as the disease continues. Animal models of AD have been used to study the relationship between IGF-1 and AD in vivo. In vivo animal studies suggest that IGF-1 is an important mediator in the clearance and regulation of beta amyloid in the brain.[21] The goal of our study is to provide an insight and comprehensive analysis of the relationship between serum IGF-1 and Alzheimer's disease in humans. The study was carried out in the Department of Biochemistry in association with Department of Psychiatry, Jawaharlal Nehru Medical College and Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha, Maharashtra, India.

MATERIALS AND METHOD

A comparative and cross-sectional study was conducted. Institutional Ethics Committee approved the study. The study was done from August 2018 to February 2019, total sample size 100 including males and females and divided into two groups. Informed written consent was taken for the study purpose. 50 study group with Alzheimer's disease who attended the outpatient clinic of the Psychiatry Department of AVBRH Hospital, Sawangi (Meghe), Wardha, India and 50 age and sex matched healthy controls. All patients with known history of Alzheimer's disease within the age group of 60-80 years included in the study. Information about subject's age, sex, lifestyle, hypertension, family history of diabetes and other chronic diseases/disorders were written in pre-design format.

Estimation of serum IGF-I :

Quantitative measurement of serum IGF-I was done by competitive ELISA.

SAMPLE COLLECTION

Blood samples were collected from patient upon admission taking all aseptic precautions, about 5 mL of blood was drawn by venipuncture from a peripheral vein, with a disposable syringe and thereafter transferred to a clean dry glass tube where it was allowed to stand for 30 minutes for retraction of clot. This was centrifuged at 3000 rpm for 10 minutes to separate the serum. The serum sample was stored at -20°C in the refrigerator for analysis. Care was taken to avoid haemolysis of sample.

Inclusion criteria:

All the study subjects were diagnosed by the consultant psychiatric according to DSM IV and NINCDS-ADRDA criteria.[22]

Exclusion criteria:

Patient suffering from any significant comorbid physical illness, clinically diagnosed DSM V psychiatric illness, any nutrition deficient status or patient not accompanied by any care giver.

Statistical Analysis

Statistical analysis was done between patients of Alzheimer's disease and age matched controls using SPSS-22.0 and GraphPad Prism 6.0 version. The data were expressed as mean ± SD, $p<0.005$ was considered significant and mean ± SD, $p<0.001$ was highly significant. Measurable investigation was finished by utilizing chi-square test, unpaired t test, Pearson's coefficient.

RESULTS

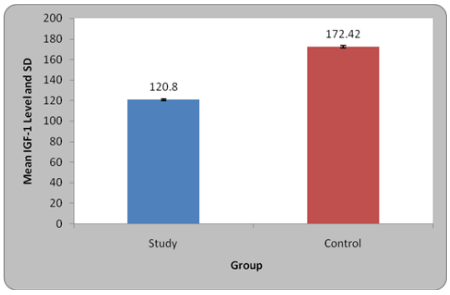
The present study was carried out to evaluate the role of IGF-I and its effect on cognitive status of patient suffering from Alzheimer's disease. The mean value of serum IGF-1 (ng/ml) in the cases of Alzheimer's disease and the control group were found to be 120.80 ± 2.54 and 172.42 ± 3.48 respectively. There was lower serum IGF-1 levels observed in Alzheimer's disease patient as compared to the control group and the difference was statistically highly

significant (p<0.0001).

Table 1: Comparison of IGF-1 level in two groups Student's unpaired t test

Group	N	Mean	Std. Deviation	Std. Error Mean	t-value	p-value
Study	40	120.80	2.54	0.40	75.33	0.0001,S
Control	40	172.42	3.48	0.55		

Graph 1: Comparison of IGF-1 level in two groups



The above table and graph shows serum IGF-1 levels in cases of Alzheimer's disease and the control group.

DISCUSSION

In the present study, 50 Alzheimer's disease patients and 50 age matched controls were taken. In our study serum IGF-I was significantly lower among the patients in comparison to controls which was statistically significant (p<0.0001). Studies suggested that metabolically significant IGF-I deficiency in Alzheimer's disease patients is commonly present.[23]

IGF-1 mRNA and receptor concentrations change as the disease progresses[24], which may result in progression- dependent IGF-1 changes in CSF and serum.

Another confounding variable is the lack of stratification according to patient heterogeneity.

Recent evidence points to the idea that AD is not a homogenous disease and that there may be different molecular mechanisms at play in different patients. Gamma secretase mutations for example are commonly associated with familial AD, however in some sporadic AD patients gamma secretase activity is also altered.[25] Furthermore, different mutations in presenilin 1, a cause of familial AD, result in different changes in molecular pathways that manifest as AD.[26] Another gene of interest is IGF-1 which may present with clinically relevant polymorphisms.

A specific IGF-1 polymorphism (rs972936 GG) was not only associated with increased serum IGF-1 levels, but was also more common in AD patients[27], whereas another IGF- 1 mutation (rs35767) increased serum IGF-1[28] without association with AD. Thus, IGF-1

polymorphisms may alter the activity or function of IGF-1 in a manner which may be more relevant to AD pathology than serum levels.[29] It is therefore possible that different mechanisms resulting in AD would not only manifest with varying IGF-1 levels but also respond differently to supplementation. Among several hypothesis of pathogenic mechanisms involved in this disease, disrupted insulin signaling in neurons is gaining support. Insulin resistance may be a pathogenic mechanism in Alzheimer's dementia by compromising cell energy resources and contributing to the formation of amyloid deposits. Since serum IGF-I can enter the brain, changes in serum levels may lead to changes in IGF-I input to the brain. In the case of familial Alzheimer's disease the primary pathogenic event is a mutation – until now, all of them affecting amyloid β-related proteins – therefore, low IGF-I levels may be downstream of the resulting amyloidosis. In the case of lateonset Alzheimer's, IGF-I resistance may originate from a prior insulin resistance or any other unknown cause.[30]

CONCLUSION

Amyloid deposits in the brain have become the primary therapeutic target in Alzheimer's dementia because the amyloidogenic cascade hypothesis is currently the best documented mechanism proposed to trigger neuronal death. Low IGF-I signaling, a closely related neurotrophic peptide, may also be involved, even as a primary cause in the development of this disease. Lack of proper IGF-I signaling may first increase brain amyloid β burden through reduced peripheral clearance, may also originate insulin resistance and eventually decrease the ability of neurons to cope with insults. Preliminary studies indicate that treatment of insulin resistance in Alzheimer's patients is beneficial. Studies in a mouse model of Alzheimer's disease demonstrate a substantial decrease in brain amyloid-β burden after IGF-I therapy. Together with new therapeutic proposals including statins, nonsteroidal anti-inflammatory drugs and amyloid vaccines, treatment of insulin resistance and IGF-I deficiency, IGF-I resistance brings new hope to this untractable disease.

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