

Role of Complements and Immunoglobulins in Alzheimer's Disease

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Abstract

Our findings show that the value of IgG in serum of Alzheimer's Disease patients is (17.2059 ± 2.6317) g/l and in controls *i.e.* (17.6720 ± 3.1457) g/l. Values of IgM in AD patients go down up to 62.5% in comparison to healthy subjects. A sudden change was observed in the levels of IgA of AD patients. It has been put on the value 137.9% high in comparison to healthy subjects. The levels of complement C₃ have also value of lower side and go down up to 52.66% in AD patients. The value of levels of complement C₄ shows no deflection from the control values. On the basis of regression and multiple correlation analysis, we found that the partial correlation coefficients $r_{GA,M}$, which has value 0.44815 in AD patients and 0.45555 in controls, do not show any resemblance. The multiple partial correlation $r_{AM,G}$ has value 0.3082 in AD patients and 0.3912 in controls slightly better correlated in comparison to healthy controls. Multiple $R_{A,M,G}$ has strongly correlation in comparison to controls. $R_{M,AG}$ is also strongly correlated. Regression coefficients and regression equations are basic foundations of correlation measurements and show a specific character of variation. A relation between all the three multiple correlations has been established in the present work and it is given by the following relation $R_{A,M,G} > R_{M,AG} > R_{G,AM}$.

Keywords

Complements, Immunoglobulins, Alzheimer's Disease, Regression Coefficients, Multiple Correlation Coefficients

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1. Introduction

Dr. Alois Alzheimer, a German physician, presented a case of 55-year-old woman in 1906 who was a patient of progressive dementia. A history of Alzheimer's disease has started with this case. Dementia has been recognized since early antiquity. It has been associated with old age [1]. Progressive mental deterioration in old age has been recognized and described nicely in the literature. Dr. Alzheimer specifically identified a collection of brain cell abnormalities as a disease. A patient of Dr. Alzheimer died after years of severe memory problems, confusion and difficulty in understanding the daily use of general questions. A brain autopsy of the dead body has been done and doctors noticed that dense deposits are surrounding the nerve cells (neuritic plaques). He observed twisted bands of fibres (neurofibrillary tangles) in the nerve cells. Now a days, this degenerative brain disorder bears Dr. Alzheimer name. These plaques and tangles mean a definite diagnosis of Alzheimer's disease (AD). Many scientists discovered a link between cognitive decline and the number of plaques and tangles in the brain. The medical community then formally recognized Alzheimer's disease as a disease. It was not a part of aging. Reger, B. [2] has given new aspects regarding this disease. People are understanding that a grandparent, parent, elderly relatives, friends can no longer remember names or faces, recognize common objects or talk in coherent sentences of daily use. These persons may be suffering from Alzheimer's disease. This disease is a growing medical and social concern. A degenerative disorder attacks brain and leads to dementia. The brains cognitive centres are very much affected. A memory loss, inability to understand situations or even question or statements are the features caused by this disorder. Due to the progression of this disease, social interactions diminish and the person loses the ability to care for him or herself. It has been noticed that before the discovery of Alzheimer's disease, scientist and non-science community have given their views on dementia. A dementia is a natural progression of age and senility was accepted as a part of aging [3]. Ronald, C. H. *et al.* [4] have reported in literature that Ronald Reagan had Alzheimer's disease galvanized the American public into recognizing their own vulnerability in a way no other public figure has done. Norman Reckwell and Rita Hayworth were both victims of this disease. They were beloved and admired. Ronald Reagan challenged politicians and law makers to properly fund research into the complete exercise of cause and treatment of the disease. Cohen, G. D. [5] had put forward historical views and evolution concept related to Alzheimer's disease. Concepts of senile dementia in general have evolved for more than 2.5 thousand years. Alzheimer's disease had traced in the start of 20th century. A relationship between Alzheimer's disease and senile dementia is not clear. A confusion has accompanied gamut of considerations about both these disorders. A focus has been nomenclature, epidemiology, etiology, diagnosis, clinical course, treatment, prognosis or prevention. This confusion has historically affected clinical practice, research and social response to both disorders. Memory is generally coming into playing an important role in the senility and senile dementia explanation. The memory in decline direction at old age has been observed. Neurofibrillary tangles and granulo vascular degeneration are described by Alzheimer and Simchowicz in 1906 and 1910 respectively. These were the major morphological additions. Rebecca, C. *et al.* [6] have projected an overview of environmental risk factors in neurodegenerative disease.

Alzheimer's disease is the prototypical degenerative disease affecting the central nervous system (CNS). This disease is a chronic progressive disease characterized by memory loss and deficits in one or more of cognitive domains. These are aphasia known as language disturbance, agnosia, apraxia, or executive function. Such types of deficits must be severe enough to interface with daily work of life. Alzheimer's disease is a form of brain disease, and can lead to confusion, memory loss, restlessness, problems with perception, speech trouble moving and fearing things, which were absent at that time. The patient may become too excited, refuse food and lose bowel or bladder control. This neurological perturbation generally starts in late middle life with slight deficits in memory and behavior. This disease occurs in both the sexes. The exact causative mechanism of the disease is unknown. It has been seen that there is a break-down of cells in the brain. There is no treatment of the disease available and a good nutrition may slow down the progress of Alzheimer's disease. This disease is no longer regarded as a natural consequence of aging. It affects a substantial proportion of the aged. Although the exact number of people affected is not exactly known because of the difficulties involved in accurate diagnosis, it is estimated and speculated that more than four million Americans people have this disease in its various stages. Ronald, C.H. *et al.* [7] have decided some factors that aggravate the symptoms in Alzheimer's disease. A generalized deterioration in functional activities of daily living is expected in patients with Alzheimer's disease. Progressive decline and gradual loss of higher cortical cognitive functions commonly spear head the deterioration. It has been seen that in some patients the rate of declining function and disability may accelerate. The reversible causes must be sought out at the time of acceleration of the disease. These causes must be treated actively. The

underlying Alzheimer's disease process is not the cause of this sudden physical or mental deterioration. A person's mental functions are controlled by the brain, which is made up of 10^{10} nerve cells called neurons. Brain functioning depends on the number of brain cells, their integrity, and the efficiency of the blood circulation. Neurons have no nutrition stores. They depend entirely on the circulation to provide them with required and adequate quantities of glucose, oxygen and different types of other nutrients. An efficient circulation removes from the brain any waste or toxic elements that have been formed by the brain cells through their metabolic activity. If the blood flow is ineffective, not only will the nerve cells be deprived but also different waste or toxic elements will accumulate in or around neurons. The nerve cells cannot function properly under these conditions. Greitz, N.H. [8] studied various inflammatory processes and suggested that cytokins may also have a role in the pathology of Alzheimer's disease. Inflammation is a general marker of the tissue damage in any disease. It may be either secondary to tissue damage in Alzheimer's disease or a marker of immunological response. Patterson, C., *et al.* [9] and Rosendorff, C., *et al.* [10] have studied and found that cardiovascular risk factor such as hypocholesterolaemia, hypertension, diabetes and smoking are associated with a high risk of onset and course of Alzheimer's disease. Soffrizzi, V., *et al.* [11] studied and found that the component of a mediterranean diet, which include fruit and vegetables, bread wheat and other cereals, olive oil, fish and red wine may reduce the risk factor of Alzheimer's disease. Master, C.L., *et al.* [12] and Glenner, G.G., *et al.* [13] have given informations regarding the pathology of Alzheimer's disease, which is very complex. There are extra cellular neuritic plaques, largely consisting of deposit of a peptide β -amyloid.

Panza, F., *et al.* [14] have studied the effect of light to moderate use of alcohol, particularly red wine associated with lower risk of Alzheimer's Disease. Stern, Y. [15] has studied cognitive reserve in Alzheimer's disease. He found that those people were engaged intellectual activities, such as reading playing board games, completing cross word puzzles, playing musical instruments or regular social interactions show a reduced risk of Alzheimer's disease. This is compatible with the cognitive reserve theory. This theory states that some life experiences result in more efficient neural functioning providing the individual a cognitive reserve that delays the onset of dementia manifestations. Some research [14] [15] have shown an increased risk of developing Alzheimer's disease with environmental factors such as intake of metals particularly aluminum. It has been reported in the literature that using Vitamin E by the Alzheimer's diseased person a significant improvement in the function of human system was also seen. A range of antioxidants is also applying to the Alzheimers to see the effect of the antioxidants to the patients. Interactions of metals like copper, zinc, iron and other metals are also studying these days to prevent the onset of this disease. The trace elements are needed for the normal brain function. A beta amyloid may be toxic due to the change in the trace elements. High blood cholestrol and blood pressure may also accelerate the onset of the disease. A high level of amino acid hemocysteine is associated with an increased risk of developing Alzheimer's. High blood pressure can damage blood vessels in the brain and reduce the brains oxygen supply. The resulting oxidative stress may accelerate the build-up of β -amyloid protein. Alzheimer's disease afflicts older people. It is increasing in incident with age significantly. Some of the researchers [16]-[18] have given their views as aging is associated with marked deterioration of the immune system. They have found a significant increase in the incident of autoimmune diseases. Kay, M.M.B., *et al.* [19] and Wechsler, M.E., *et al.* [20] have given information as the age-related decline in immune functions in partly the result of deterioration of thymus derived (T cell) functions. It may be related to the involution of the thymus. It has been reported that thymectomy accelerates the age related less of IgG and high affinity antibody response. Weksler, M.E. [21] has studied and reported that spleen cells from old animals were exposed to a young thymus gland or exogenous thymoprotein, the high affinity antibody response was completely restored. The neuropathological changes in Alzheimer's disease brain include neuronal loss, loss of dendritic spines and formation of neuritic (senile) plaques and neurofibrillary tangles. Wisniewski, H.G., *et al.* [22] have reported that underlying pathogenesis of plaques and neurofibrillary tangles is not clearly understood till now.

We wish to give a brief idea regarding various immunological factors which may play a significant role in the neuropathology of aging and Alzheimer's disease.

Many scientists [23]-[29] have provided some useful information regarding antibodies against neuronal structures in various neurological diseases such as multiple sclerosis, cerebrovascular accidents, schizophrenia, Hangtington's chorea and systemic lupus erythematosus. Ingram, C.R., *et al.* [30] have found the increased age related concentration of the γ -globulin fraction of human serum binds specifically with neurons in sections of human brain.

The CNS was believed to be immunologically privileged. Some of the researchers [31]-[41] have shown that

it is not definitely true for Alzheimer's disease. It has been reported that the immune response and inflammation might begin with scavenger cells, which phagocytose infected or damaged cells and the detritus of inflammatory response. If the scavenger cells bear major histocompatibility complex type II antigens on their surface, they can show processed fragments of their phagocytic activity, antigens, to T- and B-lymphocytes. T-helper lymphocytes are activated by such presentation and express cytokines, which activate other immune cells, specially B-cells that have also been presented with antigen. The B-cells proliferate and produce antibodies specially directed against the original antigenic stimulus. Antibodies bind to antigens in the tissue. Scavenger cells are redirected to sites of antibodies binding by means of receptors to an epitope on the E region of antibodies.

Classical pathway complement proteins also begin to attach to the antigen-antibody complex, beginning with C_{1q} at an E site on antibody. The other complement proteins follow, culminating with the membrane attack complex such as C_5-C_9 , which inserts pores in the cell wall. Some of the researchers [42] [43] have shown that cell lysis and phagocytic activity follow, with additional attraction of scavenger cells by means of binding sites on C_3 and C_5 . It has been reported that detecting brain reactive antibodies in serum samples of Alzheimer's disease, as well as antibodies, presumably from the patient and bound before the patient's death co-localized with Alzheimer's disease pathology [44] [45].

We may say that one possible source of difficulty in detecting Alzheimer's disease specific antibodies is complement. C_{1q} binds to the F_c region of immunoglobulins in the antibody-antigen complex. The remaining complement proteins then bind sequentially and may render critical epitopes on the immunoglobulin molecule inaccessible to anti-immunoglobulin antibodies. Moreover, binding affinities within the antigen-antibody- C_1 complex are relatively weak. Specific immunoglobulin binding might not survive the rigors of autolysis and tissue preparation. During autolysis serum may leak from capillaries especially in the aged brain. It is difficult to detect antibodies in brain of Alzheimer's disease.

Gaskin, F., *et al.* [45] have reported that studies based on antibodies from B-lymphocytes cloned from Alzheimer's disease and non-Alzheimer's disease patients may provide some resolution to the problem of immunoglobulin antibodies detection.

When antibodies to complement protein including C_{1q} , C_{4d} , C_{3d} and C_{5b-9} are applied to non-demented elderly brain tissue, the sections were found to be as blank. If these are applied to Alzheimer's disease samples, intense immuno-reactivity was observed in senile plaques, neurofibrillary tangles, and some neurons or dystrophic neurites. Presence of the membrane attack complex C_5-C_9 indicates that the target has been to be lysed. Some of the authors [46] [47] have shown that the data suggest that the loss of neurons and the appearance of plaques and tangles in Alzheimer's disease may in part be mediated by immune mechanisms.

Rogers, J., *et al.* [48] has reported that the immune response and inflammation are vital mechanisms in the body's defense schemes. They protect us from infectious agents and help cleanse regions of tissue damage. The CNS may be a singularly unreceptive organ for such types of benefits, whereas the removal of infected or weakened cells within and around a skin laceration may be a most helpful product of inflammatory mechanisms, it might not be in brain. New skin cells are always available to replace those lost in the inflammatory attack. Neurons are post-mitotic. It has been reported that chronic anti-inflammatory therapy in patients over 65 years of age may lessen or postpone the expression of Alzheimer's disease symptomatology.

Gottfries, C.G. [49] has studied biochemical changes in blood and CSF in Alzheimer's disease patients and reported that in living patient the investigation of CSF can give valid information about the metabolism in brain tissue.

It is possible that Alzheimer's disease is not entirely localized in the CNS. Some of the findings indicate that other parts of body are also involved in dementing disorder.

It may therefore also be of value to study changes in the blood. Findings in the blood may also reflect the metabolism of the brain to some extent.

Cohen, D., *et al.* [50] have given a thought for interrelationship between the CNS and immune functions. A correlation between serum levels of IgG and IgM found in Alzheimer's disease to be positive. The aetiology of Alzheimer's disease may involve an infectious agent, such as a virus, the γ -globulin bonding in CSF from patients with presenile dementia has been studied.

William, A., *et al.* [51] have studied serum and CSF in presenile onset dementia. The electrophoretic pattern demonstrated three homogenous bands in the gamma globulin region in five of eight patients of Alzheimer's disease. The bands were not present in serum. It has been safely said that the bands found in the CSF of Alzheimer's disease patients supported the hypothesis that an infectious agent or abnormal regulation of the immune

system is significant in the disease aetiology.

Rozemuller, J.M., *et al.* [52] and Eikelenboom, P., *et al.* [53] showed that amorphous and classical plaques contain the complement protein C_{1q}, C₄ and C₃. Some of the researchers [54] [55] have carried out the work on immuno-histochemical point of view and revealed the presence of the membrane attack complex in the corona of classical plaques. These findings indicate that in classical plaques an activation of the complement cascade had played an important role. The presence of C_{1q} and the absence of properdin indicate that the classical and not the alternative, pathway is being activated. Complement activation can occur by mechanisms other than binding to immunoglobulins.

Rogers, J., *et al.* [55] have shown that β/A_4 protein directly binds C_{1q} without immunoglobulin mediation. The binding leads to functional activation classical pathway. These fabulous findings could explain the presence of activated complement proteins from an early stage in plaque development. Mc Geer, P.L., *et al.* [56] have used molecular biological techniques to study the complement levels such as C₁, C₃ and C₄ and found that these levels were lower in normal brains and are elevated several fold in Alzheimer's disease brains. Inhibitors of complement can resist complement lysis after the formation of the membrane attack complex at the cell surface.

The findings regarding the complement proteins in Alzheimer's diseased brains suggest that the system of complement is also entangled in the generation of the pathological hall marks in Alzheimer's disease.

Eikelenboom, P., *et al.* [57] have given a thought of amyloidal plaque formation and they found that this formation is closely associated with a local, induced inflammatory response. There is a weak but identifiable immune response in Alzheimer's disease. The immune response may contribute to the pathogenesis of Alzheimer's disease. It has already been established that there are autoantibodies against neural elements in Alzheimer's disease patients and that the specific anti-Alzheimer's disease brain antibodies were also present.

Fillit, H.M., *et al.* [58] showed that more intense staining of specific areas of normal rat and human brain with Alzheimer's disease sera. They have found some reactivity with a subpopulation of Alzheimer's disease sera. Inhibition studies eliminated this antibody reaction. They also found many other types of antibody reaction. Fillits, H.M., *et al.* [59] have demonstrated that the presence of antibodies against CNS vascular membrane in Alzheimer's disease sera. This reactivity was shown to be very specific for heparan surface proteoglycan.

Singh, V.K., *et al.* [60] have studied adsorption aspects of Alzheimer's disease and control sera with pellets from various tissue homogenates. Sugiura, M., *et al.* [61] have reported a subpopulation of Alzheimer's disease sera to be positive for rabbit cerebellum neurons after absorption with liver acetone powder.

Cohen, D., *et al.* [62] have studied serum immunoglobulins and cognitive status in the elderly with reference to population. They have reported that IgG and IgA levels were elevated. The levels of IgM were not raised. Eisdorfer, C., *et al.* [63] have studied serum immunoglobulins and cognitive status in the elderly with reference to immunological behavioral relationship. They have found that serum IgG emerged as the single best predictor of behavioral status.

Koutsocraki, E. [64] studied immunological features in Alzheimer's disease and applied immunotherapy in this disorder and concluded that antibody immunization results in alleviation of memory in transgenic mice. In human beings, active vaccination may result in a trend toward cognitive benefit in antibody responders. Responders show an increased rate of hippocampal atrophy by magnetic resonance imaging (MRI). Many autopsies showed plaque clearance.

Morgan, B.P., *et al.* [65] have studied the role of complement in disorders of the nervous system. The complement system plays important roles in host defense but activation at inappropriate sites or to on excessive degree can cause host tissue damage. Complement has been implicated as a factor in the causation or propagation of tissue injury in various brain disorders. The brain is an immunologically isolated site, sheltered from circulating cells and proteins of the immune systems. There is a growing body of evidence implicating complement in different brain diseases. Bonifati, D.M., *et al.* [66] have studied the role of complement in neurodegeneration and neuroinflammation. Complement system provides an innate mechanism against pathogenic microorganisms. CNS contains many components of the immune system, including components of the complement system, which are synthesized by astrocytes, microglia and neurons. A wide range of inflammatory markers, typically not present in the normal elderly persons and present in Alzheimer's disease patients. It has become an evidence of sustaining brain inflammation could be an essential cofactor in this disease and other neurological disorders such as Parkinson disease, dementia with Lewy bodies, Huntington's and prior diseases. The complement system may be useful in eliminating aggregated and toxic proteins associated with these neurological disorders and

have a protective effect. However, an exaggerated or insufficient activation of the complement system can have deleterious effects through the activation of oxidative products.

Eikelenboom, P., *et al.* [67] have studied the role of complement and activated microglia in the pathogenesis of Alzheimer's disease. They have reported a variety of inflammatory mediators including complement activation products, protease inhibitors, and cytokines are co localized with β -amyloid deposits in the brain of Alzheimer's, activation products of the early component components C₁, C₃ and C₄ are found in neuritic plaques and to a lesser extent in varying number of diffuse plaques. No immuno histochemical evidence have been reported for the presence of late complement components C₇ and C₉ and the complement membrane attack complex in the neuropathological lesions in the brains of Alzheimer's. The late complement components C₇ and C₉ are not detectable. Authors have reported that the complement system does not act as inflammatory mediator through membrane attack complex formation. The complement system acts as an inflammatory through the actions of the C₁, C₃ and C₄ complements only.

Watts, H., *et al.* [68] have studied the significance of antineuronal antibodies in Alzheimer's disease. They have used indirect immunofluorescence and cell type-specific markers to determine whether antibodies directed against specific neural cell type were present in patients with Alzheimer's disease. Other neurological disease and normal controls-sera and CSF were also tested. It has been established that all the samples were indistinguishable in their pattern of immunoglobulin staining. Staining of neurones on frozen sections was nuclear. Surface staining of neurones were seen in CSF and sera also.

Jean, M.B., *et al.* [69] have studied immunohistochemical characteristics of human choroid plexus in vascular and Alzheimer's dementia. They have also reported that the autoimmune alterations are indirectly supported in Alzheimer's disease by the demonstration of circulating antibodies directed to the epithelial basement membrane of the choroid plexus. Specific alterations were found in Alzheimer's disease patients only. These were comprised of pseudo linear deposits of immunoglobulin G and Coarse deposits of C_{1q} along the thickened and segmented epithelial basement membrane. These were associated with IgM also. The findings suggest that immune alterations of autoimmune may be involved in Alzheimer's disease and leading to serve lesions of the choroid plexus. Such type's anomalies could be responsible for some of the alterations of cerebra-spinal fluid production or composition noted in the disease.

Elouaara, I., *et al.* [70] have studied CSF in Alzheimer's disease related to BDB function and intraethecal protein synthesis. They have found that the levels of IgG, IgA, transferrin and albumin were elevated and very higher compared to the controls. CSF heptaglobin levels were also elevated. The increased CSF/serum ratio for IgG and CSF/albumin ratio suggest that there is an increased BBB permeability in this disorder.

Nerenberg, S.T., *et al.* [71] have studied cerebrospinal fluid IgG, IgA, IgM, IgD and IgE levels in CNS disorders and found that abnormal immunoglobulin levels occurred in all conditions such as multiple sclerosis, viral meningitis and tumors. The levels of IgA, IgM and IgE were higher in benign and malignant tumors of CNS. The ratio of immunoglobulin to protein in aspectic meningitis and multiple sclerosis was significant as compared to normals.

Selkoe, D.J. [72] studied biochemistry of altered brain proteins in Alzheimer's disease. The author suggested that the progressive dysfunction of limbic and association cortices in patients is accompanied by the formation of unusual intra-neuronal and extracellular proteinaceous filaments. These striking structural changes of neurons, their processes and adjacent cerebral microvessels provide a cytopathological signature of the disease. This is a feature often lacking in other neurological disorders.

Hampel, H., *et al.* [73] have studied serum and cerebrospinal fluid in Alzheimer's, major deprement and vascular demented patients. Their data related to CSF, CSF/Serum ratio albumin/IgG for Alzheimer's disease, vascular dementia and major depression cases support the hypothesis of a blood CSF barrier leakage in a subgroup of all patients. The levels of IgG were also elevated. The authors have quoted that elevated CSF immunoglobulins combined with the blood CSF barrier impairment might be associated or caused by a general immune activation. Their data show that blood CSF barrier impairment and elevation of IgG immunoglobulin level were unspecific either for Alzheimer's disease, vascular dementia and major depression.

Constantin, B., *et al.* [74] have studied humoral immunity in aging brain and Alzheimer's disease. They suggested that human immunoglobulins can interact with tau protein and alter both the dynamics and structural organization of microtubules.

Veerhuis, R., *et al.* [75] have studied complement activation in amyloid plaques in Alzheimer's disease brains. Authors have suggested that in Alzheimer's disease high levels of the early components C₁, C₄ and C₃ were very

much present to allow the complement pathway to proceed until C_3 , C_1 through C_3 can be associated with β/A_4 deposits in Alzheimer's and controls, irrespective of the presence or absence of tau pathology or activated glial cells.

Kalaria, R.M., *et al.* [76] have studied serum proteins and the BBB in the pathogenesis of Alzheimer's disease. It has been seen that a variety of classical serum proteins including protease inhibitors involved in the coagulation. Cascade is intimately associated with the pathological lesions of Alzheimer's disease. There is no way to have a clear cut association of these molecules which may play a significant role in the pathogenesis of the disease. Authors have embarked on studies to examine the localization and origin of these amyloid associated factors in Alzheimer's disease. Authors have demonstrated that serum amyloid component and the three homologous serpins, α -antichymotrypsin, antitrypsin and antithrombin II, are all localized in amyloid deposits. It has been conventionally considered that the localization of plasma proteins in parenchymal amyloid deposits are to be evidences for breach of the BBB in Alzheimer's disease. Authors have enlightened that the brain has the remarkable capacity to express classical serum proteins during degenerative processes similar to chronic inflammatory response in the periphery.

Kayeed, R., *et al.* [77] have studied and reviewed in Alzheimer's disease emerging role of treatment for intravenous immunoglobulins. They reported that intravenously immunoglobulins preparations may be effective because they contain both anti-tau and anti- $A\beta$ natural antibodies. Apart from the presence of these antibodies, intravenously immunoglobulin may be useful for Alzheimer's disease treatment due to anti-inflammatory effects at high doses mediated in part via Fc receptor uptake of IgG by inflammatory cells.

Kumar, S., *et al.* [78] have used the method of Mancini, G., *et al.* [79] in epileptic children and found that the value of IgG was higher in comparison to healthy children and other immunological parameters such as IgA, IgM, C_3 and C_4 were lower than controls.

2. Materials and Method

2.1. Selection and Exclusion of Patients

We have selected Alzheimer's diseased patients and normal healthy controls whose aged group has a range of 50 to 69 years. The patients were on standard medicines. We did not select above this age group. Blood samples of these patients were collected from the Department of Neurology, Safdarjang Hospital, New Delhi 110 016 after the approval of ethical committee of the hospital. 10 milliliters freshly drawn blood from each patient was collected in clean and dry test tube without any anti-coagulant. The test tube was kept for 45 minutes at room temperature ($22^\circ\text{C} \pm 2^\circ\text{C}$) for the formation of clot. Sera of different patients and normal healthy controls were separated by centrifugation at 1500 r.p.m. up to 15 minutes and were collected in screw capped test tubes.

The immunological parameters (IgA, IgG, IgM, C_3 & C_4) were quantified by using singles radial immunodiffusion method of Mancini *et al.* [79] using commercially available antibody-agar plates. The plates were standardized with purified immunoglobulins. The purpose is to quantitate serum levels of immunoglobulins (IgG, IgA, IgM) and complements (C_3 and C_4). These measurements aid in the clinical diagnosis, assessment of disease activity, response to treatment, and follow-up in patients with various clinical conditions. Measurements of immunoglobulin A (IgA) and immunoglobulin M (IgM) aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.

Measurements of IgG aids in the diagnosis of autoimmune diseases, sarcoidosis, chronic liver disease, chronic and recurrent infections, lymphoid malignancies, multiple myeloma and severe and variable immunodeficiency. The complements system is the main mediator mechanism of humoral immunity. To study the levels of complements C_3 and C_4 is also our object regarding the complete knowledge of immune system in Alzheimer's disease.

2.2. Results

Experimental findings are given in **Table 1**.

We have applied statistical analysis such as regression and correlation with Student "t"-test to analyze the data for a concrete foundation of authenticity. The regression and correlation coefficients are given in **Table 2**.

Student "t"-test was applied and given in **Table 3**.

Table 1. Experimental findings in epilepsy and Alzheimer’s disease neurological disorders.

1	IgG	Serum	(18.18 ± 4.71) g/l	E	Kumar, S., et al. [78]
2	IgG	Serum	(17.24 ± 2.89) g/l	C	Kumar, S., et al. [78]
3	IgM	Serum	(1.38 ± 0.31) g/l	E	Kumar, S., et al. [78]
4	IgM	Serum	(2.42 ± 1.54) g/l	C	Kumar, S., et al. [78]
5	IgA	Serum	(2.05 ± 1.13) g/l	E	Kumar, S., et al. [78]
6	IgA	Serum	(2.83 ± 0.62) g/l	C	Kumar, S., et al. [78]
7	C ₃	Serum	(1.53 ± 0.25) g/l	E	Kumar, S., et al. [78]
8	C ₃	Serum	(1.58 ± 0.14) g/l	C	Kumar, S., et al. [78]
9	C ₄	Serum	(0.26 ± 0.13) g/l	E	Kumar, S., et al. [78]
10	C ₄	Serum	(0.28 ± 0.09) g/l	C	Kumar, S., et al. [78]
11	IgG	Serum	(17.2059 ± 2.6317) g/l	AD	Present work
12	IgG	Serum	(17.6720 ± 3.1457) g/l	Controls	Present work
13	IgA	Serum	(4.0288 ± 1.4283) g/l	AD	Present work
14	IgA	Serum	(2.9110 ± 0.6717) g/l	Controls	Present work
15	IgM	Serum	(1.5459 ± 0.5568) g/l	AD	Present work
16	IgM	Serum	(2.4290 ± 1.5455) g/l	Controls	Present work
17	C ₃	Serum	(0.7952 ± 0.1284) g/l	AD	Present work
18	C ₃	Serum	(1.568 ± 4.2571) g/l	Controls	Present work
19	C ₄	Serum	(0.2682 ± 0.2877) g/l	AD	Present work
20	C ₄	Serum	(0.260 ± 0.0968) g/l	Controls	Present work

Table 2. Regression and correlation coefficient of Alzheimer disease.

S.No.	Mode of Sample	Correlation Co.	Partial Correlation Coefficient	Multiple Correlation Coefficient	Regression Co.	Regression Equation
1	A.D.	$r_{GA} = 0.4006$	$r_{GAM} = 0.44815$	$R_{GAM} = 0.2186$	$b_{GA} = 0.7381$	$IgG = 0.7381 IgA + 14.2249$
	C	$= 0.4442$	$= 0.45555$	$= 0.2105$	$b_{AG} = 0.2174$	$IgA = 0.2174 IgG + 0.2983$
					$b_{GA} = 2.0789$	$IgG = 2.0789 IgA + 11.6204$
2	A.D.	$r_{GM} = 0.1470$	$r_{AMG} = 0.3082$	$R_{AMG} = 0.2402$	$b_{GM} = 0.6947$	$IgG = 0.6947 IgM + 16.132$
	C	$= 0.0610$	$= 0.3912$	$= 0.3201$	$b_{MG} = 0.0311$	$IgM = 0.0311 IgG + 1.0149$
					$b_{GM} = 0.1240$	$IgG = 0.1240 IgM + 17.3709$
3	A.D.	$r_{MA} = 0.2205$	$r_{MGA} = 0.2633$	$R_{MAG} = 0.2478$	$b_{MA} = 0.0859$	$IgM = 0.0859 IgA + 1.1990$
	C	$= 0.3770$	$= 0.1282$	$= 0.5162$	$b_{AM} = 0.5656$	$IgA = 0.5656 IgM + 3.1645$
					$b_{MA} = 0.8674$	$IgM = 0.8674 IgA - 0.096$
4	A.D.	$r_{c_3c_4} = 0.0669$	-	-	$b_{c_3c_4} = 0.0298$	$C_3 = 0.0298 C_4 + 0.7873$
	C	$r_{c_3c_4} = 0.0205$	-	-	$b_{c_4c_3} = 0.1498$	$C_4 = 0.1498 C_3 + 0.1491$
					$b_{c_3c_4} = -0.9015$	$C_3 = -0.9015 C_4 + 1.8023$
					$b_{c_4c_3} = -0.0004$	$C_4 = -0.0004 C_3 + 0.2606$

Table 3. Student “t”-test-normal sample and Alzheimer disease.

S.No.	Immunological Parameters	$t_{(exp)}$	P value & d_f	$t_{(theo)}$	Result	Null Hypothesis
1	IgG	0.592	0.9541 (Paired) $d_f = 9$	0.70	$t_{theo} > t_{exp}$	Rejected
		0.4318	0.6826 (Unpaired) $d_f = 25$	0.68	$t_{theo} > t_{exp}$	Rejected
2	IgM	2.1254	0.0625 (Paired) $d_f = 9$	1.83	$t_{exp} > t_{theo}$	Accepted
		2.1540	0.0411 (Unpaired) $d_f = 25$	2.06	$t_{exp} > t_{theo}$	Accepted
3	IgA	2.2982	0.0471 (Paired) $d_f = 9$	2.26		
		2.3357	0.0278 (Unpaired) $d_f = 25$	2.06	$t_{exp} > t_{theo}$	Accepted
4	C_3	9.4865	0.001 (Paired) $d_f = 8$			
		13.6028	0.0001 (Unpaired) $d_f = 24$			
5	C_4	0.0549	0.9575 (Paired) $d_f = 8$			
		0.1633	0.8717 (Unpaired) $d_f = 24$			

Our findings on immunoglobulins and complements show that the levels of IgG in Alzheimer’s disease do not change and completely resemble with controls. Levels of IgM go down up to 62.5% in Alzheimer’s disease in comparison to controls. A drastic change in the levels of IgA has been seen and found that these levels go up to 137.9% in comparison to healthy controls.

The levels of C_3 go down up to 52.66% in comparison to normals. The levels of C_4 do not show any change in the present study.

3. Discussion

Central nervous system (CNS) is relatively isolated from systemic immune response in the absence of disease. There is no mechanism found for antibody production within the normal condition of CNS. This system has been described as an immunologically privileged site due to paucity of normal immune surveillance. If a virus penetrates the blood brain barrier (BBB) that excludes most infectious agents, the same barrier may stop viral clearance. Immune responses in the CNS during infection are recruited from the systemic circulation in a relatively selective and specific fashion. Cells and antibodies found in the CNS during infections differ from these that follow non specific rupture in the BBB. During the stage of viral infection, we have an early increase in permeability of vessels, which allow transudation of serum proteins, cell entry is immunologically specific. The cells, which are entering have a specific kinetics and do not simply mirror the proportions of cell phenotypes in the blood. These cells in turn are caused to replicate cells, which may persist for long periods of time within CNS. On the basis of the above mentioned facts a review immune response in the CNS is quit necessary and required. Some of the researchers have proposed the hypothesis of immunological mechanism for the involvement of pathogenesis in Alzheimer’s disease. Many of the patients of AD have immune deficient state.

It is believed that the changes in the levels of immunological parameters in the present study and after the review of the literature are due to manifestation of the factors, which are responsible for this disease. Immunity is related with the food, which we eat. It has already been established that content of the food have some trace elements. The trace elements play a role in human immunity. If the level of these elements goes beyond the limit of normalcy even death may occur. On the other hand, if the levels are lower side of the normal range something unnatural can happen. A relation between immunoglobulin complement and trace element is considered in the future preview of the study.

Our findings show that the value of IgG in serum of Alzheimer’s Disease patients is (17.2059 ± 2.6317) g/l and in controls, *i.e.* (17.6720 ± 3.1457) g/l. Values of IgM in AD patients go down up to 62.5% in comparison to healthy subjects. A sudden change was observed in the levels of IgA of AD patients. It has been put on the value 137.9% high in comparison to healthy subjects. The levels of complement C_3 has also value of lower side and go down up to 52.66% in AD patients. The value of levels of complement C_4 shows no deflection from the control

values.

Regression and multiple correlation analysis give a good presentation of our work. It has been found that the partial correlation coefficients $r_{GA,M}$, which has value 0.44815 in AD patients and 0.45555 in controls. We have found that these correlations do not show any resemblance and do not show any deflection, while $r_{AM,G}$ has value 0.3082 in AD patients and 0.3912 in controls slightly better correlated in comparison to healthy controls. There is a correlation such as $r_{MG,A}$ has a variation more than fifty percent for control values. Multiple correlation $R_{G,AM}$ has a trend and does not show any change in comparison to healthy controls, while $R_{A,MG}$ has strongly correlation in comparison to controls. $R_{M,AG}$ is also strongly correlated. Regression coefficients and regression equations are basic foundations of correlations measurements and show a specific character of variation.

4. Conclusion

On the basis of analysis of immunoglobulins and complements, we have reached at a point where we can give some ideas related to study of Alzheimer's disease. The measured values of levels of immunoglobulins and complements have a variation. Statistical variations such as regression and correlation analysis with a test called Student "t"-test were employed to the present work. The variations are in the present work. The measured levels of IgA have gone up to 137.9% on the higher side in comparison to healthy subjects. The levels of IgM were lower up to 62.5% in comparison to normals. The levels of complements C_3 were also found on the lower side up to 52.66% in comparison to healthy subjects. The alterations in the immunoglobulological parameters are a subject of study, which can give more information related to Alzheimer's disease. We can say that the present study is a step in understanding the mechanism of the immunological changes in the brain of Alzheimer's disease patients. On the basis of partial and multiple correlation analysis, a trend has been found between all the immunoglobulins, which is given here as

- 1) $r_{GA} > r_{MA} > r_{G,M}$
- 2) $r_{G,A,M} > r_{A,M,G} > r_{M,G,A}$
- 3) $R_{A,MG} > R_{M,AG} > R_{G,AM}$

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