Intravenous Immunoglobulin Therapy for the Treatment of Alzheimer’s Disease

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Intravenous Immunoglobulin Therapy for the Treatment of Alzheimer’s Disease

Abstract

Background: Alzheimer’s disease (AD) is the 6th leading cause of death and affects 5.4 million Americans. It is thought to be caused, in part, by the deposition of β-amyloid plaques in the brain. Intravenous immunoglobulin (IVIg) is a medication with a reputable safety record that contains natural anti-β-amyloid (Aβ) antibodies. Decades of research have led to the proposal of IVIg for the treatment of AD.

Method: An exhaustive search of medical literature was conducted. Key words searched included: intravenous immunoglobulin, Alzheimer’s disease, immunotherapy, and Aβ. Articles were screened to fit criteria and assessed using the GRADE method.

Results: Three studies met criteria. Study 1 showed at 9, 18, and 36 months, the group treated with IVIg continuously (n=16) had statistically less decline in cognitive function compared to placebo (n=8). Patients treated with IVIg 0.4g/kg/2weeks continuously over 36 months showed no decline in ADAS-Cog or ADCS-CGIC assessments. Study 2 measured Aβ load and cognitive function of 8 patients during 6 months of therapy, followed by a 3-month washout, and 9 months of resumed therapy. Aβ load was statistically lower at 6 months, returned to baseline after the washout, and was again statistically lower after 9 months of return to therapy (P<0.003). The mean MMSE increased 2.5 points at 6 months and was unchanged from baseline to 18 months. Study 3 measured Aβ load and cognitive function of 5 patients treated with IVIg at baseline and after 6 months of treatment. Aβ load decreased in all patients (mean: 30.1%, P<0.05). A slight improvement of 3.7 ± 2.9 points on the ADAS-Cog was calculated at 6 months.

Conclusion: IVIg therapy at a dose of 0.4g/kg/2weeks may be an effective treatment for AD. Limitations of the studies include low number of subjects, potential bias, and flawed study designs. The very low quality of evidence makes a definitive conclusion impractical. There is a need for larger, placebo-controlled, randomized, double-blind clinical trials. The Gammaglobulin Alzheimer Partnership (GAP) study is in progress, and includes 360+ AD patients, has an appropriate design, and may provide further evidence of the efficacy of IVIg in AD.
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Intravenous Immunoglobulin Therapy for the Treatment of Alzheimer’s Disease

Katie Williams

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Hillsboro, OR
For the Masters of Science Degree, 2013

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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Katie Williams was born in Phoenix, Arizona. She received her Bachelor of Science degree from Arizona State University in Human Nutrition in 2010. Prior to pursuing a degree as a physician assistant, she worked as a physical therapy technician at a predominantly geriatric hospital in Sun City, Arizona.
Abstract

**Background:** Alzheimer’s disease (AD) is the 6th leading cause of death and affects 5.4 million Americans. It is thought to be caused, in part, by the deposition of β-amyloid plaques in the brain. Intravenous immunoglobulin (IVIg) is a medication with a reputable safety record that contains natural anti-β-amyloid (Aβ) antibodies. Decades of research have led to the proposal of IVIg for the treatment of AD.

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**Conclusion:** IVIg therapy at a dose of 0.4g/kg/2weeks may be an effective treatment for AD. Limitations of the studies include low number of subjects, potential bias, and flawed study designs. The very low quality of evidence makes a definitive conclusion impractical. There is a need for larger, placebo-controlled, randomized, double-blind clinical trials. The Gammaglobulin Alzheimer Partnership (GAP) study is in progress, and includes 360+ AD patients, has an appropriate design, and may provide further evidence of the efficacy of IVIg in AD.

**Keywords:** Intravenous immunoglobulin, Alzheimer’s disease, immunotherapy, β-amyloid
To my family: Your constant guidance and encouragement enables me to stay positive and focused. Although it has been a struggle being so far away from you, I know you will always be there for me and I love you very much.

To Tyler: Having you with me has turned this challenge into a fun, amazing journey. You have loved and supported me every step of the way and I could not be more thankful.
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List of Abbreviations

Aβ..............................................................................................................................amyloid-beta peptide
AD.....................................................................................................................................Alzheimer’s disease
ADAS-Cog..............................................Alzheimer’s Disease Assessment Scale-cognitive subscale
ADCS-CGIC........Alzheimer’s Disease Cooperative Study - Clinical Global Impression of Change
APP...........................................................................................................amyloid precursor protein
CERAD...............................................Consortium to Establish A Registry for Alzheimer’s Disease
CSF........................................................................................................................cerebral spinal fluid
ECG........................................................................................................................electrocardiogram
ELISA....................................................................................Enzyme-Linked Immunosorbent Assay
ICAD...........................................................................................................International Conference on Alzheimer’s Disease
IVIg......................................................................................................intravenous immunoglobulin
NINCDS-ADRDA....................................................................National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorder Association
MMSE..........................................................................................................Mini-Mental State Exam
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Appendix A…………………NINCDS-ADRDA; Alzheimer Disease Diagnosis Criteria
Intravenous Immunoglobulin Therapy for the Treatment of Alzheimer’s Disease

BACKGROUND

Alzheimer’s disease (AD) is a debilitating, progressive disorder that currently affects the lives of 5.4 million Americans and is expected to exceed 100 million worldwide by 2050.\textsuperscript{1,2} It is the sixth leading cause of death in the United States with an average life expectancy of five to eight years after diagnosis.\textsuperscript{1,3} An estimated $200 billion will be spent in the United States this year alone to care for adults with this distressing condition.\textsuperscript{1} At this time, providers can do nothing to prevent their patients from developing AD, nor can they prescribe anything to cure it or even halt its progression.\textsuperscript{1,3} There is an urgent need for a safe and effective therapy.

The cause and pathogenesis of Alzheimer’s disease is uncertain. The two currently accepted theories include the deposit of misfolded, amyloid-beta peptide (Aβ) plaques in the brain and aggregation of misfolded tau protein in neurofibrillary tangles.\textsuperscript{2,4} The Aβ peptide is made of 38-43 amino acids and is produced from the cleavage of the amyloid precursor protein (APP). Plaques made of Aβ are found in the diseased brain.\textsuperscript{5,6} In healthy individuals, low levels of Aβ can be detected in the serum and cerebral spinal fluid (CSF).\textsuperscript{7,8} In AD, however, it has been suggested that there is either increased production or decreased clearance of Aβ, or a specific, neurotoxic formation of Aβ.\textsuperscript{8,9} Current research is aimed at strategies to prevent further deposition of Aβ and removing the plaques and neurofibrillary tangles that have already been formed.\textsuperscript{2}
Intravenous immunoglobulin (IVIg) is made from pooling the plasma of thousands of healthy blood donors which contains natural anti-amyloid antibodies that are able to exhibit anti-inflammatory effects. IVIg has been FDA-approved for more than 25 years for use in patients with autoimmune diseases and immune deficiencies and has a reputable safety record.\textsuperscript{10} The safety of both long-term and high-dose use of IVIg has been studied and reported.\textsuperscript{11-13} One study\textsuperscript{11} of 293 multiple sclerosis patients receiving 0.4g/kg body weight for a total of 9 281 IVIg infusions over a period of ten years reported no severe adverse events. Minor adverse events occurred in 4.4\% of patients the first year and the percentage decreased during each subsequent year of therapy. Unlike other experimental drugs that have not yet been tested on humans, the specific adverse drug reactions to expect from IVIg are well established, and various methods of avoiding or combating these reactions are understood.\textsuperscript{11-14}

An extensive amount of intriguing research has led to the proposal of IVIg use in the treatment of Alzheimer’s disease. Consistent with the $\alpha$-amyloid neurotoxicity theory, it was discovered that patients with Alzheimer’s disease had lower concentrations of anti-$\alpha$-amyloid antibodies in their serum compared to healthy adults of the same age.\textsuperscript{15,16} The naturally occurring antibodies in IVIg made it a likely choice for research. Patients treated with IVIg for other conditions have significantly lower levels of $\alpha$-amyloid in their CSF and increased levels of $\alpha$-amyloid in their serum, along with increased serum and CSF anti-$\alpha$-amyloid antibodies.\textsuperscript{17} In vitro, these antibodies are able to block $\alpha$-amyloid fibril formation and prevent $\alpha$-amyloid-induced neurotoxicity, with the potential benefit of reducing plaque formation and loss of neurons.\textsuperscript{15} In high-quality studies involving mice,\textsuperscript{18,19} researchers found that, not only was IVIg able to cross the blood brain barrier and exude neuro-protective effects, it
also promoted phagocytosis and clearance of $\text{A}\beta$ plaques already formed. These findings strongly support the idea that IVIg could alleviate the neurotoxic load in humans with Alzheimer’s disease. Another large, retrospective study from a database of 20 million people determined that patients who were treated with IVIg at some point in their lives had a 42% reduced risk of being diagnosed with Alzheimer’s disease or a related disorder.

This systematic review will discuss the current clinical trials and the status of the therapy to date. It will attempt to examine if IVIg therapy effectively inhibits the progression of Alzheimer’s disease.

METHODS

An exhaustive search of medical literature using Medline-OVID/PubMed, CINAHL, Web of Science, and Google Scholar was conducted using the following search terms: intravenous immunoglobulin, immunotherapy, Alzheimer’s disease, and beta-amyloid. Animal studies and non-English studies were excluded. The bibliographies of relevant articles were further searched to find any other articles that fit the criteria. The results were narrowed to include clinical trials in which IVIg was investigated as a treatment in a study population with an Alzheimer’s disease diagnosis. Qualifying articles were assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).
RESULTS

The initial search of databases yielded forty-two results, excluding results from Google scholar and bibliography searching. Applying inclusion and exclusion criteria resulted in one randomized, double-blinded, placebo-controlled clinical trial and two non-randomized clinical trials to be analyzed. See Table I.

Study 1: Phase II Study of IVIg for Treatment of Mild to Moderate Alzheimer’s Disease

In this placebo-controlled, randomized, double-blind clinical trial,\textsuperscript{22} the authors strive to determine the safety, efficacy and biological mechanisms of action of intravenous immunoglobulin (IVIg) in the treatment of 24 patients with probable Alzheimer’s disease. The design of this study was found on ClinicalTrials.gov\textsuperscript{22} and the study was listed as “completed”, however the results were not included. Results, discussions, and conclusions were published in a variety of sources including a news release from the 2008 Alzheimer’s Association International Conference (ICAD),\textsuperscript{23} the 2012 ICAD,\textsuperscript{24} and a press release from the Baxter website.\textsuperscript{25} The study published in its entirety was not located. Although some details are absent, this study is still very relevant and should be included in this analysis.\textsuperscript{22-25}

Included patients were over the age of 50, diagnosed with probable AD by the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria, on a stable dose of an approved AD drug for at least three months, have an able caregiver, and had
neuroimaging studies consistent with the diagnosis. Exclusion criteria included conditions that would make the patient more prone to adverse reactions from IVIg.\textsuperscript{22-25}

Subjects were randomly assigned to treatment with IVIg (n=16) or placebo (n=8) for six months. Each member of the treatment group was randomly assigned to a specific dose. The exact doses used were not included in the published data. After six months, all subjects were given IVIg with various doses for an additional 12 months. Raters and patients were blinded to dose throughout. After 18 months, an additional 18 months of treatment at a dose of 0.4g/kg/2weeks was offered to patients so the researchers could evaluate three years of IVIg treatment.\textsuperscript{22-25}

The primary endpoint studied was cognitive function using the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Alzheimer’s Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC). Testing was carried out at baseline and every three months during the first 18 months and every six months during the 18 extension. Adverse events were recorded throughout the entire study.\textsuperscript{22-25}

Results were evaluated after nine months of treatment, after 18 months of treatment, and after three years of treatment. At baseline, groups were statistically similar in regards to prognosis. Evaluating nine months of therapy using the ADCS-CGIC, results favoring IVIg therapy were statistically significant at three, six, and nine months of therapy. Using the ADAS-cog, results favoring IVIg therapy were statistically significant at three and nine months of therapy. The group receiving IVIg at a dose of 0.4g/kg/2weeks showed the greatest outcome. No patient in the placebo group showed
comparable improvements. Evaluating 18 months of therapy using the ADCS-CGIC, patients randomized to the treatment group received an average of 1.36 percentage points higher than patients initially given placebo ($P = 0.011$). Using the ADAS-cog, the score of the treatment group decreased by 9.15 points less than the group initially assigned to placebo ($P = 0.013$). Evaluating three years of treatment includes 5 out of 8 patients originally treated with placebo and 11 out of 16 given IVIg at various doses from the time of randomization. Patients treated with IVIg 0.4g/kg/2weeks for the full three years had the best outcome with no cognitive decline evaluated by the ADAS-cog, ADCS-CGIC or any other measures. All patients treated initially with placebo or IVIg at any other dose declined significantly.\textsuperscript{22-25}

The authors explain that this is the first study to report stabilization of cognitive function in treated AD patients over a period of three years. The study suggests that using a dose of 0.4g/kg/2weeks continuously yields the best results. The authors also state that the limitations of this study include the small number of patients and the bias that can occur with an open label extension. The study was funded by the Baxter corporation which produces the specific IVIg formulation used.\textsuperscript{22-25}

**Study 2: 18-Month Study of IVIG For Treatment of Mild Alzheimer Disease**

In this open-label, dose-ranging clinical trial,\textsuperscript{26} the authors aimed to evaluate the safety and dose-related efficacy of IVIg therapy in eight patients with mild Alzheimer’s disease (AD). The study was initially designed for six months of treatment with varying doses of IVIg followed by a three-month washout period. The positive results of treatment led to a nine-month open label extension in which all patients participated.\textsuperscript{26}
Patients were included with a diagnosis of probable AD by NINCDS-ADRDA criteria, a stable dose of at least one approved AD treatment for three months, and an able caregiver. Patients were first given a test dose of IVIg at 0.4g/kg and were then randomly assigned to one of four doses of IVIg (0.4g/kg/2weeks, 0.4g/kg/week, 1g/kg/2weeks, or 2g/kg/4weeks) for six months.26

Endpoints studied included dose response, Aβ load, and cognitive function. Dose response was determined by an anti-Aβ titer performed before and after the test dose and one hour after each subsequent dose. It was observed that the test dose produced a statistically significant increase in anti-Aβ titer for all patients (P<0.005, Mann-Whitney rand sum test). Also, the anti-Aβ titer correlated positively with the IVIg dose. The Aβ load was measured in the serum using the Enzyme-Linked Immunosorbent Assay (ELISA) method at baseline, before and after multiple IVIg treatments, weekly throughout the first six months, and before and after each dose of the nine-month extension. All doses of IVIg resulted in a statistically significant increase in serum Aβ (R² = 0.77, P<0.01). CSF was obtained via lumbar punctures and the Aβ load was measured using a Biosource Aβ kit at baseline, one to three months, six months, nine months, and eighteen months. After six months of IVIg, all CSF samples showed a statistically significant decrease in Aβ (P<0.003). After the three-month washout, no CSF samples were statistically different from baseline. After the subsequent nine months of IVIg treatment, CSF samples again showed statistically decreased levels of Aβ (P<0.003). The initial mean Mini-Mental State Exam (MMSE) score was 23.5. The mean MMSE score increased to 24.9 after three months of IVIg and then to 26.0 after six months. After the three-month washout, the mean MMSE score decreased to near
baseline at 23.9. After nine months of treating again with IVIg, the mean MMSE score increased slightly to 24.0. The MMSE was administered by the same person throughout the study.26

The IVIg infusions were well tolerated with no serious adverse reactions. Minor events observed, included headache, chills, diaphoresis, fever, and transient confusion. The authors conclude that, while these positive results give hope for the use of IVIg as a treatment for Alzheimer’s disease, this study is not definitive, and that, in order for clinical recommendations to be made, large, detailed, placebo-controlled, double blinded clinical trials must be performed.26

**Study 3: IVIg Against β-Amyloid For The Treatment of Alzheimer’s Disease**

In this small, prospective clinical trial,27 the authors evaluated the safety and efficacy of IVIg treatment in five patients with Alzheimer’s disease (AD). Patients included, were from specialty outpatient clinics for those with cognitive disorders and met the criteria for clinically probable or clinically possible AD from the NINCDS-ADRDA criteria. Thorough testing ensured that the patients did not have reversible causes of dementia. Patients were allowed to continue current AD medications if they were stable for at least six months prior to the study and doses were maintained throughout the study.27

All patients were given IVIg (Octagam, Octapharma, Langenfeld, Germany) at a dose of 0.4g/kg on three consecutive days every four weeks for six months. The study was not blinded and no control group was used.27
Endpoints measured included Aβ levels of the CSF and serum and cognitive function using the ADAS-cog, Consortium to Establish A Registry for Alzheimer’s Disease (CERAD) test, and visual construction ability measurements. Patients and their family members were interviewed and any adverse drug reactions were discussed. Aβ levels were determined using a sandwich ELISA from samples drawn at baseline and at six months. Anti-Aβ titers were measured using the Wilcoxon non-parametric test, from samples at baseline and at six months. All patients demonstrated a decrease in CSF Aβ concentration, and an increase in serum Aβ concentration, and either stability or improvement in measurements of cognitive function from baseline to six months. See Table I and II.27

All patients completed the study. No serious adverse reactions occurred in the study group. Events observed included tension headache, transient confusion, and tooth infection. Vital signs, hematologic and biochemical labs, and electrocardiogram (ECG) findings remained clinically insignificant.27

The authors admit that no definitive conclusion can be made following this study secondary to the small number of participants, short follow-up, and study method that is prone to bias. This study does support the need for larger, blinded, placebo-controlled, detailed studies of IVIg as a treatment for AD.27
DISCUSSION

Intravenous Immunoglobulin (IVIg) therapy for patients with Alzheimer’s disease is a topic that has understandably drawn attention in the medical community. IVIg is already used safely to treat a variety of autoimmune disorders, immune system deficiencies, and neurologic conditions including multiple sclerosis and Guillain-Barré syndrome. Alzheimer’s disease is thought to be caused, in part, by the inappropriate deposition of β-amyloid peptide forming plaques in the brain. The naturally occurring anti-Aβ antibodies in IVIg make it a reasonable choice in the treatment of Alzheimer’s disease.

Backed by a wealth of supporting evidence, a few researchers conducted clinical trials to determine the efficacy of IVIg in the treatment of AD. Patients with AD have an average annual decrease of 3-3.5 points on the MMSE and 7-11 points in ADAS-cog. These studies consistently found that with IVIg treatment, patients with AD remained stable or improved in regards to their cognitive function from six months up to three years. The IVIg dose of 0.4g/kg/2weeks yielded the greatest results. As the levels of anti-Aβ antibodies increased in the patients’ serum and CSF, the level of Aβ increased in the serum and decreased in the CSF. These findings are consistent with the results of trials in mice.

There are also other important points to consider before IVIg can be determined an effective therapy for AD. As IVIg becomes an acceptable treatment for a broader range of medical conditions, concerns about availability and cost will arise. IVIg is currently an expensive treatment at an estimated $4551.25 per infusion. All of the IVIg
produced is currently used and strategies to cope with the increasing demand must be established. The exact correlation between $A\beta$ levels and cognitive function in the patient remains unknown, and the $A\beta$ load could not predict cognitive function. It is possible that other mechanisms of IVIg may be responsible for the observed improvement in AD patients.

Applying the GRADE criteria to each outcome in each study and then summarizing the total quality of evidence for each outcome revealed major defects. See Table 1. As a randomized clinical trial, the study began with a grade of high. Lack of precision from the small study group ($n=24$) resulted in a downgrade for the outcomes. Possible publication bias resulted in a second downgrade for the outcomes. Study 1 is graded as low quality of evidence. Study 2 was a non-randomized clinical trial. The precision deficit from a low number of subjects ($n=8$), lack of control group and blinding, and the high risk of recruitment bias resulted in a grade of very low. A dose response gradient was evident in Study 2, but the imprecision of those results make it insufficient evidence to upgrade the study. Study 3 was a non-randomized clinical trial. In this study, there was also a lack of precision with a low number of subjects ($n=5$), no control group or blinding, and a high risk of recruitment bias. There was also possible publication bias. Study 3 received a grade of very low for the outcomes. The absence of control groups for Study 2 and 3 resulted in an initial grade of very low and there was no basis for upgraded either study.

Although the results of these initial studies are positive, many limitations are present in the current studies. The number of participants in each study is remarkably low. Two studies were not blinded, randomized, nor placebo-controlled. There is
potential bias associated with an open-label study design and with studies funded by corporations that produce the medication. Serious flaws in the studies available to date make the quality of current evidence very low overall.

Research is currently moving forward on this topic. The Gammaglobulin Alzheimer’s Partnership (GAP) study is in progress. It is a randomized, double-blind, placebo-controlled, add-on three arm study aimed at investigating the efficacy of IVIg in the treatment of 360+ patients with mild to moderate AD over 18 months. The estimated completion date is February, 2013.\textsuperscript{27}

CONCLUSION

The evidence indicates that IVIg may be an effective treatment for patients with mild to moderate Alzheimer’s disease. A dose of 0.4g/kg/2weeks results in the best outcome regarding cognitive function. The use of IVIg stabilized or improved cognitive function over six months to three years in a severely limited number of patients. IVIg has resulted in the statistically significant increase in serum and CSF anti-A\textsubscript{β} antibodies, an increase in serum A\textsubscript{β}, and a decrease in CSF A\textsubscript{β}. The current studies are of very low quality according to the GRADE criteria.\textsuperscript{21} The high cost of IVIg and very low quality studies make it difficult to determine cost versus benefit at this time.

Further research to determine the mechanism of action of IVIg in Alzheimer’s disease is needed. Research to quantify the amount of CSF A\textsubscript{β} necessary to inhibit the accumulation of plaque would be beneficial. Also, larger, placebo-controlled,
randomized, double-blinded clinical trials conducted over an extended length of time to
determine the efficacy of IVIg in AD are needed.
References


**Table I: Characteristics of Reviewed Studies**

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**Cognitive Function**

- Studies 2 and 3 had lack of blinding, control group, and high risk for recruitment bias
- Very small sample sizes (n=24, 8, and 5, respectively)
- Baxter Corporation funded Studies 1 and 2 and makes Gammagard which was used in these studies

**Efficacy Measured by Aβ Load of Serum and CSF**

- Very low
- Important

**Safety Measured by Adverse Events**

- Very low
- Important
Table II and III. Results From Study 3: IVIg Against β-Amyloid For The Treatment of Alzheimer’s Disease

Table II: Total Concentration of $\text{A}\beta$

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Table III: Results of Cognitive Testing

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Appendix A:

Alzheimer Disease Diagnosis Criteria: NINCDS-ADRDA

I. Clinical Diagnosis of Probable Alzheimer’s Disease
   1. Dementia established by clinical examination and mental status testing and confirmed by
      neuropsychological testing
   2. Deficits in at least two cognitive domains
   3. Progressive cognitive decline, including memory
   4. Normal level of consciousness
   5. Onset between ages 40 and 90 (most common after 65) years
   6. No other possible medical or neurological explanation

II. Probable Alzheimer’s Disease Supported by
   1. Progressive aphasia, apraxia, and agnosia
   2. Impaired activities of daily living
   3. Family history of similar disorder
   4. Brain atrophy on CT/MRI, especially if progressive
   5. Normal CSF, EEG (or nonspecifically abnormal)

III. Other Clinical Features Consistent with Probable Alzheimer’s Disease
   1. Plateau in course
   2. Associated symptoms: depression; insomnia; incontinence; illusions; hallucinations;
      catastrophic verbal, emotional, or physical outbursts; sexual disorders; weight loss;
      during more advanced stages increased muscle tone, myoclonus, and abnormal gait
   3. CT normal for age

IV. Features That Make Alzheimer’s Disease Uncertain or Unlikely
   1. Acute onset
   2. Focal sensorimotor signs
   3. Seizures or gait disorder early in course

V. Clinical Diagnosis of Possible Alzheimer’s Disease
   1. Dementia with atypical onset or course in the absence of another
      medical/neuropsychiatric explanation
   2. Dementia with another disease not felt otherwise to be the cause of dementia
   3. For research purposes, a progressive focal cognitive deficit

VI. Definite Alzheimer’s Disease
   1. Meets clinical criteria for probable Alzheimer’s disease
   2. Tissue confirmation (autopsy or brain biopsy)