



Case Report

Positive Response of Alzheimer’s Disease Patients to Antiviral Therapy-Case Reports

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Citation: Niklasson B, Klitz W, Lindquist L (2022) Positive Response of Alzheimer’s Disease Patients to Antiviral Therapy-Case Reports. Ann Case Report 7: 814. DOI: 10.29011/2574-7754.100814

Received: 26 March 2022; Accepted: 31 March 2022; Published: 04 April 2022

Abstract

We have earlier reported the finding of picornavirus antigen in amyloid plaques in the hippocampus of Alzheimer’s disease (AD) patients. As a result of this finding, three AD patients received antiviral therapy directed against picornavirus infection. Pleconaril, ribavirin and efavirenz were used in different combinations over the 4-8 year intervals of treatment. Patients were followed using the Mini Mental State Examination score and the Alzheimer’s Quick Test. Results including mostly unchanged cognitive function in two patients and a clear improvement in one patient are in contrast with the expected progression of AD.

Keywords: Alzheimer’s disease; Picornavirus; Viral infection; Antiviral therapy; Pleconaril; Efavirenz; Ribavirin

Introduction

We have earlier reported findings of Ljungan virus (LV) antigen, a picornavirus causing neurological malformation in laboratory mice and also being associated with intrauterine death, sudden infant death and hydrocephalus in humans [1-4]. Recently, viral antigen was detected in both neurons and amyloid plaques in all 18 Alzheimer’s disease (AD) cases investigated but in none of the 11 age and sex matched healthy controls [5]. We here describe three AD patients receiving combinations of three different antiviral drugs, pleconaril (anti-picornavirus drug available on compassionate use program), efavirenz (non-nucleoside reverse transcriptase inhibitor) and ribavirin (broad spectrum antiviral compound enhancing pleconaril anti picornavirus effect), over a time period varying between 4 – 8 years [6,7]. The cognitive status of patients was followed with Mini Mental State Examination score (MMSE) and Alzheimer’s Quick Test (AQT). Both these instruments are well established and validated tools for evaluation of cognitive function in AD. MMSE has a maximum score of 30 points and decreases an average of 3 points per year as the

function decreases. AQT is measured in seconds to completion, and typically increases at 16 seconds per year [8,9].

Case reports

Patient 1

An 81-year-old woman was diagnosed with AD and vascular dementia, at the Memory Unit of the Geriatric Clinic, Karolinska University Hospital Stockholm, after a 2 year history of decreasing cognitive function (MMSE 28p). Pleconaril – ribavirin treatment was initiated at the time of diagnosis. Medication was intentionally interrupted after one year to evaluate if prolonged treatment was necessary. Medication was reinstated after 5 weeks due to rapid decline of cognitive function. The patient regained recently lost cognitive function over the following 3 months (decline and following improvement documented by clinical observation only). A rapid decline in cognitive function (MMSE -3p) was again noticed after 3 years. Under the assumption that viral resistance may have occurred a third antiviral compound, efavirenz, was added. A positive effect on cognitive function (MMSE +4p) was noticed and triple therapy was maintained for 5 years (total antiviral treatment period 8 years). The patient did not receive cholinesterase inhibitors at any time during follow up. Brain

Magnetic Resonance Imaging (MRI) done at the time of diagnosis found medial temporal lobe atrophy (MTA scale) with score 2 for right side and score 3-4 for left side (a score > 2 is considered abnormal). No MTA scale score progress was recorded when MRI was repeated 8 years later. However, a marginal degeneration of the white matter was documented at this time. The MMSE measured at the beginning and the end of the 8 years long period of treatment showed marginal decline (MMSE -1p). AQT improved over the same period with 53 sec recorded early and 47 sec recorded at the end of the period. The decreased decline rate (DDR) for MMSE and AQT was 96% and >100%, respectively (Table 1).

Patient 2

An 79-year-old man was diagnosed with AD by his general practitioner, a practitioner with a special interest in AD. The diagnosis was based on clinical assessment of rapid cognitive decline (MMSE dropping from 25p to 20p in 16 months). Antiviral treatment (pleconaril – ribavirin) was started at the time of diagnosis. The patient also received Donazepil (cholinesterase inhibitor) during the entire follow up period and was initiated more than 6 months prior to receiving antiviral therapy. After 6 month of antiviral treatment efavirenz replaced ribavirin because of suspected ribavirin related side effects. After another 18 months the patients stopped all antiviral medication dues to fatigue assessed to be associated with treatment. At this time a clear improvement of cognitive function had been recorded (MMSE +5p). Termination of pleconaril - efavirenz resulted in a dramatic drop in cognitive function (MMSE - 5p) in 2 months. The patient supported by family members then decided to continue with pleconaril only. The patient cognitive function improved again during the following months verified by MMSE +3p and pleconaril therapy was continued for an additional period of 2½ years. After at total period of 4 years antiviral treatment was terminated because pleconaril was no longer available. The MMSE measured at the beginning and the end of the 4 years long period of treatment showed a marginal improvement (MMSE + 2p). AQT on the other hand showed a minor change in the opposite direction over the same period increasing from 65 sec to 72 sec. The DDR for MMSE and AQT was >100% and 89%, respectively (Table 1). A continuous decline in cognitive function followed after terminating antiviral treatment and the patient died twelve months later.

Patient 3

An 68-year-old woman with history of decreasing cognitive function (MMSE 20) was diagnosed with AD at the Memory unit at the Geriatric clinic, Karolinska University Hospital Stockholm. The diagnosis was confirmed by analysis of cerebrospinal fluid (beta-amyloid, phosphor tau and tau). The patient received cholinesterase inhibitor, Galantamil, at the time of diagnosis. This medication was initiated 4 months prior to receiving antiviral

treatment and maintained during the entire follow up period. Antiviral treatment (pleconaril and efavirenz) was initiated 4 months after the diagnosis and maintained for 4 years (46 months). The patient showed improved cognitive function after receiving antiviral treatment. A rapid decline in cognitive function occurred first after 1 and later after 3 years due to interruption of antiviral therapy based on poor patient compliance. The cognitive function was restored in both instances when medication was reinstated. MMSE varied between 21 and 28 when measured during period with good compliance and periods of interrupted therapy. Antiviral treatment was terminated after 4 years of because pleconaril was no longer available. The MMSE measured at the beginning and the end of the 4 years long improved by 7points. AQT improved over the same period from 86 sec to 51 sec. The DDR for MMSE and AQT was >100% and >100%, respectively (Table 1). After terminating antiviral treatment patient cognitive function slowly decreased and she died 14 months later.

Summary of patients 1-3

All three patients in this case report were diagnosed with AD according to the international guidelines in place at the time of diagnosis [10]. Patient number 2 and 3 had advanced cognitive failure at the time of diagnosis. Diagnostic confirmation of the AD diagnosis by analysis of beta-amyloid, phosphor tau and tau cerebrospinal fluid was available only from patient number 3 and not available from patient 1 and 2. No longitudinally data on these biomarkers were available from any of the 3 patients. Patient number one had a minor cognitive dysfunction when diagnosed but the diagnosis was supported by MRI findings. We conclude that all three patients suffered from dementia, and despite absence of biomarker confirmation in two of three cases, it is likely that all suffered from Alzheimer's disease. All three antiviral medicines used were administrated orally. Pleconaril selectively inhibits picornavirus replication, and it prevents attachment and uncoating. The drug has excellent penetration to the CNS. Pleconaril has been used on a compassionate-use basis in patients with immune-deficiencies and severe human enterovirus infections [11]. Pleconaril is usually well tolerated with usually only minor gastrointestinal discomfort. The dose of pleconaril was 600 mg daily in all patients. Ribavirin, a nucleotide analogue of guanosine, has broad-spectrum direct antiviral effect on members of the picornavirus family. The major dose-limiting toxicity of ribavirin is hemolytic anemia. Nausea and fatigue were recorded on both patient 1 and 2. The dose of Ribavirin used varied between 400 mg and 800 mg daily. Efavirenz, a non-nucleoside reverse transcriptase inhibitor is widely used against HIV. Antiviral effect of efavirenz to picornavirus was found in a screening process using an animal model [12]. This antiviral effect on picornavirus is unexpected since picornavirus does not utilize reverse transcriptase for its replication. This suggests an additional antiviral mechanism not

yet determined. Efavirenz was well tolerated with exception for periods of gastrointestinal symptoms such as diarrhea resulting in periods of dose reduction or paused therapy. The dose of efavirenz was 400 mg or 600 mg daily. The fact that 2 of the 3 patients also received cholinesterase inhibitors makes it impossible to exclude some effect of co-treatment. However, the fact that both patients started cholinesterase treatment 4 and 6 months prior to antiviral treatment makes the effect of cholinesterase inhibitors less important for the observations made in the present report.

Discussion

The 4-8 year long follow up among our patients with more or less unchanged cognitive function in two patients and a clear improvement in one patient is in contrast with the expected disease progression of AD. In addition, the observation in all 3 patients of cognitive decline when antiviral therapy for different reasons was interrupted and the recovery of lost capacity on reinstatement of therapy suggests a direct causal impact of antiviral compounds on a viral infection in the brain. The rapid decline and deaths within one year in patients 2 and 3 when medicine was no longer available points to a viral resurgence in the absence of viral suppression. Based on the previously reported finding of picornavirus antigen in brain tissue from AD patients and positive clinical effect observed

in patients receiving antiviral treatment as part health care (present case report), a double blinded, placebo controlled, study using the combination of pleconaril and ribavarin was performed at the Karolinska Institute Stockholm, Sweden sponsored by Apodemus AB company [13]. When cognitive function for each patient was compared with their status prior to starting treatment, the patient group receiving the placebo decreased in cognitive function over time as expected. The patient group receiving active treatment showed continuous improvement until one month after termination of therapy when the curve changed direction and cognitive function started decreasing following a similar negative rate of change to that seen in the placebo group. The group receiving antiviral therapy had better cognitive function compared to the placebo group each time cognitive function was measured during the clinical trial. The positive difference between patients receiving active therapy compared to placebo controls was statistically significant at 1 and 12 months after termination of therapy. The decline in cognitive function noted in patients on active medication when treatment was terminated is in line with the “on-off” effect seen in the present case reports [13]. In conclusion, independent observations draw attention to the possibility that a picornavirus is responsible for AD, and that antiviral therapy can have a positive effect on clinical symptoms.

Patient no	Sex/age years	Duration of treatment (months)	MMSE				AQT			
			Before treatment (points)	After treatment (points)	Expected outcome with no treatment (points)	DDR %	Score before treatment (seconds)	Score after treatment (seconds)	Expected score with no treatment (seconds)	DDR %
1	F/81	96	28	27	4	96	53	47	181	>100
2	M/79	42	20	22	10	>100	65	72	121	89
3	F/68	46	20	27	8	>100	86	51	147	>100

Summary of the outcome of each individual patient in the case report based on the Decreased decline rate (DDR) for MMSE and AQT cognitive status tests before and after antiviral treatment in comparison with the expected outcome.

Table 1: Expected results were calculated on average decline rate in a historical control population. In such historical control population MMSE typically declines with average of 3 points per year and AQT time increase with 16 seconds per year. DDR in percent is used to express the difference between the expected decline rate in a statistical population and the clinical change seen in the patient. The DDR in percent is calculated using the formula $DDR = (1 - (\text{actual change}/\text{expected change})) \times 100$. With no decline at all DDR would be 100%, indicating full treatment effect. If patients have a reduced decline as a result of treatment the DDR will be between 1-100%. If patients improve instead of decline the number is expressed as >100%. For patient who decline faster than expected the DDR will show a negative outcome.

Acknowledgement

We wish to acknowledge Apodemus AB who provided Pleconaril prescribed to the patients ex tempore (named patient basis) free of charge

Statement of Ethics

The paper is exempt from ethical committee approval as the antiviral therapy was given as part of regular health care initiated on compassionate-use basis. Patients were not actively recruited for treatment. Patients or their close relatives actively requested treatment based on their knowledge of research program with antiviral treatment ongoing in Sweden at that time. Close relatives of the patients presented in this case report were also informed and agreed in writing to a publication based on non-identifiable individuals.

Conflict of Interest

Bo Niklasson was the CEO, research director and the sponsor representative in the drug company Apodemus AB during the planning and execution of a clinical trial that was partly based on information found in the case reports presented here. Lars Lindquist was the medical advisor in the same clinical trial. The result from the clinical trial is found in citation [13].

Funding sources

These case reports has not received any financial support or any funding except the antiviral compound Pleconaril provided free of charge by the company Apodemus AB

Author contributions

Bo Niklasson (MD) and Lars Lindquist (MD) was responsible for the antiviral treatment performed under named patient basis on compassionate-use basis. Bo Niklasson (MD) and Lars Lindquist (MD) was also responsible for interpretation of the clinical outcome of the treatment. William Klitz, Bo Niklasson and Lars Lindquist equally contributed to the interpretation of the results and the preparation of the manuscript.

Data availability statement

This report is based on medical records kept as part of regular health care regulated by the "Swedish Public Access to Information and Secrecy Act" making the medical records available only to the patient and to health care workers participating in the treatment of the patient. Further enquiries can be directed to the corresponding author.

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