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Case Report

Daily Observations of Preserved Cognition and Quality of Life after Multiple Therapies for Postmortem-Verified Severe Alzheimer's

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Abstract

Background: Cognitive abilities in Alzheimer's Disease are usually examined by formal tests conducted in a laboratory or facility. Such tests are useful for determining the severity of the disease but do not indicate the types of cognition exhibited in the daily lives of patients. This study shows significant preservation of cognition and quality of life in the daily routine of a woman with severe Alzheimer's who was given multiple therapeutic interventions. Alzheimer's disease involves multiple dysfunctions prompting several studies that found multiple therapeutic approaches minimized or even reversed the effects of the disease.

***Methods*:** The types of cognition displayed in daily living were recorded from the onset of a woman's symptoms at age 74 to her death 11 years later. Multiple therapies used included prescriptions, supplements, music, exercise, nutrition, extensive social and brain stimulation, and sleep hygiene. Three MRIs and an autopsy were performed.

***Results*:** Cognition and quality of life were observed daily over the 11-year course of the disease. Both were significantly preserved in the subject's final year despite severe Alzheimer's documented by postmortem and MRI findings. Possible explanations for the

preservation include multifactor therapies, cognitive/brain reserve, or some combination thereof.

***Conclusions*:** The results suggest that interventions can maintain appreciable cognition and quality of life and should be supported throughout the course of the disease.

Keywords

Alzheimer disease; dementia; neuropathology; amyloid; neurofibrillary tangles; life style; quality of life; cognition; apolipoprotein E4; autopsy

1. Introduction

Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ) plaques and Tau positive neurofibrillary tangles (NFT) that are associated with a gradual loss of neurons and resulting decline in cognitive skills, communication abilities, and quality of life (QOL) as AD progresses [1]. Widely used tests of the effects of AD on cognition are the MMSE [2] and ADAS-Cog [3]. These are highly structured examinations typically conducted in a laboratory or facility and primarily assess memory loss in mild to moderate AD [4-5]. Usually there is no postmortem verification of AD, but such verification exists in some studies involving some types of cognition including visual-spatial abilities, word fluency, attention, reasoning, executive functioning, and information processing [6-8].

Such tests have been very useful but they do not indicate the types of cognition that occur in the daily lives of individuals and they may miss types of cognition such as empathy, appreciation, pleasure, disappointment, and awareness of disability that could be of importance to researchers and caregivers. We report on various cognitive abilities displayed in the daily life of an 85-year old woman with post mortem confirmed high concentrations of Aβ plaques, NFT, and neuronal loss. She was observed daily, by her psychologist husband, over an 11-year period from the onset of AD symptoms to her death.

Since AD brains exhibit multiple deficiencies, multifaceted therapeutic interventions have been suggested recently [9-11] and found effective [10, 12, 13] but without postmortem verification of Alzheimer's. The present study used multiple therapies followed by postmortem verification of severe AD.

2. Materials and Methods

2.1 Subject

The subject, referred to as F., was a 140 lb. woman who graduated at the top of her class in both high school and college and received an MA in Library Science. She was employed as a university librarian for 3½ years after which she was a homemaker who raised 3 children. She was quite active, at first jogging about one mile a day and then switching to walking two to three miles a day at age 75. F never smoked or drank alcohol. She received a diagnosis of sleep apnea at about the time of her first AD symptoms and used a continuous positive airway pressure machine during

all of her AD. F lived at home with her husband her entire married life, the last 29 years in the same house.

F started having memory problems at age 74. Neuropsychological testing at age 75 led to the conclusion that she had emerging dementia of the Alzheimer type, a diagnosis confirmed at age 85 by post-mortem pathological changes: NIA Consensus Diagnosis: A3, B3, C3 (high correlation with Alzheimer's disease) [14]. Genetic testing revealed two APOEε4 alleles.

F had several major surgeries subsequent to her diagnosis of AD. At age 75, she had a proximal transverse to rectum colectomy for a redundant colon, and at age 84, a resection of about 3 ft. of her lower small bowel because of an obstruction. In each case, she recovered better than expected with the surgeries resulting in a brief decline followed by a return to her previous level of functioning. Cataract removal at age 79 had no cognitive effects. After the bowel resections, she was on various amounts of Lomotil or laxatives for the remainder of her life.

Since childhood, F had mild hypothyroidism and took 30 mg of Synthroid q.d. The last two decades of her life she was switched to 30 mg Armour Thyroid, increasing to 60 mg q.d. at age 84. She had no other known medical conditions with the exception of occasional acid reflux and urinary-tract infections.

2.2 AD Progression

The Mini-Mental State Exam (MMSE) [2] was given approximately every 6 months by F's psychologist husband. Her scores were 26 or 27 from the onset of symptoms until age 79 when they dropped to 25 and then 23. That was followed by a precipitous drop to 8 and 4 at ages 81 and 82, respectively. No further tests were administered since doing poorly on the test has been shown to be demoralizing for some people [15].

At age 75, F's long-term memory was quite good, but short-term memory was not. For example, she could play Scrabble™ but could not remember what word she played. At age 76, she had some trouble coming up with words, was more confused, less confident driving, somewhat depressed, and said she knew she was slipping.

At age 77, F had mild hallucinations that she found interesting. She sometimes forgot the function of some objects, such as her cell phone. Executive function, such as deciding what to wear, declined at age 78. She stopped driving, had difficulty getting up from toilets, but played Scrabble™ with help. She took short steps and dragged her heels but still walked about 1 mile per day.

She began wearing diapers at night at age 80 and required more help with activities of daily living. She occasionally exhibited bizarre behaviors, such as putting vitamins in her salad. She began having dizzy spells diagnosed as peripheral vestibulopathy not involving the horizontal canals. She realized her decline which increased her mild depression but her mood was generally good.

At age 81, she walked about ½ mile per day holding onto the arm of a caregiver and stopping frequently. She could not express complex thoughts, required extensive help with dressing and toileting, repeatedly read the same thing, and required help with bowel movements but urinated by herself. She gained weight from 140 to 156 requiring larger clothes.

She started using a walker at age 82, walking from 100 to 400 yards per day. She remembered her husband and childhood friends but not her son's death 4 years earlier, her own surgeries,

getting married, or college. She was concerned when her husband left on errands or she saw reflections in the window. Occasionally daytime diapers were used when her bowels were loose. She went to restaurants weekly and pushed the cart in grocery stores. She could sometimes sign her name. Caregivers began cleaning her teeth after she had over 30 cavities and one extraction. She was aware she had severe deficiencies.

At age 83, she thought her mother was still alive. She read children's books (e.g., Dr. Seuss) with caregiver's prompting. She was more emotional about movement, often saying "Please don't do that." She was generally continent during the day. She often dozed while watching movies in the evening. Sertraline reduced her fear and improved her mood. She still washed her own hands with some help. She said things like "I used to know how to clean glasses but now I don't" and "I am all mixed up."

She had several deep-vein thromboses at age 84 and was on Eliquis most of the time until her death. She recovered from her small intestine resection early in her 84th year and worked up to walking 300 to 400 yards a day until the end of her life. F died at age 85 years and 3 months because of kidney stones that resulted in pyelonephritis and sepsis.

2.3 Therapeutic Approaches

2.3.1 Prescription Medications

F started donepezil, 5 to 10 mg q.d., at age 75 and continued, with a few lapses, until discontinuing at age 78 because of adverse effects. Galantamine, 8 to 16 mg, was taken for about one month during a lapse in donepezil. Memantine was added at age 78 and continued, with a few off periods, for three years when it was stopped because of adverse effects. At age 83, F started Sertraline, 7.5 mg increased to 40 mg b.i.d. This appreciably reduced her fear but made her very drowsy, so Ritalin 10 mg b.i.d. was added. Estrogen cream from age 78 on helped prevent urinary tract infections.

2.3.2 Supplements

Non-prescription supplements were added shortly after the diagnosis of AD, although she had been taking some vitamins before the diagnosis. Huperzine-A 200 mg t.i.d. was introduced shortly after the AD diagnosis, as was lithium orotate 5 mg t.i.d. Other supplements were ginkgo biloba 240 mg t.i.d., acetyl L-carnitine 1000 mg b.i.d., alpha lipoic acid 150 mg b.i.d., B-12 5000 mcg b.i.d., calcium 500 mg q.d., D-3 500 IU q.d., Carlsen fish oil 3200 mg q.d., optimized curcumin 1000 mg b.i.d., magnesium glycinate 200 mg q.d., Thorne Metafem™ 2 capsules t.i.d., probiotics 10 billion q.d., and ubiquinol 100 mg b.i.d. Additionally, she drank 2 to 3 cups of gunpowder green tea daily from age 76 until her death.

2.3.3 General Nutrition

Meals before and after her diagnosis of AD consisted of free-range, antibiotic-free meats with organic vegetables and fruits except for one meal a week at a restaurant. Starches and sweets were used in moderation. She fasted from 7:00 pm until about 9:00 am. When F suddenly became unable to swallow pills at age 80, she was switched to one Alive Nutritional Shake™ with each

meal. Probiotics, ginkgo biloba, huperzine-A, and lithium orotate, in the amounts indicated above, were added to the shake. Fish oil and gunpowder tea were also maintained but not in the shake. Naturade Vegan Smart™ nutritional shake was used when the Alive brand became unavailable. Both products contained pea protein, fiber, and the highest level of vitamins and minerals that could be found in a commercial shake.

2.3.4 Environmental Factors

Only de-ionized/filtered water was used for drinking and cooking. Natural products were used for cleaning and no chemical products were kept in the house. The house had ceramic tile floors with no carpets and no or low volatile-organic-compound paints.

2.3.5 Exercise

After diagnosis, F gradually decreased daily walks from about 2 miles to about 350 yards her last year. In inclement weather, she walked in a store or at home. Balance exercises, lifting 1- and 2-lb weights, and exercises at a counter (marching in place, rising on heels or toes, squats, etc.) were done as tolerated. She also went to a balance-aerobics class until age 79 when it was disbanded and danced weekly until age 82.

2.3.6 Social/Brain Stimulation

F read newspapers, a magazine, and novels until age 80. At age 77, she went on an 18-day coast-to-coast trip with her husband and 3 years later went on another vacation for a week. She did remarkedly well in both instances. She attended a 5-hr class involving music, games, and various activities every week until her surgery at age 84. Her husband or a caregiver was usually present and interacting with her most of her waking hours, especially her last two years when someone was with her all of her waking hours.

2.3.7 Music and TV

F listened to music every day, some classical and some songs from her childhood to which she sometimes hummed along. Many old-time comedy TV shows that made her laugh were a daily event primarily in the last 5 years. Nearly every evening she watched movies, although they became increasingly difficult for her to follow and were not used after age 83.

2.3.8 Sleep

F got at least 8 hours of sleep per night. In her last couple of years, her sleep time increased to about 11 hours per night, probably because of the effect of Sertraline. She never took sleep aids.

2.4 MRI Scans and Autopsy

MRI scans of the brain were obtained at ages 75, 80 and 83. An autopsy of her brain was performed after her death. Genetic testing for APOEε4 alleles was also done.

3. Results

3.1 MRI

Images from the age 83 scan, 32 months before her death, are presented in Figure 1. The top image shows moderate to severe generalized atrophy and grey matter loss in the cerebral cortex. There is marked leukoaraiosis of the cerebral white matter with no discrete infarct found. The presumed etiology is neuronal loss/plaque-related neuronal injury with subsequent demyelination. The bottom two images reveal generalized atrophy and mild grey matter loss of the mesial temporal lobes.

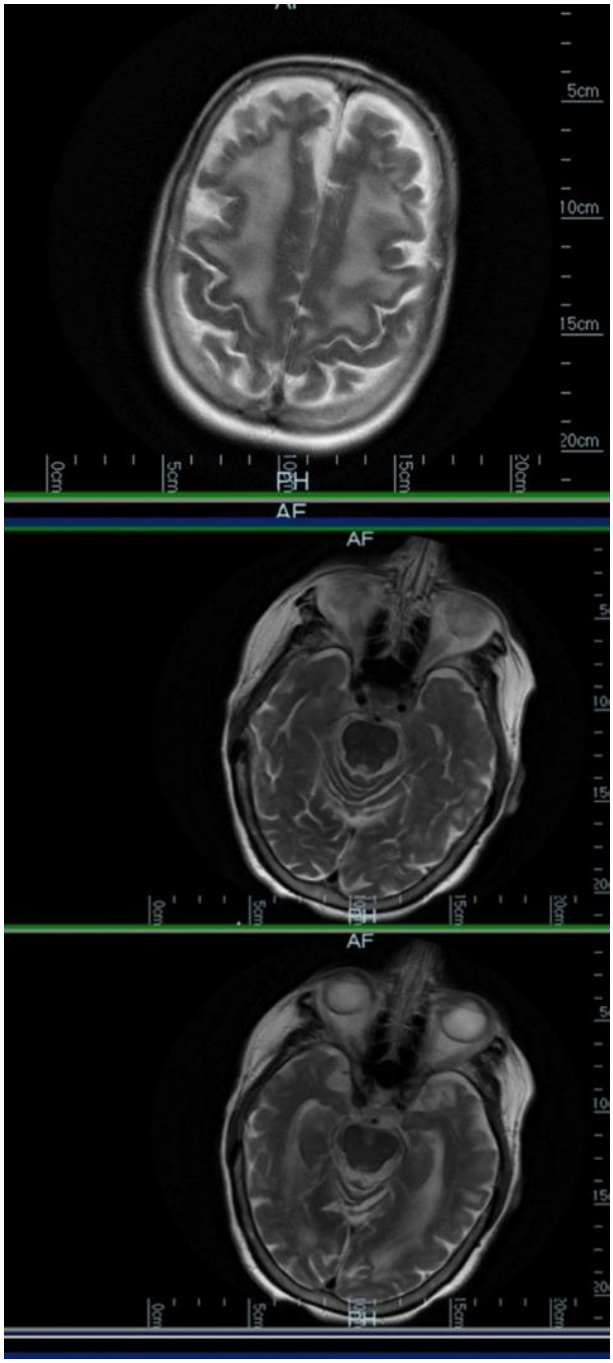

Figure 1 MRI scan at age 83. Top: cerebral cortex. Middle and bottom: mesial temporal lobes.

3.2 Autopsy Findings

Post mortem evaluation for dementia included sampling throughout the brain and antibody stains for beta-amyloid, tau protein, alpha synuclein, and TDP-43. Characteristic changes associated with Alzheimer's disease (Aβ plaques and Tau positive NFT) were found in the cerebral cortex and temporal lobes. Marked cortical neuronal loss was also found. Other findings included moderate amyloid angiopathy but essentially no cerebral atherosclerosis, and no macro or micro infarcts. The top panel of Figure 2 shows severe accumulation of Aβ plaques found in the frontal lobe cortex, parietal lobe, parahippocampal gyrus, putamen and brainstem (Thal A3). The bottom panel shows Tau positive heavy NFT concentration found in the hippocampus/parahippocampus, temporal lobe and frontal cortex (Braak B3). The concentration of Aβ neuritic plaques was also severe (CERAD C3) resulting in a combined NIA score of A3 B3 C3, high concordance with AD [14].

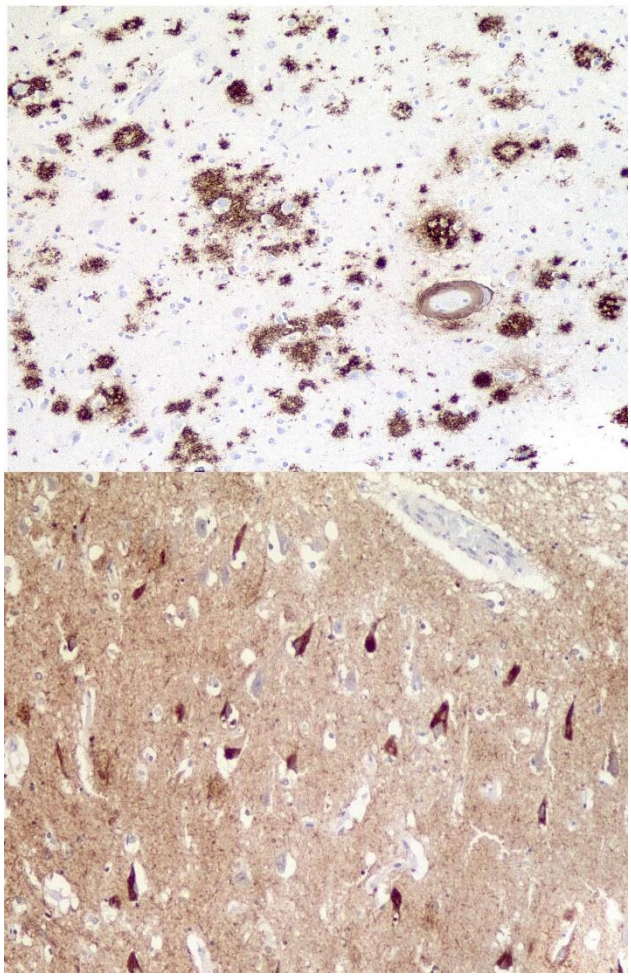

Figure 2 Stains showing βA plaques in the cerebral cortex (top) and Tau+ NFT in the temporal lobe (bottom).

The degree and distribution of amyloid plaques and tau positive NFT classifies her level of disease as high correlation with Alzheimer's disease per the National Institute on Aging consensus recommendation [14]. Extensive evaluation of the brain, including antibody studies, failed to reveal any evidence of Parkinson's, frontotemporal lobar dementia, encephalitis, tumor, multi infarct dementia, dementia with Lewy bodies or spongiform encephalopathy.

3.3 Final Cognitive Abilities

The website for the Fisher Center for Alzheimer's Research has indicated that speech in severe AD "is limited to approximately a half dozen intelligible words or fewer" [16] and the NIH Institute on Aging goes even further stating that "People with severe Alzheimer's cannot communicate" [17]. Quite in contrast, F exhibited appreciable communication and a variety of other cognitive abilities and awareness. She responded to caregivers, answered questions, showed concern for others, expressed appreciation for aid given her, displayed pleasure and displeasure, laughed appropriately, and read at a rudimentary level. Although she could not express complex thoughts, she tried, even laughing sometimes when she realized that what she said made no sense. Examples of her cognition in the last year of her life are presented in Table 1.

Table 1 Examples of cognition in F's final year [type of cognition].

Situation	Response
Husband's bad cough	"Oh dear, are you okay?" [empathy]
Caregiver helping her	"Thank you" & patted or kissed them [appreciation]
Husband's nightly kiss, saying "goodnight my pretty"	Usually said, "That's nice, thank you" [appreciation]
Giving her gummies	"Oh, I like these, thank you" [appreciation]
Seeing view outside or collectibles display	Often stopped to admire [appreciation]
Eating hot food	Realized she had to be careful [awareness]
Seeing caregiver's new shoes or other items	Noticed, said whether she liked them [awareness]
Seeing an obese woman in a clinic	Discretely elbowed caregiver and whispered, "Did you see the size of her?" [evaluation]
Seeing a caregiver out of context in a store	"Oh, it is you." [recognition but not name]
F saying something and realizing it was gibberish	Occasionally said "Oh, that is not right" and laughed [evaluation]
Son who died 8 years ago	Asked why she had not seen him [memory]
Children's books (e.g., Dr. Seuss)	Read lines with good pronunciation [reading]
Riding in a car	Looked at scenery, read signs aloud [reading]
Asking "do you have to use the bathroom or do you want" . . . (e.g., ice cream)	Answered "yes" or "no" [awareness of needs and wants]
Seeing dogs or cars out the window	Tried to tell caregiver [recognized activity]
Caregiver talking to her	Made eye contact [orienting]
Caregiver asking her to look at something	She often looked [orienting]
Caregiver asking if shake or tea was okay	"No, not really. You could do better" or "yes" [evaluation]

4. Discussion

This study documents the cognition and communication that occurred in the everyday life of an 85-year old female with severe AD and neuronal loss documented by postmortem evaluation. The strains of caregiving and the limitations imposed by AD can result in an emphasis on physical needs rather than mental and an emphasis on what patients cannot do rather than what they can. This case study suggests that a patient's cognition and QOL may have been significantly preserved by supporting various activities throughout the course of the disease.

In the present study, stimulation was provided by games, reading, exercise, music, dancing, rides, formal classes, environmental factors, and extensive interaction with others--especially caregivers. Such activities appear to have enhanced F's QOL as evidenced by her expressions of appreciation, pleasure, surprise, disappointment, frustration, concern for others, awareness of others and her surroundings, some recognition of her inabilities, some recognition that what she said did not make sense, and frequent, appropriate laughter.

Research is needed to shed light on the neurological basis for these empirical observations and permit refinement of therapeutic interventions. Such research would also have the potential for easing the AD burden of patients and their caregivers. Loss of empathy and emotional connection intensify the suffering of close caregivers, particularly family members. If this loss can be mitigated by relatively simple interventions, the impact of AD on family members and caregivers may be substantially decreased.

Other factors might have contributed to F's preservation of cognition and QOL in the presence of severe AD. Research has demonstrated that some individuals have considerable resilience in the face of severe AD [18-21]. This resilience has been attributed to cognitive reserve (differences in functional brain processes resulting from such things as intelligence, physical activity, education, and occupation, that enable individuals to cope better with neuronal loss) or brain reserve (variation in brain capacity, such as the number of neurons and synapses) [22]. Cognitive reserve may have been a factor given F's education, graduation honors, work experience, and exercise throughout her lifespan.

Multiple interventions may increase neuroplastic adaption such that alternative pathways circumvent diseased neurons thereby preserving functional capacity. Further study of the mechanisms of cognitive preservation in patients with multiple therapeutic changes may help define the neurological basis for such empirical improvements and permit refinement of interventions. In the meantime, the findings provide incentive to implement or continue such interventions in patients with cognitive impairment and to correlate clinical improvements with autopsy findings to determine the pathophysiologic role of the interventions.

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Author Contributions

K Wollen was responsible for the treatment interventions and observations of F's cognitive abilities. J Hoyt was responsible for the autopsy and reporting on the imaging and autopsy findings.

Competing Interests

The authors have declared that no competing interests exist.

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