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Case Report Open Access

Reversal of Cognitive Decline: 100 Patients

Dale E Bredesen[1*], Kenneth Sharlin[2], David Jenkins[3], Miki Okuno[3], Wes Youngberg[4], Sharon Hausman Cohen[5], Anne Stefani[5], Ronald L Brown[6], Seth Conger[6], Craig Tanio[7], Ann Hathaway[8], Mikhail Kogan[9], David Hagedorn[10], Edwin Amos[11], Amylee Amos[12], Nathaniel Bergman[13], Carol Diamond[14], Jean Lawrence[15], Ilene Naomi Rusk[16], Patricia Henry[16] and Mary Braud[16]

[1]*Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA*
[2]*Sharlin Health and Neurology/Functional Medicine, Ozark, MO, USA*
[3]*NeuroHub, Sydney, Australia*
[4]*Youngberg Lifestyle Medicine Clinic, Temecula, CA, USA*
[5]*Resilient Health, Austin, TX, USA*
[6]*Carolina Healthspan Institute, Charlotte, NC, USA*
[7]*Rezilir Health, Hollywood, FL, USA*
[8]*Integrative Functional Medicine, San Rafael, CA, USA*
[9]*GW Center for Integrative Medicine, George Washington University, Washington, DC, USA*
[10]*Coastal Integrative Medicine, Jacksonville, NC, USA*
[11]*Department of Neurology, University of California, Los Angeles, Los Angeles, CA, USA*
[12]*Amos Institute, Los Angeles, CA, USA*
[13]*Center for Functional Medicine, Cleveland Clinic, Cleveland, OH, USA*
[14]*Mount Sinai Hospital, New York, NY, USA*
[15]*Lawrence Health and Wellness, Toccoa, GA, USA*
[16]*Brain and Behavior Clinic, Boulder, CO, USA*

Abstract

The first examples of reversal of cognitive decline in Alzheimer's disease and the pre-Alzheimer's disease conditions MCI (Mild Cognitive Impairment) and SCI (Subjective Cognitive Impairment) have recently been published. These two publications described a total of 19 patients showing sustained subjective and objective improvement in cognition, using a comprehensive, precision medicine approach that involves determining the potential contributors to the cognitive decline (e.g., activation of the innate immune system by pathogens or intestinal permeability, reduction in trophic or hormonal support, specific toxin exposure, or other contributors), using a computer-based algorithm to determine subtype and then addressing each contributor using a personalized, targeted, multi-factorial approach dubbed ReCODE for reversal of cognitive decline.

An obvious criticism of the initial studies is the small number of patients reported. Therefore, we report here 100 patients, treated by several different physicians, with documented improvement in cognition, in some cases with documentation of improvement in electrophysiology or imaging, as well. This additional report provides further support for a randomized, controlled clinical trial of the protocol and the overall approach.

Keywords: Alzheimer's; Mild cognitive impairment; Programmatics; ReCODE; Precision medicine; Amyloid precursor protein; Synaptoblastic; Synaptoclastic

Introduction

Alzheimer's disease is now the third leading cause of death in the United States [1-6], and the development of effective treatment and prevention is a major healthcare goal. However, clinical trials of drug candidates for Alzheimer's disease treatment have been almost uniformly unsuccessful. There may be several reasons for such repeated failure: (1) given the long pre-symptomatic period, treatment is typically initiated late in the pathophysiological process; (2) what is referred to as Alzheimer's disease is not a single disease, but rather exhibits several different subtypes [3,4]; (3) just as for other complex chronic illnesses such as cardiovascular disease, there may be many potential contributors to Alzheimer's disease, such as inflammation, various chronic pathogens, trophic withdrawal, insulin resistance, vascular compromise, trauma, and exposure to specific toxins. Therefore, a monotherapeutic, monophasic approach is likely to be suboptimal, and personalized, multiphasic programs based on each individual's genetics and biochemistry may be preferable. Indeed, such personalized programs may offer advantages in future clinical trials of drug candidates. (4) The model of Alzheimer's disease on which the drug targets (e.g., amyloid-β peptide) have been based may be an inaccurate or incomplete model of the disease.

We have argued for a fundamentally different view of Alzheimer's disease [1,2,5,7] in which APP, the amyloid precursor protein, functions as a molecular switch due to its activity as an integrating dependence receptor [8-10]: in the presence of sufficient support from trophic signaling, APP is cleaved at the alpha site, leading to the production of two synaptoblastic peptides, sAPPα and αCTF. In contrast, in the absence of sufficient support from trophic signaling, APP is cleaved at the beta, gamma, and caspase sites, leading to the production of four synaptoclastic peptides, sAPPβ, Aβ, Jcasp, and C31. In this model, inflammation exerts an anti-trophic effect on APP signaling, at least in part *via* the NF-κB (nuclear factor κ-light chain enhancer of B cells) induction of BACE (beta-amyloid cleaving enzyme) and gamma-secretase activity. Similarly, toxins such as divalent metals (e.g., mercury) also exert an anti-trophic effect on APP signaling, since these lead to a net increased production of the toxin-binding peptide, Aβ. This

***Corresponding author:** Dale E Bredesen, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA, Tel: +014152541041; E-mail: dbredesen@buckinstitute.org

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model is compatible with the finding that the Aβ peptide functions as an antimicrobial peptide [11], together suggesting that what is referred to as Alzheimer's disease is a protective, network-downsizing response to several classes of insults: pathogens/inflammation, toxins, and withdrawal of nutrients, hormones, or trophic factors [5].

This model suggests that the probability of developing Alzheimer's disease is proportional to the ratio of synaptoclastic signaling to synaptoblastic signaling [5]. This notion has led to a treatment regimen in which the dozens of contributors to synaptoblastic and synaptoclastic signaling are measured for each patient, and a personalized program is generated to target each contributor, thus increasing synaptoblastic signals and reducing identified synaptoclastic signals. Some examples include: (1) identifying and treating pathogens such as Borrelia, Babesia, or Herpes family viruses; (2) identifying gastrointestinal hyperpermeability, repairing the gut, and enhancing the microbiome; (3) identifying insulin resistance and protein glycation, and returning insulin sensitivity and reduced protein glycation; (4) identifying and correcting suboptimal nutrient, hormone, or trophic support (including vascular support); (5) identifying toxins (metallotoxins and other inorganics, organic toxins, or biotoxins), reducing toxin exposure, and detoxifying. Since each patient has a different combination of the many potential contributors to cognitive decline, the approach to treatment is targeted and personalized.

Here we describe 100 patients with cognitive decline treated with this multi-component, precision medicine approach, and showing documented improvement.

Case Studies

Patient 1

A 68-year-old professional woman began to note paraphasic errors in her speech, severe enough that it created confusion in her listeners. She also developed depression, and was treated with an antidepressant. She began to have difficulty with everyday work such as shopping, cooking, and working at the computer. She struggled to complete a gingerbread man with her granddaughter, even though she had done this without difficulty many times before. She confused the minute hand and hour hand on a clock. She had difficulty with spelling. Her symptoms progressed, and she began to forget daily tasks. She became very concerned when she forgot to pick up her grandchildren at school twice in a two-week period.

She was found to be heterozygous for the ε4 allele of apolipoprotein E (ApoE 3/4). An amyloid PET scan (florbetapir) was positive. MRI demonstrated a hippocampal volume of 14th percentile for her age. High-sensitivity C-reactive protein (hs-CRP) was 1.1 mg/L, fasting insulin 5.6 mIU/L, hemoglobin A1c 5.5%, homocysteine 8.4 micromolar, vitamin B12 471 pg/mL, free triiodothyronine (free T3) 2.57 pg/mL, thyroid-stimulating hormone (TSH) 0.21 mIU/L, albumin 3.7 g/dL, globulin 2.7 g/dL, total cholesterol 130 mg/dL, triglycerides 29 mg/dL, serum zinc 49 mcg/dL, complement factor 4a (C4a) 7990 ng/mL, transforming growth factor beta-1 (TGF-β1) 4460 pg/ml, and matrix metalloprotease-9 497 ng/mL.

A diagnosis of Mild Cognitive Impairment (MCI) was made, and she was placed on a trial of an anti-amyloid antibody. However, with each administration, her cognition became worse for 3-5 days, then returned toward her previous MCI status. After she had become worse with each of the first four treatments, she discontinued her participation in the study.

She began treatment with the programmatic approach described previously [1]. Her MoCA increased from 24 to 30 over 17 months, and has remained stable for 18 months. Hippocampal volume increased from 14th percentile to 28th. Her symptoms improved markedly: her ability to spell returned, her speech improved, and her ability to shop, cook, and work at the computer all improved and have remained stable on follow-up.

Patient 2

A 73-year-old female physician presented with a history of memory decline and word-finding problems that had begun insidiously nearly 20 years previously, but had accelerated over the past year, leading her significant other to describe her memory as "disastrous." She could not remember recent conversations, plays she had seen, or books she had read, and mixed up the names of people and pets. She had trouble navigating, even difficulty finding her way back to her restaurant table after using the restroom.

Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) scan revealed a decrease in glucose utilization in the anterior superior precuneus bilaterally, as well as the anterolateral left temporal lobe. MRI revealed mild biparietal atrophy, with decreased hippocampal volume (16th percentile for age). On-line cognitive testing placed her at the 9th percentile for her age. ApoE genotype was 3/3, fasting glucose 90 mg/dL, hemoglobin A1c 5.3%, fasting insulin 1.6 mIU/L, homocysteine 14.1 micromolar, TSH 4.1 mIU/mL, free T3 2.6 pg/mL, reverse T3 22.6 ng/dL, vitamin B12 202 pg/mL, vitamin D 27.4 ng/mL, total cholesterol 226 mg/dL, LDL 121 mg/dL, HDL 92 mg/dL, and mercury 7 ng/mL.

She was treated with the programmatic approach described previously [1], and over 12 months, her on-line cognitive assessment improved from the 9th percentile to the 97th percentile. Her significant other noted that her memory had improved from "disastrous" to "just plain lousy" and finally to "normal." She remains on the therapeutic program, and has sustained her improvement.

Patient 3

A 62-year-old woman presented with cognitive decline, fatigue, poor sleep, and depression. She had lost the ability to remember names, do the accounting she had done previously, and run her business.

Body mass index was 24, with increased abdominal fat. MoCA was 20. She was ApoE4 heterozygous (3/4). Fasting serum glucose 101 mg/dL, hemoglobin A1c 6.1%, fasting insulin 14 mIU/L, hs-CRP 1.7 mg/L, 25-hydroxycholecalciferol 24 ng/mL, TSH 2.4 mIU/L, free T3 2.9 pg/mL, reverse T3 19 ng/dL, estradiol<6 pg/mL, and pregnenolone 38 ng/dL. Pathogen testing was negative for Borrelia, other tick-borne infections, and Herpes family viruses. Toxin testing showed no evidence of mercury or lead toxicity.

She was treated with the personalized program described previously [1], which in her case included bio-identical hormone replacement, restoring insulin sensitivity with a mildly ketogenic, plant-rich diet, regular exercise, and stress reduction; enhancing her microbiome with probiotics and prebiotics; reducing systemic inflammation with omega-3 fats; enhancing vitamin D and vitamin K2; enhancing methylation with methyl-cobalamin and methyl-tetrahydrofolate; and brain training.

Over the next 12 months she improved her metabolic status: her BMI dropped to 21.8, fasting glucose 87 mg/dL, hemoglobin A1c 5.2%, fasting insulin 5.5 mIU/L, hs-CRP 0.5 mg/L, free T3 3.2 pg/mL, TSH 2.1 mIU/L, estradiol 51 pg/mL. Her symptoms resolved, she was able to reopen her business, and her follow-up MoCA score had risen from 20 to 28. Her improvement has been sustained.

(Table 1) lists 100 patients with cognitive decline due to Alzheimer's disease, pre-Alzheimer's conditions MCI (Mild Cognitive Impairment) or SCI (Subjective Cognitive Impairment), or cognitive decline without definitive diagnosis, all of whom demonstrated documented improvement using the same targeted, multi-component program used for the three patients described above.

Patient	ApoE	Sx	Dx	Evaluation	F/u	Comment
1) 68F	3/4	Exec, calc	MCI	Am-PET+	MoCA 24→30	Patient 1 (above)
2) 73F	3/3	Amnestic	MCI	FDG-PET+	9→97%ile on-line	Patient 2 (above)
3) 59F	3/4	Exec	AD	HC vol <1%ile	MoCA 14→21	
4) 62F	ND	Multi-domain	AD		MoCA 9→17	Returned to work
5) 75F	3/4	Multi-domain	MCI	CSF ATI+	MoCA 21→25; MSQ 47→6	
6) 65M	3/4	Multi-domain	AD	CSF ATI+	MoCA 8→12; MSQ 45→20	
7) 69M	ND	Amnestic, VS, calc	AD	MRI, CSF ATI+	MoCA 19→26	
8) 57M	ND	Amnestic, exec, VS	AD	CSF ATI+	MoCA 15→27	
9) 68F	ND	Amnestic, exec	MCI	MRI	MoCA 26→27; MSQ 34→18	Marked functional improvement
10) 85M	3/3	Amnestic, VS	MCI	HC vol 9%ile	MoCA 20→21; MSQ 11→7	
11) 86M	ND	Amnestic, exec, VS	MCI	CSF ATI+	MoCA 22→24	
12) 60M	3/4	Amnestic, exec, VS	AD	MRI, NP	MoCA 17→21; MSQ 43→25	Improved QOL
13) 64F	ND	Amnestic, exec, VS	AD	MRI	MoCA 20→24; MSQ 40→10	
14) 77M	ND	Amnestic, VS, calc	MCI	MRI	MoCA 24→28; MSQ 91→42	
15) 64M	ND	Amnestic, exec, calc, VS	AD	FDG-PET+	MoCA 13→19	
16) 50M	3/3	Amnestic, aphasic	SCI	MRI	MoCA 27→28; MSQ 88→57	
17) 70M	ND	Amnestic, exec, aphasic, VS	AD	FDG-PET+	MoCa 19→24; MSQ 16→4	Marked subjective improvement; cont'd high-level employment
18) 80M	3/4	Amnestic, exec, VS	MCI	CSF ATI+	MoCA 19→20	
19) 57M	ND	Severe multi-domain	AD	MRI, NP, CSF	MoCA 0→5; MSQ 36→16	
20) 80M	3/3	Amnestic	SCI		MoCA 26→29; MSQ 25→4	
21) 69M	ND	Amnestic	MCI		MoCA 26→30; MSQ 31→20	
22) 56F	4/4	Amnestic, exec, VS	AD	FDG-PET+	MoCA 5→8; MSQ 14→8	
23) 69M	ND	Amnestic	AD	MRI	MoCA 19→26; MSQ 29→17	Doing well at work
24) 83F	3/4	Amnestic	MCI	MRI	MoCA 23→27; MSQ 31→20	
25) 71F	3/3	Amnestic, exec	AD	qEEG	MoCA 18→23; CNS-VS exec 1→63%ile; cog flex 1→58%ile; qEEG 2SD increase beta power	Marked memory improvement; return to driving and independence
26) 75M	ND	Exec	MCI	qEEG	MoCA 21→29; qEEG normalized	
27) 67F	3/4	Amnestic, exec	AD	qEEG	MoCA 15→19	Insomnia resolved
28) 61F	ND	Amnestic, exec	SCI	qEEG	CNS-VS NCI 40→73%ile; qEEG global beta power normalized	Marked subjective improvement
29) 61F	2/4	Exec	MCI	qEEG	CNS-VS 4→68%ile	Able to DC stimulant medication
30) 71M	3/3	Amnestic, exec	SCI	qEEG	CNS-VS 30→81%ile	
31) 63F	4/4	Amnestic, exec	AD	qEEG	MoCA 3→4	Decline halted
32) 78M	3/3	Amnestic, exec	AD	qEEG	MoCA 9→13	Marked subjective improvement, regained dressing and independent bathroom use
33) 50M	3/4	Amnestic, exec, calc	AD	Am-PET+, FDG-PET+	MoCA 0→9	Marked subjective improvement
34) 71M	2/3	Amnestic	MCI		MoCA 24→29	
35) 81F	3/4	Amnestic	AD	HC atrophy	MoCA 10→12	Marked subjective improvement
36) 78M	4/4	Amnestic	AD	HC volume <1%ile	MoCA 16→20	Able to run his business
37) 77M	3/4	Amnestic	AD	FDG-PET+	MoCA 14→18	Clear subjective improvement
38) 85F	3/4	Amnestic	AD		MoCA 21→24, stable 1.5y+	Word recall markedly improved
39) 70M	ND	Amnestic	AD	FDG-PET+, CSF ATI+	MoCA 19→27; MSQ 16→7	
40) 54F	ND	Amnestic	AD		MoCA 19→23; MSQ 84→41	
41) 70F	3/3	Amnestic	SCI		CVLT 39→59%ile	
42) 79M	3/4	Amnestic	AD		SLUMS 14→18	
43) 85M	3/4	Amnestic, exec	AD		SLUMS 17→22	
44) 84M	3/3	Amnestic, exec	MCI	MRI	SLUMS 19→26	
45) 79F	3/3	Amnestic	AD		MoCA 14→18	
46) 65M	4/4	Amnestic, exec	MCI	MRI, PET	SLUMS 21→28	
47) 68F	3/3	Amnestic	MCI		CVLT 18→26%ile	
48) 54M	4/4	Amnestic	SCI		CVLT 54→62%ile	
49) 77F	4/4	Amnestic	MCI	MRI	MoCA 23→25; MSQ 17→7	

50) 64M	3/3		AD		SLUMS 15→20	
51) 58F	3/3	Amnestic, exec	AD	CT: Cerebral atrophy	CNS-VS memory 1→27%ile	Marked subjective improvement
52) 70M	3/4	Amnestic	AD		MoCA 18→21	
53) 62M	3/4	Amnestic, calc	MCI	MRI	NP on-line 36→53%ile	Marked subjective improvement
54) 58F	3/3	Exec, calc	MCI	NP	CNS-VS 23→55%ile	
55) 77M	3/4	Amnestic	AD	CT: cerebral atrophy	CNS-VS 33→55%ile	
56) 66F	4/4	Amnestic	AD	Cerebral atrophy	CNS-VS 1→14%ile	Returned independence
57) 72M	4/4	Amnestic	MCI	HC vol <5%ile	CNS-VS 7→12%ile	
58) 77M	3/4	Amnestic	MCI		MoCA 23→25	
59) 83M	3/3	Amnestic	AD	Am-PET+	MMSE 24→28	
60) 64M	4/4	Amnestic	AD	HC atrophy	MMSE 22→29	
61) 71M	3/4	Aphasic, exec	AD	MRI	MoCA 5→ Declined	Vastly improved, conversing again, dressing himself, calling grandchildren by name, working again
62) 73F	3/4	Amnestic	AD	qEEG, evoked potentials	MoCA 9→20; AQ21 20→8; P300b lat. 608→576; P300b amp. 13→15.6	
63) 62F	ND	Amnestic	MCI/ AD		MoCA 20→28	Patient 3 (above)
64) 73M	4/4	Amnestic	MCI		MoCA 25→30	
65) 69F	3/4	Amnestic, exec	AD		MoCA 16→19	Minimal speech→fluid normal speech
66) 58M	3/4	Amnestic	MCI	MRI; HC vol 12%ile	MoCA 26→28; HC vol 12→24%ile	Rapid decline prior to treatment
67) 70F	3/3	Amnestic	MCI	CNS-VS	NCI 32→61%ile; psych speed 3→68%ile	
68) 91M	ND	Exec	AD		MMSE 22→27	
69) 76F	3/4	Amnestic, exec	AD	MRI; HC vol 47%ile	MoCA 17→25	Returned ability to read
70) 69M	3/3	Amnestic, calc	AD	Am-PET+	MoCA 15→25	
71) 80M	3/4	Amnestic	AD	FDG-PET+	Memory score ↑15%	Able to DC anti-hyp., statin; glucose improved
72) 64M	4/4	Amnestic, exec	AD	MRI: HC vol 10%ile, gen. atrophy	MoCA 20→24	
73) 75M	3/4	Amnestic, exec, VS	AD	MRI: HC vol 12%ile	MoCA 6→9	Declined off protocol, improved back on
74) 62M	ND	Amnestic, exec	AD		MMSE 20→24	Improved writing and map following
75) 76M	3/3	Amnestic	AD	MRI	MoCA 20→22	Improved memory
76) 50M	3/3	Exec	AD	FDG-PET+	MMSE 23→27	Marked subjective improvement
77) 53F	3/3	Exec, calc	AD	Am-PET+	MoCA 10→16	
78) 50F	2/4	Amnestic	MCI	NP	NP normalized, prosop. cleared, word finding improved	Regained ability to play piano; sustained improvement 3y ongoing; f/u of pt. reported previously [4]
79) 68F	2/4	Amnestic, exec	MCI		MoCA 25→29	Memory, driving directions much improved
80) 80F	3/3	Amnestic, exec	AD		MoCA 18→24	Memory much improved
81) 61F	3/3	Exec	AD	FDG-PET: temp hypometab	NCI 33→79%ile; exec 1→77%ile; cog flex 1→77%ile	Marked subjective improvement
82) 54F	3/3	Amnestic, exec	AD	FDG-PET+	MoCA 19→21	Reading, navigating again; earlier f/u reported [4]
83) 78F	3/4	Amnestic, exec, praxis	AD	MRI: HC vol <1%ile	MoCA 0→3	Striking change: speaking, dressing, dancing, biking, emailing, kayaking all returned
84) 74M	3/4	Amnestic	AD	FDG-PET+	CVLT-IIB 3→84%ile	Improvement sustained at 4.5 yr; f/u to initial report [4]
85) 69F	3/4	Exec	AD	MRI: cerebral atrophy	MoCA 18→27	Driver's license returned; follows recipes again; nurse asked, "What happened?!"
86) 68M	3/4	Amnestic	MCI	Am-PET+; FDG-PET+	HC vol 17→75%ile	Sustained improvement 4 yr; f/u to initial report [4]
87) 56M	3/3	Amnestic, exec, calc	MCI	FDG-PET+		Improved math, memory, able to play poker at high level again
88) 54F	4/4	Amnestic	MCI		NP: cog assessment 35→98%ile	Sustained improvement 6 yr; f/u to [4]
89) 57F	4/4	Amnestic	MCI	NP	NCI 16→73%ile	Sustained improvement 2y; f/u to [4]
90) 76M	4/4	Amnestic	AD	FDG-PET+	MMSE 23→30	Declined when DC'd protocol, improved back on; f/u to [4]

91) 56F	4/4	Amnestic, exec, word finding	MCI		Composite memory 32→61%ile	F/u to [4]
92) 48F	3/4	Amnestic	MCI		MoCA 23→30	Marked symptomatic improvement
93) 72M	ND	Amnestic, behavioral	AD			Improved memory, writing, reduced anxiety
94) 73F	3/4	Exec	MCI		MoCA 23→27	
95) 70M	3/4	Amnestic, VS	MCI	Am-PET+	NP 30→50%ile	Improved memory, navigation
96) 67F	4/4	Amnestic, exec, calc, behavioral	AD		SAGE 0	Return of addition, subtraction, multiplication, division; holding conversations again
97) 63M	3/4	Amnestic, exec, calc	AD	MRI: gray matter atrophy	MoCA 17→29	Able to return to work
98) 74F	4/4	Amnestic, exec	AD	MRI: HC vol 18%ile, cortical atrophy	MoCA 14→21	
99) 79M	3/3	Amnestic	AD	MRI	MoCA 11→15; MSQ 47→34	
100) 78M	4/4	Amnestic	AD	MRI	MoCA 20→23; MSQ 40→10	

AD: Alzheimer's Disease; Am-PET: Amyloid Positron Emission Tomography Scan; Anti-hyp: Antihypertensive; ApoE: Apolipoprotein E; ATI: Beta-Amyloid-Tau Index; Calc: Dyscalculia; CNS-VS: CNS Vital Signs; Cog: Cognitive; CSF: Cerebrospinal Fluid; CVLT: California Verbal Learning Test; DC: Discontinue; Dx: Diagnosis; Exec: Executive Function; F: Female; F/u: Follow-up; FDG-PET: Fluorodeoxyglucose Positron Emission Tomography Scan; Flex: Flexibility; HC vol: Hippocampal Volume; Hypometab: Hypometabolism; M: Male; MCI: Mild Cognitive Impairment; MMSE: Mini-Mental Status Exam; MoCA: Montreal Cognitive Assessment; MRI: Magnetic Resonance Imaging; MSQ: Mental Symptoms Questionnaire (score 0-284, higher=more symptomatic); NCI: Neurocognitive Index; ND: Not Done; NP: Neuropsychology; Prosop: Prosopagnosia; Psych: Psychomotor; Pt: Patient; qEEG: Quantitative Electroencephalogram; QOL: Quality of Life; SAGE: Self-Administered Gerocognitive Exam; SCI: Subjective Cognitive Impairment; SD: Standard Deviation(s); SLUMS: St. Louis University Mental Status Exam; Sx: Symptoms; Temp: Temporal; VS: Visuospatial Dysfunction.

Table 1: Summary of 100 patients treated with a multi-factorial, precision medicine approach to cognitive decline [1,2] and showing improvement.

Discussion

Alzheimer's disease represents a major healthcare problem, and the failure to develop effective treatment and prevention for Alzheimer's would have dire consequences nationally and globally, the bankruptcy of Medicare being among them. Therefore, the development of effective treatments is a high priority for translational biomedicine and public health programs throughout the world. However, the area of neurodegenerative diseases is arguably the area of greatest biomedical therapeutic failure from Alzheimer's to Parkinson's to Lewy body disease to amyotrophic lateral sclerosis to frontotemporal dementia to progressive supranuclear paralysis to macular degeneration and other neurodegenerative diseases, there has been no effective treatment with a sustainable, disease-modifying effect.

There may be several reasons for such uniform failure: attempting to treat without identifying the cause(s) and contributors for each patient may be one reason. Assuming a single cause, attempting to treat with a monotherapy, uniform and monophasic, may all contribute to previous suboptimal and ineffective approaches. Furthermore, targeting the mediators (e.g., Aβ peptides) instead of the root causes (e.g., pathogens, toxins, and insulin resistance) may be yet another reason for the lack of success to date.

Here we have taken a very different approach, evaluating and addressing the many potential contributors to cognitive decline for each patient. This has led to unprecedented improvements in cognition. Most importantly, the improvement is typically sustained unless the protocol is discontinued, and even the initial patients treated in 2012 have demonstrated sustained improvement. This effect implies that the root cause(s) of the degenerative process are being targeted, and thus the process itself is impacted, rather than circumventing the process with a monotherapeutic that does not affect the pathophysiology. Therefore, the sustained effect of the protocol represents a major advantage over monotherapeutics.

The current study expands on results reported earlier for 19 patients [1,2], here describing 100 patients with cognitive decline and documented improvement. Most of these patients were shown to have Alzheimer's disease or a pre-Alzheimer's condition, MCI or SCI; the remainder may or may not have had Alzheimer's disease, since the evaluations in those cases did not provide definitive evidence of Alzheimer's, nor did they provide definitive evidence of any other specific degenerative condition. The patients shown to improve included some whose laboratory values suggested each of the major subtypes [3,5] Inflammatory, atrophic, glycotoxic (insulin resistant), and toxic suggesting that the efficacy of this general approach is not restricted to a single subtype of Alzheimer's disease.

The results presented here were obtained by multiple physicians at multiple sites, suggesting that the approach should be scalable and practicable for many physicians. These results should also provide background to support randomized, controlled, prospective clinical trials. Gaining approval for such trials may be difficult, however, since they will necessarily be multi-variable and non-uniform (i.e., personalized). Furthermore, it is highly unlikely that the therapeutic response will act as a linear system, and thus the effect of the program as a whole is unlikely to equal the sum of the effects of each component, making the dissection of the protocol components difficult. However, alternative approaches, such as the removal of single components systematically, or the comparison of large numbers of program effects differing by a few components, may offer some insight into the most and least important components (although of course these may vary from patient to patient).

In the current set of 100 patients, for those evaluated by MoCA, MMSE, or SLUMS pre- and post-treatment (72 of the 100), there was a mean improvement of 4.9 points, with a standard deviation of 2.6 and a range of 1-12. Since the natural history is one of decline, the improvements that were documented must be considered as additional to the prevention of decline that would otherwise have occurred. Of course these numbers must be tempered with any failures that occur, so that it will be important to revise these in the context of a randomized, controlled clinical trial.

One of the benefits of the protocol used here is that it may enhance pharmaceutical testing and clinical trials: given the lack of improvement in the vast majority of monotherapeutic trials to date, it is possible that one problem results from a floor effect, i.e., there may be a threshold

effect needed to measure improvement. However, the positive effects described here might conceivably place the patients in a dynamic range in many cases, such that smaller effects both positive and negative might be detectable.

As more patients are treated with this approach, patterns of improvement *vs.* lack of improvement, timing, which domains typically improve and which do not, and related insights are likely to emerge. Although this was not a focus of the cases reported here, certain observations were made repeatedly. One of these was that the significant others of the patients typically reported that the patients were "more engaged" and more responsive with treatment. Facial recognition, navigation, and memory were often improved, whereas calculation and aphasia were less often improved. For those in whom specific pathogens or toxins were identified, either improvement did not occur until those were targeted therapeutically, or further improvement occurred when they were targeted. Not surprisingly, those patients showing less decline at the time of initiation of treatment responded more readily and completely than those who were further along in the course of the illness. However, there were examples of improvement even with MoCA scores as low as zero.

In summary, a targeted, personalized, precision medicine approach that addresses the multiple potential contributors to cognitive decline for each patient shows promise for the treatment of Alzheimer's disease and its harbingers, MCI and SCI. The improvements documented in the 100 patients reported here provide support for the performance of a prospective, randomized, controlled clinical trial, especially given the current lack of effective treatment for this common and otherwise terminal illness.

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