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Authors

Melikyan, Zarui A
Corrada, María M
Leiby, Anne-Marie
et al.

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Brief communication

Cognitive resilience to three dementia-related neuropathologies in an oldest-old man: A case report from The 90+ Study

Zarui A. Melikyan[a,*], María M. Corrada[a,b,c], Anne-Marie Leiby[b], Seyed Ahmad Sajjadi[a,b], Syed Bukhari[d], Thomas J. Montine[d], Claudia H. Kawas[a,b,e]

[a] Institute for Memory Impairments and Neurologic Disorders, University of California, Irvine, CA, USA
[b] Department of Neurology, University of California, Irvine, CA, USA
[c] Department of Epidemiology, University of California, Irvine, CA, USA
[d] Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA
[e] Department of Neurobiology and Behavior, University of California, Irvine, CA, USA

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ABSTRACT

Cognitive resilience provides insights into maintaining good cognition despite dementia-related neuropathologic changes. It is of special interest in the oldest-old (age 90+) because age is the strongest risk factor for dementia. We describe the only participant of *The 90+ Study*, among 367 autopsies, who maintained normal cognition despite intermediate-high levels of 3 dementia-related neuropathologic changes, advanced age, and comorbidities associated with cognitive impairment. This man remained cognitively normal throughout 13 semi-annual study visits, last one being 4 months before his death at 96. His cognitive test scores remained around the 90th percentile for non–timed tests and declined from 90th to 50th percentile (significant for semantic fluency) for timed tests. He remained physically and cognitively active until death, despite extrapyramidal signs in the last year of life. Neuropathological examination revealed intermediate level of Alzheimer's disease neuropathologic change (Thal phase 5, *Braak NFT stage IV,* CERAD score 3), Lewy bodies and neurites in the olfactory bulb, brainstem and limbic areas *(Braak PD stage 4),* TDP-43 inclusions in the amygdala and hippocampus (LATE stage 2), and a microvascular lesion in putamen. This case demonstrates that cognitive impairment is not inevitable even in the oldest-old with mutltiple dementia-related neuropathologic changes.

1. Introduction

Individuals with cognitive resilience – normal cognition despite the presence of dementia-associated neuropathologic changes including beta-amyloid, pathologic tau, hippocampal sclerosis, TAR DNA-binding protein 43 (TDP-43), microvascular lesions – might provide insights into ways of maintaining good cognition into old age (Latimer et al., 2017; Montine et al., 2019; Robinson et al., 2018). Here we describe a cognitively resilient oldest-old (age 90+) participant of *The 90+ Study* (Corrada et al., 2012).

2. Materials and method

This male participant was in the study from age 90 until death at 96 years. He completed 13 semi-annual visits (the last was 4 months before death) that included health history, neurologic, and cognitive examinations. Blood was drawn at visits 2–5, and 9. Neuropathological evaluation was completed upon death according to standard guidelines (Montine et al., 2012). We used the following antibodies for the neuropathologic investigation: (1) β-Amyloid (4G8), Biolegend, cat#800701, working dilution 1:1000; (2) PHF-Tau (AT8), ThermoScientific, cat#MN1020, working dilution 1:1000; (3) α-synuclein, pS129, Abcam cat#ab51253; (4) pTDP-43, pS409/410, BioLegend cat#829901.

The 90+ Study was approved by the University of California Irvine IRB. The participant provided written informed consent to participate in the study. Written informed consent for publication of this case report was obtained from a surviving family member.

* Corresponding author at: Institute for Memory Impairments and Neurologic Disorders, University of California, 1511 Hewitt Hall 843 Health Sciences Road, Irvine, CA 92697. Tel.: (949) 824-9124; fax: (949) 768-7695
E-mail address: zmelikya@uci.edu (Z.A. Melikyan).

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3. Results

3.1. Demographics and family history

He was a White, right-handed, college-educated, retired engineer who lived with his wife until his death. His parents did not have exceptional longevity; his mother died at age 77 of a stroke, his father died at age 30 of unknown cause. There was no history of Alzheimer's disease or dementia in close relatives.

3.2. Relevant medical history

The history included remote head trauma with loss of consciousness (36 year), transient ischemic attack (TIA) (83 year), hypertension (91 year), atherosclerosis and paroxysmal atrial fibrillation (unknown ages), congestive heart failure (CHF) (91 year), skin (80 year and 94 year), prostate (94 year) and metastatic (96 year) cancers, and arrhythmia (unknown age). His blood pressure was normal across visits with 135/65 mm Hg at the first and 118/50 mm Hg at the last visit. His body mass index was normal at 20.2 at the first visit and in the underweight range at 17.7 at the last visit. Two brain CT scans following falls at ages 95 and 96 showed moderate atrophy, mild white matter disease, and bilateral subinsular lacunar infarcts (Fig. 1). Bloodwork showed normal thyroid function and slightly elevated C-reactive protein and lipids. His apolipoprotein E (*APOE*) genotype was $\varepsilon 3/\varepsilon 4$. No other genetic testing was done. Medications included aspirin (81 mg), diltiazem hydrochloride (180 mg), tamsulosin (0.4 mg), several vitamins and supplements, including "mind-boosting" ones. His Modified Hachinski Ischemic Scale score was 3. His primary cause of death was cardiopulmonary arrest with prostate cancer a contributing cause.

3.3. Cognitive and daily functioning, neurologic examinations

He was cognitively normal at each study visit. At visit 11 (95 year), when undergoing cancer treatment, he was slower to complete cognitive tests. Across all visits, his cognitive test scores remained within normal limits (Fig. 1). His scores for non–timed tests (global cognition, word list memory, naming, working memory, visual-spatial, and construction) were stable around the 90th percentile (Whittle et al., 2007). Although scores for timed tests (indexing language, attention, executive function, and motor speed) showed a downward trajectory from 90th and 50th percentile, the difference between first and last visit was only significant for Animal fluency, according to the Reliable Change Index (Jacobson and Truax, 1991). His scores continued to be excellent despite new onset of subjective cognitive complaints (93 year) and signs of depression (depressive appearance, Geriatric Depression Scale score = 5, 93 year); depression was not formally diagnosed or treated.

He remained physically and cognitively active: volunteering and learning a foreign language at least up until 2 years before his death; going on bus trips, exercising daily and swimming at least up until a year before his death; reading daily, doing housework, managing his investments, and daily walking until his death. At age 94 he stopped driving after a car accident (unclear who was at fault) and started using public transportation. Although he was aware of his medications and ordered them, at age 95 he occasionally started forgetting to take them, so his wife set them in the pillbox.

Initial physical exams revealed balance problems, peripheral neuropathy, wide-based, and shuffling gait. His gait speed was in the 50th–75th percentile in the first and in 25th–50th percentile in the last visit compared to age-matched men in the study. At 95 he began using a cane and walker. At age 96 extrapyramidal signs of moderate severity were noted. His vision and hearing abilities did not interfere with study evaluations.

3.4. Neuropathological examination

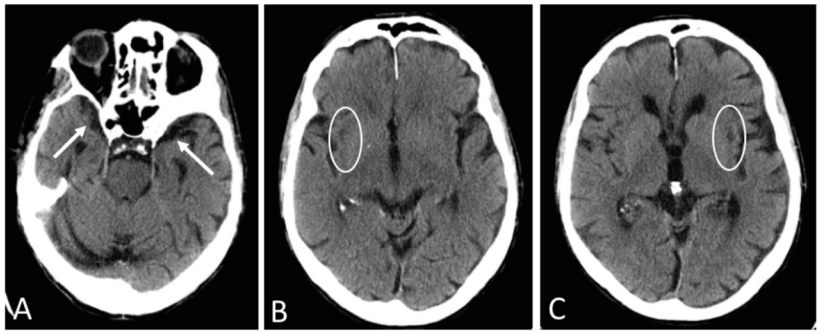
His brain weight was 1198 grams, which is in the 43rd percentile of 95–97-year-old cognitively normal men of *The 90+ Study*. Among neuropathologic changes associated with cognitive impairment in the oldest-old, examination revealed an intermediate level of Alzheimer's disease neuropathologic change with high levels of amyloid plaques (A score 3 of 3; Thal phase 5), moderate neurofibrillary degeneration (B score 2 of 3; *Braak NFT stage* IV), and frequent neuritic plaques by Consortium to Establish Registry for Alzheimer's Disease (CERAD) (C score 3 of 3). Diffuse beta-amyloid plaques were observed in the neocortex, allocortex, and brainstem. Neurofibrillary tanges were present in both mid hippocampi (at the level of lateral geniculate nucleus). Lewy bodies and neurites were present in the olfactory bulb, brainstem, and limbic areas *(Braak PD stage 4).* Although Lewy bodies were identified in multiple fields in the cingulate cortex, the highest frequency was 1 Lewy body per 10X field. Intracytoplasmic phosphorylated TDP-43 (pTDP-43) inclusions were present in the amygdala and hippocampus (LATE neuropathologic change stage 2 of 3). The highest frequency of pTDP-43 inclusions was 6 per 10X field in the hippocampus and 2 per 10X field in the amygdala (Fig. 1). One microvascular lesion was found in the deep gray matter (putamen). Additional findings were cerebral amyloid angiopathy involving both meningeal and parenchymal small vessels in the cerebral cortex and cerebellum, aging-related tau astrogliopathy (ARTAG) in gray and white matter, and mild atherosclerosis.

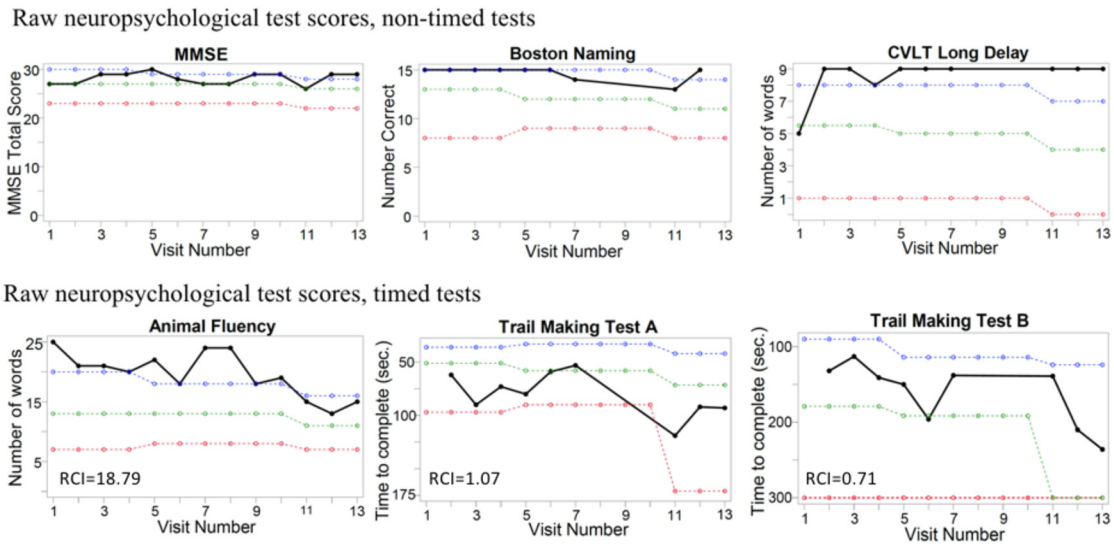
4. Discussion

Cognitive resilience demonstrates that cognitive impairment is not inevitable in the face of dementia-related neuropathologic changes. We described an oldest-old man with normal cognition who by virtue of his advanced age, *APOE* genotype, comorbidities associated with cognitive impairment: head trauma, TIA, CHF, and intermediate-high levels of 3 dementia-related neuropathologic changes, had a high risk of dementia (Corrada et al., 2010). Although the possibility of dementia if he had lived even longer cannot be excluded, we think this man exemplifies the definition of cognitive resilience.

Cognitive resilience to intermediate-high levels of one dementia-related neuropathologic change is not uncommon, seen in up to 47% in community- or population-based studies with mean age at death in the mid-80s (Sonnen et al., 2011). However, resilience to more than one neuropathologic change is notably less common, 4%–6% (Sonnen et al., 2011). Cognitive resilience in the oldest-old may be even less prevalent because of high dementia risk (Corrada et al., 2010) and prevalence of multiple neuropathologic changes (Kawas et al., 2015). Indeed, out of 367 autopsies in *The 90+ Study,* 30 (8%) had at least 3 dementia-related neuropathologic changes, but only this participant was cognitively resilient.

Several factors associated with cognitive resilience (Casaletto et al., 2020) were present in this participant. He had a high level of education, modest number of comorbidities, modest sensory and motor impairments, despite moderate levels of Lewy pathology, and continued to be physically and cognitively active. His late onset of hypertension is thought to be associated with a lower risk of dementia in the oldest-old (Corrada et al., 2017), although it is hard to tease apart the effect of hypertension from the effect of antihypertensive therapy. Propensity to some cancers, including skin





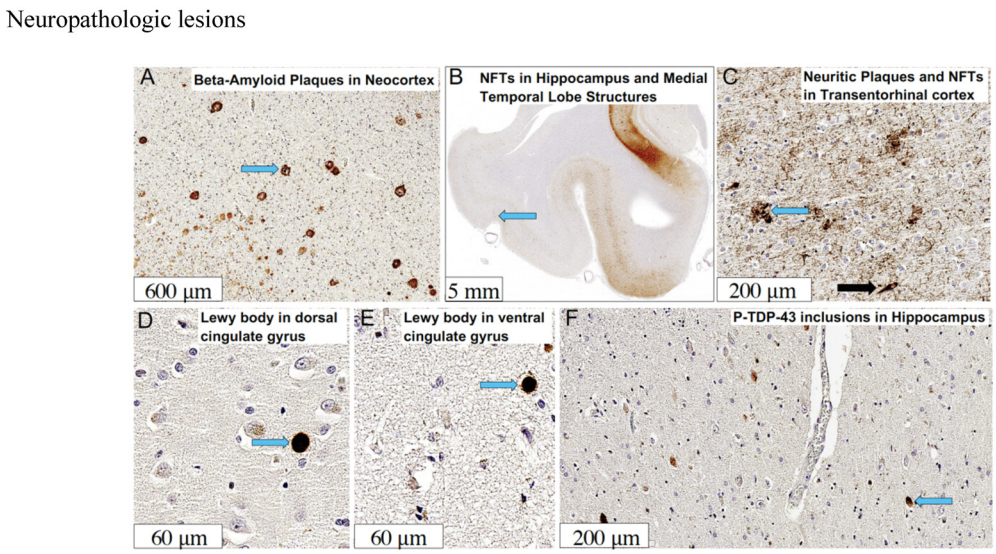


Fig. 1. Brain CT scan, raw neuropsychological test scores, and neuropathologic lesions. Clinical brain CT scan done at age 96 following a fall: (A) medial temporal lobe atrophy (arrows), (B) right subinsular lacunar infarct (circled area), (C) left subinsular lacunar infarct (circled area). Raw neuropsychological test scores from select tests (illustrating observed trends) for 13 visits relative to the 90th (blue), 50th (green), and 10th (red) percentiles of the normative oldest-old group from The 90+ Study (Whittle et al., 2007). Some tests were not completed on visits 1, 8–11 due to participant's fatigue or request for a short visit. Scores on non–timed tests (top row) were mostly near the 90th percentile. Scores on timed tests (bottom row) were between 50th and 90th percentile. Reliable Change Index (RCI) indicates whether the score change between visit 1 and 13 is statistically significant. RCI $\geq$1.96 indicates significant change. Photomicrographs of pathologic lesions (A – C) of Alzheimer's disease show immunoreactivity for (A) beta-amyloid in plaques (blue arrow) in neocortex (middle frontal gyrus) that also were present in hippocampus, striatum, and midbrain, (B) paired helical filament tau in hippocampal formation and temporal isocortex (blue arrow) that at higher magnification shows (C) neuritic plaques (blue arrow) and neurofibrillary tangles (black arrow). Immunohistochemistry for phospho-129-α-synuclein revealed Lewy bodies in the (D) dorsal and (E) ventral cingulate gyrus. Phospho-TDP-43 inclusions were in hippocampus (F) and in amygdala (Color version of the figure is available online.)

and prostate cancers that he has developed in the last 2 years of his life, as well as cancer treatments, may decrease the risk of dementia according to some, but not all epidemiologic studies (for review see Houck et al., 2018). He had some slowing in Animal fluency and gait, which is typical of normal aging (Salthouse, 2010).

5. Conclusions

Health and lifestyle factors in this cognitively normal oldest-old man may provide some insight into understanding cognitive resilience in the face of 3 dementia-related neuropathologic changes *and comorbidities associated with cognitive impairment*.

Disclosures statement

The authors have no actual or potential conflicts of interest.

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