Association between cognitive decline progression and α-synuclein oligomers in patients with dementia with Lewy bodies

Hiroaki Sekiya, M.D., Ph.D.[1], Lukas Franke[1], Daisuke Ono, M.D., Ph.D.[1], Tanis J. Ferman, PhD[2], Pamela J. McLean, Ph.D.[1], Dennis W. Dickson, M.D.[1]

[1] Department of Neuroscience, Mayo Clinic, Jacksonville, FL, [2] Department of Psychiatry & Psychology, Mayo Clinic, Jacksonville, FL

ABSTRACT

BACKGROUND

Our previous study demonstrated that patients with Parkinson's disease with cognitive impairment showed more α-synuclein oligomers in the hippocampus compared to those without cognitive impairment[1]. We sought to understand the association between cognitive trajectory and α-synuclein oligomers in prospectively assessed patients with dementia with Lewy bodies (DLB).

METHODS

Thirteen cases were identified from our brain bank who met the following criteria: (1) Clinical diagnosis of DLB with pathological confirmation of Lewy body disease, (2) Longitudinal neuropsychological follow-up at Mayo Clinic Jacksonville, (3) Underwent Mini-Mental State Examination (MMSE) three or more times, (4) Initial MMSE score ≥ 24, and (5) Final MMSE within three years of death. The annual rate of MMSE decline was calculated for each case. Hippocampal sections from four cases each of the rapid decline group (annual MMSE decline > 4) and the slow decline group (annual MMSE decline < 2) were subjected to α-synuclein proximity ligation assay staining[2,3] to detect α-synuclein oligomers and phosphorylated- α-synuclein immunohistochemistry. Each pathological burden was assessed semi-quantitatively.

RESULTS

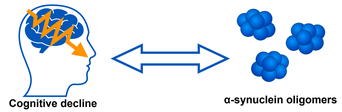
The rapid and slow trajectory groups did not differ in age at death (74±8 vs. 77±4; P=0.51), disease duration (7±2 vs. 10±4; P=0.44), Braak neurofibrillary tangle stage (median 4.5 vs. 2; P=0.06), or Thal amyloid phase (median 4.5 vs. 1.5; P=0.06). The rapid decline group had a higher α-synuclein oligomer burden in the CA1 subfield of the hippocampus compared to those with slow cognitive decline (P = 0.03). There was also a trend for a higher α-synuclein oligomer burden in CA2 (P = 0.11) and CA4 (P= 0.07) in the rapid decline group. No difference in Lewy-related pathology burden was observed in any of these regions between the two groups.

CONCLUSIONS

Given the toxicity of α-synuclein oligomers, their accumulation in the hippocampus may accelerate cognitive decline.

OBJECTIVES

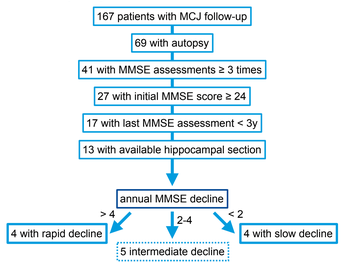
- To understand the association between cognitive trajectory and α-synuclein (αSYN) oligomers in patients with dementia with Lewy bodies who underwent prospective cognitive assessments.



METHODS 1

- We identified 13 patients from the Mayo Clinic brain bank who met the following criteria.
  1) Clinical Dx = DLB and Pathological Dx = Lewy body disease
  2) Longitudinal neuropsychological follow-up at MCJ
  3) MMSE assessment ≥ 3 times
  4) Initial MMSE score ≥ 24
  5) Final MMSE within 3 years of death
- Annual rate of MMSE decline was calculated and identified the rapid and slow cognitive decline groups (N = 4 each).

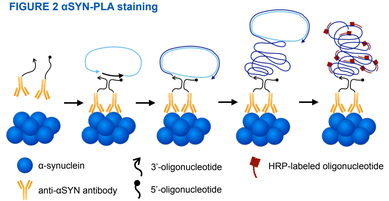
FIGURE 1 Study design



METHODS 2

- αSYN oligomers were visualized using αSYN proximity ligation assay (αSYN-PLA) staining[1,2,3].
- Phosphorylated αSYN immunohistochemistry was conducted to detect Lewy-related pathologies (LRPs).

FIGURE 2 αSYN-PLA staining



RESULTS 1

- Annual MMSE change was -7.1 in the rapid decline group and -1.4 in the slow decline group (P = 0.03).
- Age at death, disease duration, Braak neurofibrillary tangle stage, Thal amyloid phase were not significant different.

TABLE Patient characteristics

	ID	Age at death	Sex	Disease duration	Braak NFT stage	Thal Aβ phase	Annual MMSE change
	1	85	M	5.2	IV	5	-9.2
Rapid	2	65	M	11.0	III	3	-9.3
Group	3	76	M	6.5	V	4	-4.2
	4	68	F	7.1	V	5	-5.6
	5	81	M	7.8	III	2	-1.2
Slow	6	72	M	7.6	II	1	-1.8
Group	7	75	M	16.5	II	0	-1.2
	8	80	M	6.6	I	3	-1.2
P value (Rapid vs Slow)		0.51		0.44	0.06	0.06	**0.03***

RESULTS 2

FIGURE 3 αSYN oligomers in neuropil and neurons

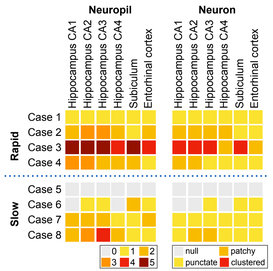


FIGURE 4 αSYN oligomer and LRP burden

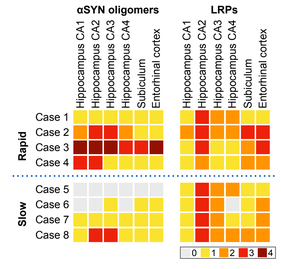


FIGURE 5 αSYN oligomers in CA1

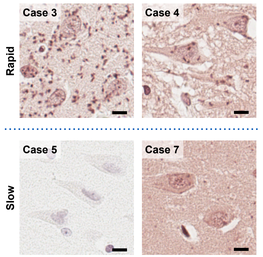
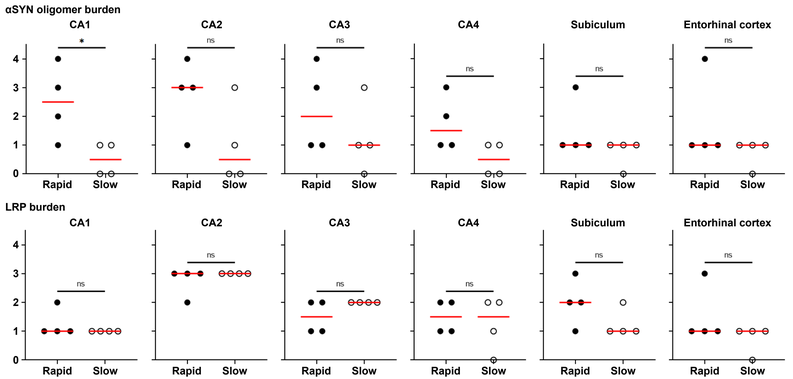


FIGURE 6 Comparison of each αSYN aggregate between patients with rapid and slow cognitive decline



DISCUSSION

- We examined both early- and late-stage αSYN aggregates in the hippocampus and entorhinal cortex in DLB patients and compared their burden between patients with rapid and slow cognitive decline as determined by longitudinal neuropsychological assessments.
- Patients with rapid cognitive decline had more abundant αSYN oligomers in the CA1 compared to those with slow decline.
- LRP burden was not significantly different in any regions between patients with rapid and slow cognitive decline.
- Accumulating evidence has shown that αSYN oligomers are more toxic than LRPs[4,5].
- It has been reported that aSYN oligomers in the hippocampus are more abundant in patients with Parkinson's disease[1] and multiple system atrophy with cognitive dysfunction[6].
- Our results suggest that αSYN oligomers in the hippocampus not only cause cognitive dysfunction, but also contribute to its progression.

CONCLUSIONS

- The present study demonstrated that DLB patients with rapid cognitive decline had more abundant αSYN oligomers in the hippocampal CA1 subregion compared to those with slow decline.
- Given the toxicity of αSYN oligomers, their accumulation in the hippocampus may accelerate cognitive decline.

REFERENCES

1. Sekiya H, et al. *Acta Neuropathol Commun.* 2022
2. Roberts F, et al. *Brain.* 2015
3. Sekiya H, et al. *Acta Neuropatol.* 2019
4. Cremades N, et al. *Cell.* 2012
5. Winner B, et al. *Proc Natl Acad Sci USA.* 2011
6. Miki Y, et al. *Neuropathol Appl Neurobiol.* 2022