

Progression of Extrapyrarnidal Signs in Alzheimer's Disease: Clinical and Neuropathological Correlates

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Abstract.

Background: Extrapyrarnidal signs (EPS) are frequent in Alzheimer's disease (AD) and core manifestation of related diseases, i.e., dementia with Lewy bodies and Parkinson's disease; furthermore, Lewy bodies and AD-type pathology occur in all three conditions.

Objective: To identify clusters of EPS progression over time and their clinical and neuropathological correlates.

Methods: 3,502 AD patients with longitudinal assessment from the National Alzheimer's Coordinating Center database were included; 394 provided neuropathological data. k-means algorithm was employed to identify clusters of EPS progression and those were compared in terms of cognitive profile, neuropsychiatric features and neuropathological findings.

Results: Three clusters of EPS progression were identified: no/low ($n = 1,583$), medium ($n = 1,259$), and high ($n = 660$) EPS burden. Compared to those with no/low and medium EPS, those with high EPS had greater cognitive and neuropsychiatric impairment, specifically hallucinations. Despite similar AD-pathology across the three clusters, the high EPS cluster had a significantly number of subjects diagnosed with dementia with Lewy bodies.

Conclusions: Cluster analysis of EPS progression over time identified different subgroups of AD patients with distinct clinical and neuropathological features.

Keywords: Alzheimer's disease, extrapyramidal signs, Lewy bodies, longitudinal studies, K-means clustering

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive impairment, predominantly in the memory domain, and is the leading cause of dementia in the elderly [1]. Most studies assess AD as a single phenotypic outcome (presence versus absence of the disease), neglecting the

heterogeneity of the disease. In fact, motor and psychiatric manifestations, in particular extrapyramidal signs (EPS) and hallucinations, are frequently observed. In patients with incident AD, the frequency of EPS is approximately 12% in the early stages of the disease and increase at an annual rate of about 1.3% [2]. In addition, patients with EPS tend to have a faster rate of cognitive decline compared to those without EPS [3]. Hallucinations in AD are also frequent, can be visual or auditory [4], and are associated with faster cognitive and functional decline [5].

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These clinical signs and symptoms are present in AD as well as in dementia with Lewy bodies (DLB) [6] and in Parkinson's disease (PD) [7], with these three entities also sharing neuropathological features. The brains of patients clinically diagnosed with AD often have Lewy bodies in addition to amyloid plaques and neurofibrillary tangles. For DLB, the 2005 Criteria Consortium [6] revised the pathologic diagnosis, highlighting the degree of overlap between AD and Lewy body pathology, with a focus on the anatomic distribution of the latter. Therefore, these most recent definitions have moved toward defining DLB as a clinicopathologic entity. Ultimately, brains of patients diagnosed with PD often show, in addition to Lewy bodies, neurofibrillary tangles and amyloid plaques [8]. Thus, while AD, DLB, and PD are currently defined as individual disease entities, it remains possible that they actually reflect a continuum of a single spectrum disorder [9].

Clinical and neuropathological substrates of EPS in patients with AD have generated conflictive results: in order to clarify this aspect of the disease, we capitalized on the data extracted from the National Alzheimer's Coordinating Center (NACC) cohort aiming to group subjects into clusters with respect to the presence and progression of EPS over time and to investigate clinical and neuropathological correlates of these clusters. Many statistical methods have been developed to address this issue: k-means [10] is one of the most popular clustering algorithms applied to longitudinal data.

METHODS

Study sample

The study population consisted of patients enrolled in the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) [11]. Patients were seen approximately annually at one of the 34 Alzheimer's Disease Centers (ADCs). The Uniform Data Set (UDS) includes standardized data collection forms that capture information on demographic and clinical subject characteristics. Written informed consent was obtained from all participants and their study partners. Research using the NACC database was approved by the Institutional Review Board at the University of Washington. More detailed information on the NACC database can be found online (<http://www.alz.washington.edu>).

For inclusion in this study, patients: (1) were 60–90 years old at the initial UDS visit; (2) had a primary

diagnosis of probable or possible AD dementia [12] at the initial UDS visit; and (3) had a least two UDS visits with non-missing Unified Parkinson's Disease Rating Scale (UPDRS) – part III score at the time of data abstraction. Individuals with diagnosis other than AD were then excluded. Visits with reported use of medications for PD (e.g., levodopa or dopaminergic agents) or antipsychotic medications were excluded from further analyses. Data from visits six or more years after the initial visit were excluded.

Main outcome

Extrapyramidal signs were measured by trained and certified clinicians for neurodegenerative disorders using the UPDRS-part III [13] approximately annually for up to five years. For each visit, UPDRS items were summed to create a total score ranging from 0 (absence of extrapyramidal signs) to a maximum of 108 (maximum impairment).

Clinical assessment

Potential correlates of EPS progression included neuropsychiatric symptoms and cognitive function. The Neuropsychiatric Inventory (NPI-Q) [14] collects information regarding depression, apathy, hallucinations, delusions, and nighttime behaviors. Reported cognitive fluctuation was also considered as additional correlate. Cognitive function was measured using the Mini-Mental Status Examination (MMSE) [15] and the Clinical Dementia Rating Sum of Boxes score (CDR-SB) [16]. The CDR rates subjects' cognitive and functional abilities in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The clinician, incorporating input from the subject's co-participant, evaluated impairment in each domain as none (0), questionable or very mild (0.5), mild (1), moderate (2), or severe (3). The scores for each domain were summed to create a Sum of Box score ranging from 0 to 18, with higher scores indicating more severe impairment.

Neuropathological assessment

Neuropathology data were available for a subset of these participants that had the last clinical evaluation within two years of death ($n=394$, 11%). For this group of patients, we compared clusters across the following diagnoses: 1) primary neuropathologic diagnoses, including AD [17] and DLB (adapting the 2005

Consensus criteria [6], which considered the overlap of AD and Lewy body type pathology in order to profile the likelihood that the clinical syndrome is due to DLB pathology) and 2) presence of large artery infarct or hemorrhagic events and small artery infarcts and/or hemorrhages (i.e., lacunes). For most analyses, neuropathological categories were collapsed; for example, three categories were created for Braak stage [18]: lesser stages (0 through II), intermediate stages (III and IV) and higher stages (V and VI, representing extensive neocortical neurofibrillary tangles). Features assessed by neuropathologists are described in the NACC Neuropathology Guidebook (<https://www.alz.washington.edu/NONMEMBER/NP/npguide9.pdf>).

Covariates

Analyses were adjusted for I) gender, II) age at most recent UDS visit, III) age at cognitive symptom onset, IV) number of follow-ups, and V) years of education. Age at onset of cognitive decline is reported by the clinician with input from medical records, direct observation, and subject/informant report.

Statistical analysis

Progression of extrapyramidal signs was determined by drawing sub-clusters of escalating severity employing the *KmL* package (<http://cran.r-project.org/web/packages/kml/>), an implementation of *k*-means designed to cluster longitudinal data. Briefly, this is a hill-climbing algorithm belonging to the EM class (Expectation-Maximization). First, the algorithm picks *n* items and labels them as initial centroids; then, it assigns each point to the nearest centroid and finally updates the centroid of each cluster on the basis of the elements that are grouped together. The previous steps are then repeated until every point is stably assigned to one of *n* clusters. The selection method does not require normality or other parametric assumptions, nor any assumption regarding the trajectory's shape. In addition, it is independent of time scaling and able to handle missing data. The optimal number of clusters is unknown *a priori*: one possible solution is to run multiple analyses with different numbers of clusters and ultimately choose the best model. Alternatively, use of the Calinski & Harabatz criterion [19] allows selection of the optimal number of clusters. This approach combines the within-cluster and between-cluster covariance matrix (i.e., indicators of cluster's compactness and distance).

Optimal clusters distinction has large between-cluster variance and a small within-cluster variance, thus the higher Calinski-Harabasz index value, the better the solution of clusters found.

Study demographics and cluster assignment were explored through χ^2 statistics, Kruskal-Wallis tests, or analysis of variance depending on the nature of the variable. The association between clinical and demographic characteristics with EPS progression cluster assignment was evaluated using multinomial logistic regression, reported as odd ratios (OR). Demographic and cognitive assessment data came from the most recent UDS visit; the subjects were labeled as free of neuropsychiatric symptoms if never reported in any of the available follow-ups. In the reduced model, each characteristic was the predictor and the EPS cluster indicator was the outcome measure, adjusting for gender, age at onset, age at last evaluation, number of available follow-ups, and years of education. As supplementary analyses, we employed a generalized linear mixed model that included the different ADC centers as a random effect to adjust for possible center variability.

Differences in the proportion of subjects for each primary neuropathological diagnoses, Braak staging, and Lewy body pathology (and their overlap) were tested using a χ^2 test or Jonckheere Trend Test. Fisher's exact tests were computed when sparse or unbalance tables did not meet assumptions for asymptotic methods.

Post-hoc testing was carried out in order to address comparisons between the three clusters, adjusting for false discovery rate (FDR) correction [19]. Analyses were performed using R version 3.0.2 and SAS version 9.3.

RESULTS

Of the 9,655 subjects with possible/probable AD in the NACC-UDS database, 3,502 met all study inclusion criteria, and of these, 394 (11%) provided neuropathology data. A flow chart describing the exclusion criteria and resulting sample sizes at each step is reported in Fig. 1

KmL analyses

The *K*-means algorithm was applied to UPDRS longitudinal data from the NACC data set, restricted to patients who met all inclusion criteria described above. Potential cluster numbers ranging from two to six were tested in order to choose the model that best described the UPDRS trajectories in the study population. On the basis of the Calinski and Harabatz criterion (highest

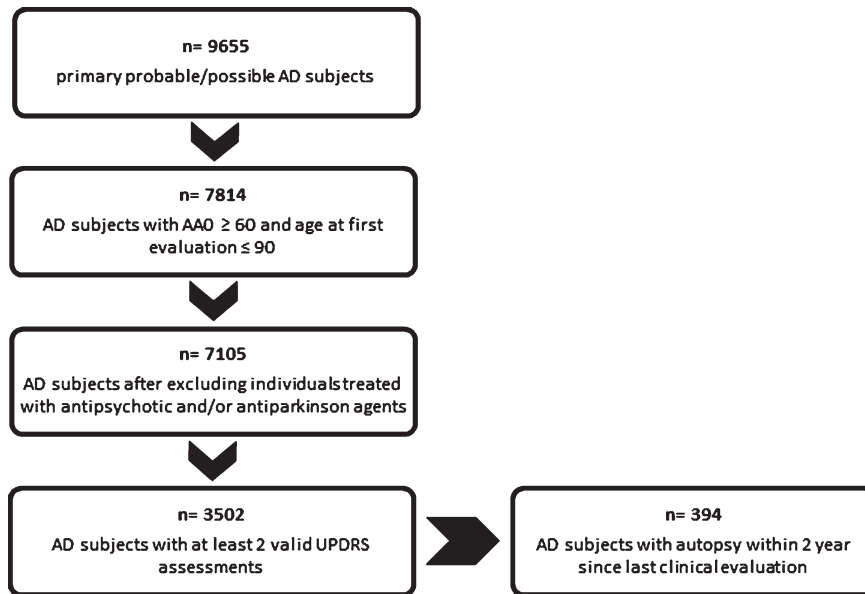


Fig. 1. Flow chart showing selection criteria and sample numerosity at each step. AD, Alzheimer's disease; AAO, age at onset; UPDRS, Unified Parkinson's Disease Rating Scale.

score = best partition), the "three clusters" was selected as the best solution (Fig. 2). The three clusters solution resulted in 1,583 subjects in cluster A (no/low EPS); 1,259 in cluster B (medium EPS); and 660 in cluster C (high EPS): a spaghetti plot of observed trajectories and the three resulting cluster trajectories are illustrated in Fig. 3. Overall, the UPDRS total score for the entire sample progresses from a median of 2 to a median of 4, after a maximum of five years of follow-up. Cluster analysis, on the contrary, disentangled the heterogeneity of the whole sample by identifying three distinct clusters: cluster A (no/low EPS) ranging from 0 points at baseline to 0 points at the end of follow-up, cluster B (medium EPS load) ranging from 4 to 7, and cluster C (high EPS load) ranging from 12 to 19 points. A Kruskal-Wallis test showed that the three clusters were significantly different from each other in terms of UPDRS score at each time interval ($p < 0.001$).

Study demographics

Study demographics and clinical characteristics are illustrated in Table 1. Subjects in the cluster with medium EPS load were less likely to be female compared to the other two clusters. Clusters with medium and high EPS showed an older age of onset and consequently an older age at last evaluation ($p < 0.001$ for both variables); ultimately, time from onset to study enrollment was not significantly different across the three clusters.

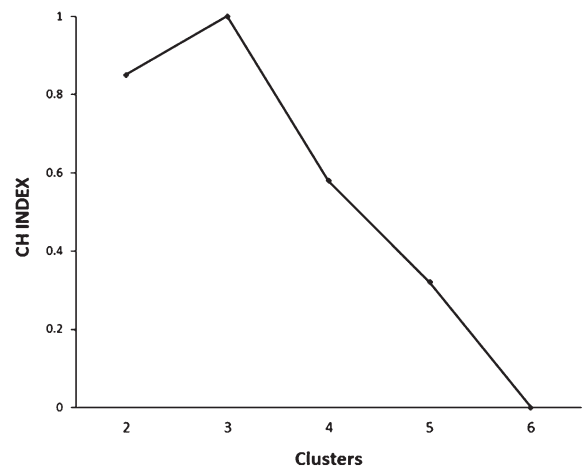


Fig. 2. Potential cluster solutions and Calinski-Harabatz (CH) index. X-axis shows all potential cluster solutions tested; Y-axis shows standardized CH index (1 = best solution; 0 = worst solution).

Clinical assessment

Compared to those with no/low EPS, those with medium and high EPS (labeled as cluster "A", "B", and "C", respectively in Table 2) more often had apathy and nighttime aberrant behaviors. No significant differences were found between the three clusters with regards to delusions or depression. When those with high EPS were compared to those with medium EPS, only hallucination and cognitive fluctuation proved to be statistically different ($p \leq 0.001$), whereas no

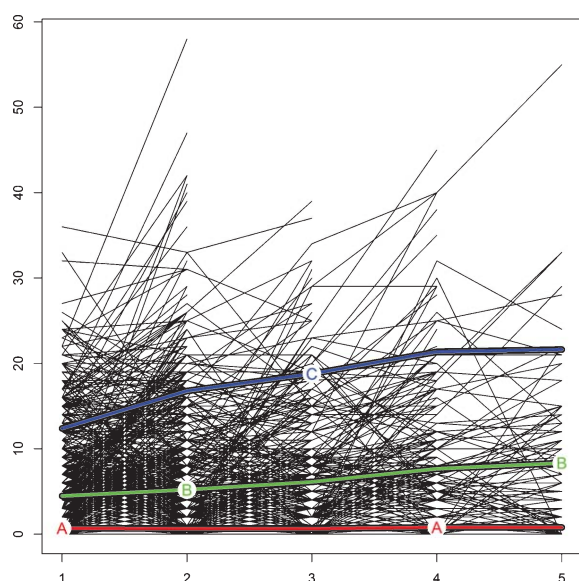


Fig. 3. KmL plot. Each line defines a single patient's UPDRS score progression during follow-up. The "A" line represents the cluster with no/low EPS load, the "B" line the cluster with medium EPS load, and the "C" line the cluster with high EPS load. X-axis, years of follow-up; Y-axis, UPDRS total score.

significant differences were found between individuals with no/low and medium EPS.

Global cognitive measures were all significantly different across the three clusters: MMSE and CDR at the last visit indicated significantly more severe impairment for subjects in the cluster with high EPS compared to those in clusters with medium and no/low EPS (Table 2). Results obtained through the multinomial logistic regression model were further confirmed through the generalized linear mixed model adjusting for ADC centers as a random effect.

Neuropathological assessment

Patients with available neuropathological data were included if they had their last clinical evaluation within two years of death ($n = 394$; 124 were in the no/low EPS cluster, 155 in the medium EPS cluster, and 115 in the high EPS cluster; Table 3). Overall, AD was reported as the primary neuropathological diagnosis for 295 individuals (75%). Other primary diagnoses were as follow: 16 vascular dementia (4%), 19 frontotemporal dementia (5%), and 9 hippocampal sclerosis (2%).

Table 1
Demographics and clinical characteristics of the dataset, overall and stratified by extrapyramidal signs (EPS) cluster

Overall population ($n = 3,502$)			
Age at most recent visit mean (SD)		79.8 (6.6)	
Female (%)		54.6	
Age at onset mean (SD)		72.9 (6.6)	
Education (years) mean (SD)		14.4 (3.7)	
UPDRS median (IQR)			
Baseline		2 (6)	
Last visit		4 (11)	
Subjects known to be deceased (%)		880 (25.1)	
Cluster	A (no/low EPS)	B (medium EPS)	C (high EPS)
Number of individuals	1,583	1,259	660
Female (%)	57.9	50.8	54.2
Education (years) mean (SD)	14.5 (3)	14.4 (3)	14.1 (4)
Age of onset of cognitive decline mean (SD)	71.5 (6)	73.6 (6)	75.1 (6)
Age at baseline (SD)	76.0 (6)	78.2 (6)	80.0 (6)
Age at most recent visit mean (SD)	78.3 (6)	80.5 (6)	82.2 (6)
Depression (%)	54.2	54.8	55.6
Hallucinations (%)	13.2	14.1	20.3
Apathy (%)	63.8	69.3	70.7
Delusions (%)	29.3	31.5	32.8
Erratic nighttime behaviors (%)	46.2	53.2	55.3
Fluctuating cognition (%)	11.6	11.8	23.2
Mean MMSE at baseline (SD) [†]	22.9 (5)	22.4 (5)	20.9 (6)
Mean CDR-SB at baseline (SD) ^a	4.2 (3)	4.9 (3)	5.9 (4)
Mean MMSE at last visit (SD) [†]	18.1 (6.4)	17.0 (6.3)	15.9 (7.0)
Mean CDR-SB at last visit (SD) ^a	7.9 (4.0)	8.9 (4.1)	10.1 (4.4)
UPDRS median (IQR)			
Baseline	0 (1)	4 (7)	12 (10)
Last visit	0 (2)	7 (6)	19 (12)

[†]8 subjects in cluster A, 14 subjects in cluster B and 15 subjects in cluster C were missing MMSE score.

Table 2
Results of multiple multinomial logistic regression comparing odds of UPDRS trajectory type stratified by subject features in AD

Characteristic	Cluster B versus A (medium versus no/low EPS)		Cluster C versus A (high versus no/low EPS)		Cluster C versus B (high versus medium EPS)	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Neuropsychiatric assessment						
Depression	1.14 (0.98–1.33)	0.15	1.30 (1.07–1.58)	0.02	1.14 (0.94–1.39)	0.18
Delusions	1.10 (0.93–1.30)	0.44	1.12 (0.91–1.37)	0.44	1.02 (0.83–1.25)	0.87
Apathy	1.31 (1.11–1.54)	0.001	1.55 (1.26–1.91)	<0.001	1.19 (0.96–1.47)	0.11
Nighttime behaviors						
Hallucinations	1.29 (1.11–1.50)	0.001	1.45 (1.20–1.76)	<0.001	1.13 (0.93–1.37)	0.22
Cognitive fluctuation	1.10 (0.88–1.37)	0.39	1.68 (1.31–2.17)	<0.001	1.53 (1.18–1.97)	0.001
Cognitive assessment						
MMSE score	1.10 (0.85–1.41)	0.47	2.73 (2.06–3.61)	<0.001	2.49 (1.87–3.39)	<0.001
CDR-SB score	0.96 (0.95–0.98)	<0.001	0.93 (0.91–0.94)	<0.001	0.96 (0.94–0.97)	<0.001
	1.10 (1.06–1.10)	<0.001	1.16 (1.14–1.20)	<0.001	1.08 (1.05–1.10)	<0.001

OR, odds ratio; CI, confidence interval; *p*, *p*-value. *p*-values are presented in bold if significant after multiple testing correction. Analyses adjusted for gender, age at last visit, age at onset, number of follow-ups, and years of education.

Table 3
Neuropathological findings stratified by cluster in those undergoing autopsy (*n* = 394)

	Cluster A (no/low EPS)	Cluster B (medium EPS)	Cluster C (high EPS)	<i>p</i> *
Number of individuals	124	155	115	
Age at death (SD)	81.7 (7)	84.5 (6)	84.5 (5)	<0.001
Primary diagnosis				
Diagnosis of Alzheimer's disease (%)	101 (81)	113 (73)	81 (70)	ns
Diagnosis of dementia with Lewy bodies (%)	3 (2)	5 (3)	13 (11)	<0.05
Diagnosis of frontotemporal dementia (%)	3 (2)	10 (6)	6 (5)	ns
Diagnosis of vascular dementia (%)	1 (1)	8 (5)	7 (6)	ns
Diagnosis of hippocampus sclerosis (%)	2 (2)	7 (4)	0 (0)	ns
Normal Brain (%)	3 (2)	0 (0)	2 (2)	ns
Other (%)	11 (9)	12 (8)	6 (5)	ns
Braak staging[†]				
0–I–II (%)	0 (0)	2 (2)	1 (1)	ns
III–IV (%)	12 (12)	16 (14)	16 (20)	
V–VI (%)	89 (88)	94 (84)	64 (79)	
Missing	0	1	0	
Vascular assessment				
large artery cerebral infarcts	9 (7)	12 (8)	12 (10)	ns
Hemorrhages	6 (5)	10 (6)	3 (3)	ns
lacunes (small artery infarcts and/or hemorrhages)	16 (13)	35 (22)	16 (14)	0.06

* χ^2 test for a difference in proportions among the 3 clusters for primary neuropathological diagnosis; Trend test for Braak stages. [†]Analyses restricted to those with AD as a primary neuropathological diagnosis. Percentages have been rounded to nearest whole percent; ns = non significant.

Five individuals, despite being diagnosed with dementia, had normal brains (1%). Twenty-one individuals were assigned to the DLB group (5%) as having a “high likelihood” of diagnosis according to the 2005 Consensus criteria. Finally, 29 subjects had very rare diagnoses (one individual per category, <1%) or multiple coexisting pathologies such as no diagnosis could be assigned as a predominant cause of the dementia. The frequency of AD identified as the primary underlying cause of the dementia was higher in the cluster with none/low EPS progression, although results were not significant after multiple testing correction (none/low EPS = 81%, medium EPS = 73%, and high EPS = 70%;

Table 3). However, the likelihood that the clinical syndrome was due to DLB pathology was higher for those subjects in the high EPS cluster (11%) as compared to clusters with no/low (2%) or medium EPS (3%). None of the other neuropathological diagnoses significantly differed across clusters. All findings were confirmed employing the generalized linear mixed model with ADC center as a random effect (data not shown). We also compared clusters by AD pathology: restricting the analysis to those with AD as a primary diagnosis, Braak staging did not differ significantly across clusters (*p* = 0.10). Differences in the vascular pathology were also tested: no cluster showed statistically

significant higher frequency of such events (albeit the cluster with moderate EPS show higher occurrence of lacunes at a trend level).

DISCUSSION

Using data from the National Alzheimer's Coordinating Center, we analyzed a large cohort of patients with clinically diagnosed AD, focusing on extrapyramidal signs, a frequent but often underestimated manifestation of the disease. The study cohort included up to five yearly follow-up visits with diagnostic, neurological, and neuropsychiatric assessments; compared to cross-sectional designs, longitudinal studies are known to be more robust in model selection and show higher statistical power [20].

The clustering algorithm identified specific subgroups of AD patients showing no/low, medium, and high EPS burden. By grouping together profiles of EPS progression in a large AD cohort, we investigated the heterogeneity of the rate of EPS progression avoiding reductive and arbitrary descriptions in terms of presence/absence of extrapyramidal signs.

Several findings were of particular interest. First, the cluster with no/low EPS grouped together individuals who had a median score of 0 with interquartile range from 0 to 2 points through the follow-up: this is not surprising since a score of 1 on many UPDRS sub-domains (i.e., mild impairment) is only mildly informative and can be considered normal. In addition, inter-rater agreement is poor for low scores [21]. Second, EPS increase corresponded to more severe cognitive impairment (i.e., high EPS cluster > medium EPS cluster > no/low EPS cluster), in line with the notion that motor impairment in AD is associated with faster cognitive decline. Third, compared to cluster with no/low EPS, clusters with medium and high EPS load exhibited more severe neuropsychiatric impairment (nighttime behaviors and apathy). On the contrary, hallucination and cognitive fluctuation proved to be significantly more frequent in the high EPS cluster whereas did not differ between the no/low and medium EPS cluster: in other words, hallucinations tend to be co-expressed with high EPS burden.

Neuropathology data confirmed distinct characteristics between the clusters: the high EPS cluster stood out, showing the higher percentage of individuals diagnosed with DLB (11%) compared to the no/low (2%) and medium EPS (3%) clusters. This is also in line with the reported higher frequency of hallucinations in the high EPS cluster and with previous reports showing a strong association between reported hallucinations and

Lewy body pathology at autopsy [22]. Thus, the high EPS cluster might be referred to what is commonly defined as the "Lewy body variant of AD" [23].

On the contrary, similar neuropathological findings in the clusters with no/low and medium EPS allow us to propose that EPS in clinically diagnosed AD might underpin a more heterogeneous pathogenic process: this might explain why previous observations showed inconsistent findings, such as linking EPS to Lewy bodies or, on the contrary, failing to demonstrate such association [24] or, ultimately, reporting association between EPS and other neuropathological features, e.g., tangle pathology [25, 26].

In order to exclude alternative causes of EPS, presence of large artery ischemic or hemorrhagic events or small arteries measures were compared across clusters; however, no statistically significant differences were found between the three clusters.

This approach also has caveats. First, in clustering analyses, there is often no "correct answer" for the right number of clusters [27]; this limitation should then be taken into account and further validations with alternative methods considered. Nevertheless, we validated the three clusters by showing their differences in terms of clinical and neuropathological features. Second, although excluding visits with reported antipsychotic and antiparkinsonian agents reduced bias for drug-induced events, it could not be ruled out that EPS or hallucinations were independently present. Third, subjects in the cluster with no/low EPS could be in an earlier stage of the disease and would have later developed EPS along with neuropsychiatric manifestations; nevertheless, albeit showing lower age at evaluation (cluster A < cluster B < cluster C), age of onset is accordingly lower for cluster with no/low EPS. Furthermore, time from disease onset to study enrollment was similar, making it unlikely that the three clusters are earlier or later stages of the same diseases process while it suggests a faster disease progression for subjects with EPS compared to those without EPS. This concern might also be true for the neuropathology assessment, although findings of similar Braak staging for those with an AD diagnosis again suggests that the three clusters reflect different diseases expressions rather than stages of disease. Fourth, we assessed EPS as a total score without dissecting the structure of UPDRS (e.g., rigidity, tremor etc.): the latter has never been investigated in AD to our knowledge (data are only available for PD), thus profiling specific sub-domains of EPS might be controversial. Finally, the NACC database collects data from AD research centers and is not population-based; further, subjects who are

followed and/or who have donated brains for autopsy may not be generalizable to any specific population and represent only a small portion of the initial clinical sample. To account for inter-center variability, a generalized linear mixed model was also employed, with the AD centers as a random effect: nevertheless, all reported results were confirmed.

Our data provide further evidence that the neuropathological underpinning of AD differs for distinct phenotype patterns. These results also demonstrate that k-means clustering analysis is a useful method for characterizing the heterogeneous nature of AD and for examining the relationships between clinical and neuropathological findings in AD sub-phenotypes. This approach may be particularly helpful in generating hypotheses that could investigate the variability of symptoms and support the development of novel treatment approaches for AD.

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REFERENCES

- [1] Alzheimer's Association (2013) 2013 Alzheimer's disease facts and figures. *Alzheimers Dement* **9**, 208-245.
- [2] Portet F, Scarmeas N, Cosentino S, Helzner EP, Stern Y (2009) Extrapyramidal signs before and after diagnosis of incident Alzheimer disease in a prospective population study. *Arch Neurol* **66**, 1120-1126.
- [3] Mangone C (2003) [Clinical heterogeneity of Alzheimer's disease. Different clinical profiles can predict the progression rate]. *Rev Neurol* **38**, 675-681.
- [4] Paulsen JS, Salmon D, Thal L, Romero R, Weisstein-Jenkins C, Galasko D, Hofstetter C, Thomas R, Grant I, Jeste D (2000) Incidence of and risk factors for hallucinations and delusions in patients with probable AD. *Neurology* **54**, 1965-1971.
- [5] Ropacki SA, Jeste DV (2005) Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. *Am J Psychiatry* **162**, 2022-2030.
- [6] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalara RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londo E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M; Consortium on DLB (2005) Diagnosis and management of dementia with Lewy bodies Third report of the DLB consortium. *Neurology* **65**, 1863-1872.
- [7] Zhu K, Hilten JJ, Putter H, Marinus J (2013) Risk factors for hallucinations in Parkinson's disease: Results from a large prospective cohort study. *Mov Disord* **28**, 755-762.
- [8] Halliday GM, Leverenz JB, Schneider JS, Adler CH (2014) The neurobiological basis of cognitive impairment in Parkinson's disease. *Mov Disord* **29**, 634-650.
- [9] Swerdlow RH, Newell KL (2012) "Untangling" the relationship between Alzheimer disease and dementia with Lewy bodies. *Neurology* **6**, 1938-1939.
- [10] Genolini C, Falissard B (2011) KmL: A package to cluster longitudinal data. *Comput Methods Programs Biomed* **104**, e112-e121.
- [11] Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, Hubbard JL, Koepsell TD, Morris JC, Kukull WA, NIA Alzheimer's Disease Centers. (2007) The National Alzheimer's Coordinating Center (NACC) database: The uniform data set. *Alzheimer Dis Assoc Disord* **21**, 249-258.
- [12] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-939.
- [13] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N; Movement Disorder Society UPDRS Revision Task Force. (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS):

- Scale presentation and clinimetric testing results. *Mov Disord* **23**, 2129-2170.
- [14] Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez OL, DeKosky ST (2000) Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* **12**, 233-239.
- [15] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.
- [16] Morris JC (1993) The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* **43**, 2412-2414.
- [17] Mirra S, Hart MN, Terry R (1993) Making the diagnosis of Alzheimer's disease. A primer for practicing pathologists. *Arch Pathol Lab Med* **117**, 132-144.
- [18] Braak H, Alafuzoff I, Arzberger T, Kretschmar H, Del Tredici K (2006) Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol* **112**, 389-404.
- [19] Calinski T, Harabasz J (1974) A dendrite method for cluster analysis. *Commun Stat Theory Methods* **3**, 1-27.
- [20] Zeger SL, Liang K-Y (1992) An overview of methods for the analysis of longitudinal data. *Stat Med* **11**, 1825-1839.
- [21] Richards M, Marder K, Bell K, Dooneief G, Mayeux R, Stern Y (1991) Interrater reliability of extrapyramidal signs in a group assessed for dementia. *Arch Neurol* **48**, 1147-1149.
- [22] Toledo JB, Cairns NJ, Da X, Chen K, Carter D, Fleisher A, Householder E, Ayutyanont N, Roontiva A, Bauer RJ, Eisen P, Shaw LM, Davatzikos C, Weiner MW, Reiman EM, Morris JC, Trojanowski JQ, Alzheimer's Disease Neuroimaging Initiative (ADNI) (2013) Clinical and multimodal biomarker correlates of ADNI neuropathological findings. *Acta Neuropathol Commun* **1**, 65.
- [23] Hansen L, Salmon D, Galasko D, Masliah E, Katzman R, DeTeresa R, Thal L, Pay M, Hofstetter R, Klauber M, et al. (1990) The Lewy body variant of Alzheimer's disease A clinical and pathologic entity. *Neurology* **40**, 1-8.
- [24] Stern Y, Jacobs D, Goldman J, Gomez-Tortosa E, Hyman BT, Liu Y, Troncoso J, Marder K, Tang MX, Brandt J, Albert M (2001) An investigation of clinical correlates of Lewy bodies in autopsy-proven Alzheimer disease. *Arch Neurol* **58**, 460-465.
- [25] Liu Y, Stern Y, Chun MR, Jacobs DM, Yau P, Goldman JE (1997) Pathological correlates of extrapyramidal signs in Alzheimer's disease. *Ann Neurol* **41**, 368-374.
- [26] Schneider JA, Li J-L, Li Y, Wilson RS, Kordower JH, Bennett DA (2006) Substantia nigra tangles are related to gait impairment in older persons. *Ann Neurol* **59**, 166-173.
- [27] Pham DT, Dimov SS, Nguyen C (2005) Selection of K in K-means clustering. *Proc IME C J Mech Eng Sci* **219**, 103-119.