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Rapidly Progressive Alzheimer's Disease in Two Distinct Autopsy Cohorts

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Abstract

Background—A rapidly progressive phenotype of Alzheimer's disease (AD) has been described in some prion disease cohorts. Limited information regarding rapidly progressive AD (rpAD) is available from longitudinal national cohorts.

Objective—To compare the clinical characteristics of rpAD in two different national cohorts.

Methods—A retrospective analysis was performed on AD subjects with available neuropathology in the National Alzheimer's Coordinating Center (NACC) database and among neuropathologically characterized AD cases from the National Prion Disease Pathology Surveillance Center (NPDPSC) that were evaluated for suspected prion disease. In the NACC cohort, rpAD was delineated by the lower 10th percentile of follow up duration from pre-dementia to death duration among subjects meeting pathological diagnosis of AD.

Results—rpAD from the NPDPSC had a shorter mean symptom duration than the NACC identified rpAD cases (11.6 months versus 62.4 months) and were also younger at the time of their death (60.0 versus 81.8 years). NACC identified rpAD subjects, beginning from a prodementia stage, had slower rate of MMSE change per year than NPDPSC cases (2.5 versus 6.0 points).

Conclusions—rpAD constitute an important subset of AD subjects in whom a rapid course of symptomatic clinical decline is noted, as confirmed in both national cohorts. rpAD was best characterized by survival time (< 3 years), as there were clear differences between the rpAD cohorts in terms of symptom duration, age at death, and MMSE change per year, likely due to the strong selection biases. rpAD could shed light on the biology of rate of progression in AD.

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Keywords

Alzheimer's disease; dementia; rapidly progressive dementia; rate of decline

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INTRODUCTION

Alzheimer's disease (AD) affects more than 35 million people worldwide and is characterized by a progressive decline in cognitive function. It is increasingly recognized that there is significant heterogeneity in AD phenotype and clinical trajectories [1, 2]. Estimates of mean survival in AD are often stated to range from 3 to 10 years [3–21]. AD survival in these studies were calculated either from time of study entry [4, 5, 8, 10, 13, 14], onset of AD dementia [3, 6, 9, 11, 16, 17, 19], or from retrospectively estimated dates of symptom onset [20, 21].

A rapidly progressive subtype of AD (rpAD), where the survival duration (often with variable symptom onset determination) is reported between less than one year to up to four years, has been described in some case series and in reports from prion disease centers among patients referred for suspected prion disease [22–24]. More recently, differences in the allelic frequency of *APOE ε4*, structural organization of the amyloid- β ($A\beta$) species, and plaque composition between rpAD and typical AD support the view that they represent AD subtypes with distinct pathogenic characteristics [25–27].

In spite of enormous interest, no clear consensus exists regarding the defining characteristics of rpAD, likely due to the difficulty of longitudinal characterization of rpAD. Additional concerns with regard to the nature of rpAD include: 1) long standing lack of clarity on whether rpAD should be characterized by survival time or the rate of cognitive decline and, if so, by which cognitive scale, 2) often no consistent definition of the time of onset of progressive clinical deterioration, with variability on whether they meet criteria of mild cognitive impairment (MCI) or dementia at initial evaluation; 3) poor characterization of comorbidities and cognitive variables that are common confounders that impact rapid mortality and evaluation of rate of cognitive decline [19, 28–30]; and 4) lack of comparisons of rpAD patient samples from prion disease centers to those from other case series and longitudinal cohorts.

We therefore undertook a survey of possible rpAD subtypes in two distinct national cohorts, the National Prion Disease Pathology Surveillance Centre (NPDPSC) and a longitudinal cohort, the National Alzheimer's Coordinating Center (NACC), to begin to address some of these concerns. Our aims were to:

1. Compare the clinical characteristics of rapid progression in AD in two national cohorts with two different patient recruitment criteria, a national prion disease center with referrals related to suspected prion disease, and a national longitudinal cohort, where AD diagnosis was clinically suspected and later confirmed by neuropathology.

2. Determine if rpAD in a national longitudinal dementia cohort can be reliably characterized with respect to both survival times from the pre-dementia stage and rate of cognitive decline, in comparison to a prion disease center cohort.
3. Evaluate rpAD cases in NACC for potential confounders that could impact rapid mortality and rate of cognitive decline where reliable data was available (education, depression, hallucinations, delusions, parkinsonism, smoking history, and Hachinski scores).

MATERIALS AND METHODS

National Prion Disease Pathology Surveillance Center cohort

14.5% of all referrals to the NPDSC with sufficient tissue of neuropathology have been diagnosed with AD [31]. The rpAD cohort from the NPDSC has also been previously described [25]. In brief, 276 patients were referred to the NPDSC from 2002 to 2012 with a rapidly progressive dementia and subsequently diagnosed by autopsy with definite AD. In all cases, familial or sporadic prion diseases were excluded after sequencing the PRNP gene, conducting neuropathology and immunohistochemistry for the pathogenic prion protein (PrP^{Sc}), and molecular typing of PrP^{Sc} by western blots. Following the standard NPDSC protocol, case records were retrospectively analyzed by trained personnel for time of onset of symptoms noted by the physician and/or obtained from caregivers via telephone interviews. 186 patients met criteria for inclusion into the rpAD cohort with: 1) initial referral to NPDSC and classification as possible prion disease due to the clinical appearance in accordance with the consensus official criteria valid at the time of referral [30,31]; 2) decline of more than six Mini-Mental State Examination (MMSE) points per year and/or death within 3 years of initial neurological diagnosis of atypical dementia [30, 32]; 3) absence of autosomal dominant pattern of dementia inheritance; 4) absent pathogenic mutations in the human prion protein (PrP) gene (PRNP); 5) neuropathology and immunohistochemistry of tau proteins and A β with unequivocal classification as AD; 6) absence of neuropathologic comorbidity; and 7) distribution of means and proportions of demographic data within 95% confidence interval of the whole group, resulting in no difference in means and proportions between those selected and all AD cases in the NPDSC database. Because there are no definite clinical criteria for rpAD [24] and to prevent contamination of this cohort with outliers, for further analysis we selected 30 cases within the normal distribution interval of disease duration calculated as $UQ + 1.5 \times IQR$, where UQ is upper quartile, and IQR is inter-quartile range.

National Alzheimer's Coordinating Center cohort

The NACC maintains a database of participant information collected from 34 past and present Alzheimer's Disease Centers funded by the National Institute on Aging. Data from the uniform data set (UDS) maintained by NACC between September 2005 and September 2015 were used for the present analysis. Details on data collection and curating are well documented [33]. The primary and secondary diagnosis for each of the subjects in the analysis was made by the neuropathologist at autopsy based on the burden of pathology. Estimated symptom duration was calculated from the age at symptom onset determined by

the UDS question, ‘What age did the cognitive decline begin’ (based upon the clinician’s assessment) to the age at death. Geriatric depression scale (GDS) was used as a measure of depression, while clinician documentation of hallucinations, delusions and presence of any parkinsonian signs were used in subject characterization.

Within in the NACC cohort, the subject inclusion/exclusion criteria were designed to maximize scientific rigor by ensuring all subjects met AD diagnosis and furthermore that there was clear demarcation of the nature and severity of AD pathology at autopsy, mixed pathology was excluded, and their rate of progression from a pre-dementia stage to death was captured on follow up visits.

In the NACC data, 2,287 subjects had a neuropathologic diagnosis of AD as a primary or contributing diagnosis, and 118 NACC subjects fulfilled criteria of: CERAD criteria of definite AD; AD as primary diagnosis as per neuropathologist and not a secondary diagnosis; Braak neurofibrillary tangle stage > III; CDR-Global (CDR-G) score <1 and MMSE ≥ 25 at initial visit; ≥ 3 longitudinal visits.

We aimed to characterize their rate of progression from a pre-dementia stage to death with at least 3 visits and to overcome potential biases that would result from including subjects with unclear baseline cognitive status.

rpAD subjects were delineated a priori as subjects in the 10th percentile of survival duration data among the 118 subjects.

Cognitive measures

MMSE and CDR Sum of Boxes (CDR-SB) were used to track rate of disease progression. MMSE is often used as a general measure of cognitive impairment [34] and had been collected in the available NACC dataset. The Clinical Dementia Rating (CDR-Global) Scale assesses the participant’s current cognitive and functional status. The CDR Sum of Boxes (CDR-SB) is an operationalized measure of cognitive and functional ability. CDR-SB scores are calculated by simply adding the ‘box scores’, and can range from 0 to 18 (higher scores indicate more impairment) [35].

Statistical analysis

Mann Whitney and Chi square tests were used to assess differences between diagnostic groups in the variables of interest. A difference of $p \leq 0.05$ was considered statistically significant. All the analyses were done with SPSS software.

RESULTS

The frequency of clinical characteristics of interest in the NACC data meeting inclusion/exclusion criteria are detailed in Table 1.

Comparing the clinical characteristics between rpAD in the NPDPS and NACC cohorts, those in the NPDPS group were significantly younger at death and had a shorter estimated symptom duration than in NACC ($p < 0.0001$) (Table 1). In the well characterized NACC

rpAD group with consecutive follow up visits, the average MMSE drop per year was 2.5/year with an average total drop over entire follow being just 7.5 point (Table 2). A MMSE drop of ≥ 6 MMSE points per year was documented in only 5 of the 11 subjects, with all rpAD subjects having a follow up before death within a range of 9 months. *APOE* $\epsilon 4$ frequency was lower among subjects meeting rpAD subjects in both NACC and NPDPS samples, compared to the NACC AD sample as whole (36.4 versus 55.0%). Comparable frequencies of potential confounders that impact rapid mortality and rate of cognitive decline (depression, hallucinations, delusions, parkinsonism signs, smoking history, and Hachinski scores) were noted between rpAD cases in NACC and all AD subjects meeting inclusion/exclusion criteria (Tables 1 and 2).

DISCUSSION

This study provides comparisons between rpAD in two different national cohorts with very different ascertainment methods. In spite of these different cohort ascertainment methods, some commonalities in rpAD between the two national cohorts were noted: 1) rpAD cases with MMSE drop of ≥ 6 MMSE points per year and survival duration less than three years were noted in both NPDPS and NACC cohorts providing a robust confirmation of the rpAD phenotype; and 2) *APOE* $\epsilon 4$ allelic frequency was lower among rpAD cases in NACC and NPDPS, a trend noted in other reports [23], but which again did not meet statistical significance in comparison to all AD cases in NACC ($p = 0.06$) in this study too, likely from small rpAD numbers.

The study also noted differences in rpAD between the two national cohorts in: 1) age at death with a younger age of death in the NPDPS cohort; 2) estimates of symptom duration with a shorter reported clinical course in the NPDPS than NACC; and 3) smaller average rate of MMSE decline at MCI stage of AD in NACC. These suggest either potential selection biases and/or biological differences between the rpAD seen within these national cohorts and warrants further investigation.

The average MMSE change of 2.5 points/year among rpAD over three years of follow up before death in NACC is striking in light of rpAD in the literature being often defined in terms of MMSE change/year at ≥ 6 points/year and a large meta-analysis of AD noting a mean MMSE decline of 5.5 points/year among mild to moderate clinical AD patients [36]. In comparison to previous studies on characterizing annual rate of MMSE change in AD, it should be pointed out that all NACC rpAD subjects in the current analysis: 1) met CERAD neuropathology criteria for definite AD; 2) were evaluated as not likely from mixed pathology; 3) were followed from a pre-dementia stage with initial MMSE ≥ 25 to death; and 4) did not have higher frequencies of common confounders of rapid progression (education, depression, hallucinations, delusions, parkinsonism signs, smoking history, and higher Hachinski score) than the rest of the AD subjects in NACC. Given the non-linear course of cognitive decline from pre-dementia to dementia noted in AD, where the rate of decline has been noted to accelerate after the downward course of dementia begins [36], the smaller MMSE change per year noted in our study which tracks patients beginning at a pre-dementia stage is not surprising. A drop of ≥ 6 MMSE points/year was noted in the rpAD NACC subjects only among 5 of 11 subjects and was more likely in the last year of their 3-year

symptomatic follow up. The short survival time noted among the rpAD subjects here, in spite of the slower average rate of MMSE decline compared to what is often seen in later stages of dementia, clearly suggests that rate of decline on MMSE alone cannot be used as a reliable stand-alone factor in defining rpAD in all cohorts, especially in the earlier stages of the disease. CDR-SB change/year between the NACC cohort as a whole and rpAD within NACC noted robust differences (0.9 versus 2.0 points). No comparable data was available for the NPDPSA cohort. Tracking CDR-SB could therefore be potentially more informative than MMSE in delineating rpAD in future longitudinal studies.

The particular limitations inherent to national cohorts have been leveraged to better illuminate the likely spectrum of rpAD. The limitations of any longitudinal autopsy cohort, including the NACC, regarding potential bias in participant recruitment and in their agreeing for final autopsy confirmation of diagnosis are well recognized. As our study focused on detailing the natural history of rpAD starting from a pre-dementia stage it could override the above concerns by taking the first steps in clarifying the existence of rpAD in a longitudinal cohort for future more careful evaluations. Furthermore, there are concerns that AD survival may be overestimated in studies of prevalent disease or underestimated when subjects at different stages of AD are included in the analysis instead of at the point of disease onset, and as AD trajectories have a non-linear trajectory with faster declines later in disease [17, 37]. These concerns were taken into account in selecting our AD patient inclusion criteria. The median symptom duration (8.2 years) in the NACC autopsy sample using our patient selection is closer to the mean symptom duration reported previously in AD incidence studies, which have better addressed underestimation and overestimation biases [17]. Despite the mild stage of disease at baseline in the NACC cohort, the subjects had a notably high frequency of parkinsonism. It is possible that including subjects with even minimal parkinsonian signs when present (with no minimum threshold of Unified Parkinson's disease rating scale, Part III motor as cut off) could have biased the results towards the higher frequency of parkinsonism noted.

Some potential biases of the NPDPSA cohort where the clinical cases of rapid dementia are initially identified in the community include, the expectation or diagnosis of a rapid course of dementia being made in the absence of clear history in some cases or being confounded by other medical comorbidities that were incompletely characterized or documented. Adequate precautions were taken to prevent contamination of this cohort by these biases and with outliers as documented earlier [25]. Reliable data on medical confounders (e.g., metabolic, endocrinological, vascular factors) was limited due to wide geographic and non-systematic clinical characterization of the referred NPDPSA cases, although it is notable that previous reports suggest a limited impact of common medical confounders on mortality and rate of AD clinical progression in longitudinal cohorts [19, 37–39]. The use of medications including cholinesterase inhibitors, memantine, and antipsychotics could also impact rate of decline and mortality, but again was not able to be reliably captured in the NPDPSA cases [40–42]. Atypical AD clinical features including myoclonus, pyramidal signs and akinetic mutism often lead to a consideration of a prion disease in the differential diagnosis of a rapidly progressive dementia, but these features were not consistently reported in the clinical records of samples sent to NPDPSA. It is therefore difficult to judge if these signs are useful in rpAD diagnosis or represent a source of bias. It is clear that future studies of rpAD will

need to longitudinally characterize these clinical features. The striking age differences at death between the rpAD cases within NACC and NPDPSD also suggest obvious biases in the recruitment between the samples. It is further unclear if the distinct biological subtype of A β species are to be considered in rpAD [25, 26] or rpAD phenotype relates to differences in tau pathology too.

Our analysis of rpAD in two different cohorts could shed light on some of the previous concerns regarding rpAD characterization and point the way to some future clarity in this area.

1. In our cohorts, rpAD was better characterized by survival time (≥ 3 years), rather than by rate of cognitive decline by MMSE, as the non-linear cognitive decline trajectory in AD makes it difficult to use similar criteria of MMSE rate of decline for subjects in early versus later stages of AD. It is therefore important to make the distinction between 'Rapid cognitive decline' and 'Rapid Alzheimer's disease', with the latter being used more carefully in cases (with AD neuropathology confirmation without mixed pathology and less strongly with positive AD biomarkers alone with mixed pathology not being ruled out) with less than 3 years survival from earliest symptom onset.
2. Careful delineation of the time of onset of symptoms from an objective clinical characterization of MCI to death is necessary as there is often the likelihood of confirmation bias in over or underestimating the duration of first onset of symptoms by the clinician or the family depending on the diagnosis most under consideration (AD versus prion versus autoimmune, etc.). Tracking CDR as noted in this study could potentially be more informative in this light than MMSE in future longitudinal studies of rpAD. Furthermore, in the Alzheimer's Disease Neuroimaging Initiative CDR scores tracked cognitive decline nearly linearly across different severities of AD [43].
3. Delineation of cognitive and medical variables that impact rapid mortality and rate of cognitive decline are necessary.

Following these clinical guidelines could help improve the quality of clinical characterization and generate comparable data across centers in this poorly understood subtype of AD.

Summary

Autopsy confirmed rpAD cases with survival duration less than 3 years were noted in two very different national cohorts with different recruitment biases. It is clear that there are methodological limitations on the use of clinical scores alone in the definition of rpAD. There is a need for elucidating the clinical-pathological-molecular correlations with *in vivo* novel biomarkers and by postmortem studies in the future to better define rpAD. Efforts in this direction by evaluation of inflammatory and immune markers and characterization of the variation in A β and tau 3D structure and their variants in AD subtypes are needed. Systematic prospective studies of rpAD are sorely needed to better understand the clinical

and biological characteristics at different stages of the AD process in order to help find effective treatments for this aggressive form of AD.

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REFERENCES

- [1]. Cummings JL (2000) Cognitive and behavioral heterogeneity in Alzheimer's disease: Seeking the neurobiological basis. *Neurobiol Aging* 21, 845–861. [PubMed: 11124429]
- [2]. Wilkosz PA, Seltman HJ, Devlin B, Weamer EA, Lopez OL, DeKosky ST, Sweet RA (2010) Trajectories of cognitive decline in Alzheimer's disease. *Int Psychogeriatrics* 22, 281–290.
- [3]. Aronson MK, Ooi WL, Geva DL, Masur D, Blau A, Frishman W (1991) Dementia: Age-dependent incidence, prevalence, and mortality in the old old. *Arch Intern Med* 151, 989–992. [PubMed: 2025148]
- [4]. Molsa PK, Marttila RJ, Rinne UK (1995) Long-term survival and predictors of mortality in Alzheimer's disease and multi-infarct dementia. *Acta Neurol Scand* 91, 159–164. [PubMed: 7793228]
- [5]. Heyman A, Peterson B, Fillenbaum G, Pieper C (1996) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), part XIV: Demographic and clinical predictors of survival in patients with Alzheimer's disease. *Neurology* 46, 656–660. [PubMed: 8618662]
- [6]. Geerlings MI, Deeg DJ, Schmand B, Lindeboom J, Jonker C (1997) Increased risk of mortality in Alzheimer's disease patients with higher education? A replication study. *Neurology* 49, 798–802. [PubMed: 9305343]
- [7]. Aevarsson O, Svanborg A, Skoog I (1998) Seven-year survival rate after age 85 years: Relation to Alzheimer disease and vascular dementia. *Arch Neurol* 55, 1226–1232. [PubMed: 9740117]
- [8]. Ostbye T, Hill G, Steenhuis R (1999) Mortality in elderly Canadians with and without dementia: A 5-year follow-up. *Neurology* 53, 521–526. [PubMed: 10449114]
- [9]. Brookmeyer R, Corrada MM, Curriero FC, Kawas C (2002) Survival following a diagnosis of Alzheimer disease. *Arch Neurol* 59, 1764–1767. [PubMed: 12433264]
- [10]. Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L, Kukull WA (2004) Survival after initial diagnosis of Alzheimer disease. *Ann Intern Med* 140, 501–509. [PubMed: 15068977]
- [11]. Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST (2005) Alzheimer disease and mortality: A 15-year epidemiological study. *Arch Neurol* 62, 779–784. [PubMed: 15883266]
- [12]. Waring SC, Doody RS, Pavlik VN, Massman PJ, Chan W (2005) Survival among patients with dementia from a large multi-ethnic population. *Alzheimer Dis Assoc Disord* 19, 178–183. [PubMed: 16327343]
- [13]. Heeren TJ, van Hemert AM, Rooymans HGM (1992) A community-based study of survival in dementia. *Acta Psychiatr Scand* 85, 415–418.

- [14]. Helmer C, Joly P, Letenneur L, Commenges D, Dartigues JF (2001) Mortality with dementia: Results from a French prospective community-based cohort. *Am J Epidemiol* 154, 642–648. [PubMed: 11581098]
- [15]. Doody R, Pavlik V, Massman P, Kenan M, Yeh S, Powell S, Cooke N, Dyer C, Demirovic J, Waring S, Chan W (2005) Changing patient characteristics and survival experience in an Alzheimer's center patient cohort. *Dement Geriatr Cogn Disord* 20, 198–208. [PubMed: 16088145]
- [16]. Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B (1999) Mortality from dementia in advanced age: A 5-year follow-up study of incident dementia cases. *J Clin Epidemiol* 52, 737–743. [PubMed: 10465318]
- [17]. Helzner EP, Scarmeas N, Cosentino S, Tang MX, Schupf N, Stern Y (2008) Survival in Alzheimer disease: A multi-ethnic, population-based study of incident cases. *Neurology* 71, 1489–1495. [PubMed: 18981370]
- [18]. Armstrong RA (2014) Factors determining disease duration in Alzheimer's disease: A postmortem study of 103 cases using the Kaplan-Meier estimator and Cox regression. *Biomed Res Int* 2014, 623487. [PubMed: 24579083]
- [19]. Staekenborg SS, Pijnenburg YA, Lemstra AW, Scheltens P, Vd Flier WM (2016) Dementia and rapid mortality: Who is at risk? *J Alzheimers Dis* 53, 135–142. [PubMed: 27104894]
- [20]. Wolfson C, Wolfson DB, Asgharian M, M'Lan CE, Ostbye T, Rockwood K, Hogan DB (2001) A reevaluation of the duration of survival after the onset of dementia. *N Engl J Med* 344, 1111–1116. [PubMed: 11297701]
- [21]. Doody RS, Massman P, Dunn JK (2001) A method for estimating progression rates in Alzheimer disease. *Arch Neurol* 58, 449–454. [PubMed: 11255449]
- [22]. Josephs KA, Ahlskog JE, Parisi JE, Boeve BF, Crum BA, Giannini C, Petersen RC (2009) Rapidly progressive neurodegenerative dementias. *Arch Neurol* 66, 201–207. [PubMed: 19204156]
- [23]. Schmidt C, Redyk K, Meissner B, Krack L, von Ahnen N, Roeber S, Kretzschmar H, Zerr I (2010) Clinical features of rapidly progressive Alzheimer's disease. *Dement Geriatr Cogn Disord* 29, 371–378. [PubMed: 20453509]
- [24]. Schmidt C, Wolff M, Weitz M, Bartlau T, Korth C, Zerr I (2011) Rapidly progressive Alzheimer disease. *Arch Neurol* 68, 1124–1130. [PubMed: 21911694]
- [25]. Cohen ML, Kim C, Haldiman T, ElHag M, Mehndiratta P, Pichet T, Lissemore F, Shea M, Cohen Y, Chen W, Blevins J, Appleby BS, Surewicz K, Surewicz WK, Sajatovic M, Tatsuoka C, Zhang S, Mayo P, Butkiewicz M, Haines JL, Lerner AJ, Safar JG (2015) Rapidly progressive Alzheimer's disease features distinct structures of amyloid-beta. *Brain* 138, 1009–1022. [PubMed: 25688081]
- [26]. Drummond E, Nayak S, Faustin A, Pires G, Hickman RA, Askenazi M, Cohen M, Haldiman T, Kim C, Han X, Shao Y, Safar JG, Ueberheide B, Wisniewski T (2017) Proteomic differences in amyloid plaques in rapidly progressive and sporadic Alzheimer's disease. *Acta Neuropathol* 133, 933–954. [PubMed: 28258398]
- [27]. Aubert L, Pichierri S, Hommet C, Camus V, Berrut G, de Decker L (2015) Association between comorbidity burden and rapid cognitive decline in individuals with mild to moderate Alzheimer's disease. *J Am Geriatr Soc* 63, 543–547. [PubMed: 25752337]
- [28]. Mann UM, Mohr E, Chase TN (1989) Rapidly progressive Alzheimer's disease. *Lancet* 2, 799.
- [29]. Tosto G, Gasparini M, Brickman AM, Letteri F, Renie' R, Piscopo P, Talarico G, Canevelli M, Confaloni A, Bruno G (2015) Neuropsychological predictors of rapidly progressive Alzheimer's disease. *Acta Neurol Scand* 132, 417–422. [PubMed: 25903925]
- [30]. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL (2008) Rapidly progressive dementia. *Ann Neurol* 64, 97–108. [PubMed: 18668637]
- [31]. Chittravasi N, Jung RS, Kofskey DM, Blevins JE, Gambetti P, Leigh RJ, Cohen ML (2011) Treatable neurological disorders misdiagnosed as Creutzfeldt-Jakob disease. *Ann Neurol* 70, 437–444. [PubMed: 21674591]
- [32]. Schmidt C, Haik S, Satoh K, Rábano A, Martinez-Martin P, Roeber S, Brandel JP, Calero-Lara M, de Pedro-Cuesta J, Laplanche JL, Hauw JJ, Kretzschmar H, Zerr I (2012) Rapidly progressive Alzheimer's disease: A multicenter update. *J Alzheimers Dis* 30, 751–756. [PubMed: 22460329]

- [33]. 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. [PubMed: 17804958]
- [34]. 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. [PubMed: 1202204]
- [35]. Morris JC (1993) The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* 43, 2412–2414.
- [36]. Ito K, Ahadiet S, Corrigan B, French J, Fullerton T, Tensfeldt T, Alzheimer's Disease Working Group (2010) Disease progression meta-analysis model in Alzheimer's disease. *Alzheimers Dement* 6, 39–53. [PubMed: 19592311]
- [37]. Barocco F, Spallazzi M, Concari L, Gardini S, Pelosi A, Caffarra P (2017) The progression of Alzheimer's disease: Are fast decliners really fast? A four-year follow-up. *J Alzheimers Dis* 57, 775–786. [PubMed: 28304306]
- [38]. Ferrari C, Lombardi G, Polito C, Lucidi G, Bagnoli S, Piaceri I, Nacmias B, Berti V, Rizzuto D, Fratiglioni L, Sorbi S (2018) Alzheimer's disease progression: Factors influencing cognitive decline. *J Alzheimers Dis* 61, 785–791. [PubMed: 29226870]
- [39]. Pillai JA, Butler RS, Bonner-Jackson A, Leverenz JB (2016) Impact of Alzheimer's disease. Lewy body and vascular co-pathologies on clinical transition to dementia in a national autopsy cohort. *Dement Geriatr Cogn Disord* 42, 106–116. [PubMed: 27623397]
- [40]. Rountree SD, Chan W, Pavlik VN, Darby EJ, Siddiqui S, Doody RS (2009) Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. *Alzheimers Res Ther* 1, 7. [PubMed: 19845950]
- [41]. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, Kales HC (2015) Antipsychotics, other psychotropics, and the risk of death in patients with dementia: Number needed to harm. *JAMA Psychiatry* 72, 438–445. [PubMed: 25786075]
- [42]. Koponen M, Taipale H, Lavikainen P, Tanskanen A, Tiihonen J, Tolppanen AM, Ahonen R, Hartikainen S (2017) Risk of mortality associated with antipsychotic monotherapy and polypharmacy among community-dwelling persons with Alzheimer's disease. *J Alzheimers Dis* 56, 107–118. [PubMed: 27935554]
- [43]. Cedarbaum JM, Jaros M, Hernandez C, Coley N, Andrieu S, Grundman M, Vellas B, Alzheimer's Disease Neuroimaging Initiative (2013) Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. *Alzheimers Dement* 9, S45–S55. [PubMed: 22658286]

Table 1

Demographics of rpAD subjects within NACC and NPDPS

	NACC AD subjects meeting inclusion/exclusion criteria	rpAD NACC	rpAD NPDSC	p-value between rpAD groups
Number of subjects	118	11	30	
Estimated age at symptom onset (Mean y SD) (% with data)	69.7 (11.6) (77%)	75.2 (13.1) (83.3%)		
Age at death (Mean y, SD)	80.7 (11.1)	81.8 (13.1)	60 (8.7)	n.a
Duration of follow up before death (Mean mo, Range)	64.1 (27–97)	32.71 (27–36)		$p < 0.0001$
Estimated symptom duration (Mean mo, SD)	103.2 (33.6)	62.4 (8.4)	11.64 (<36)	n.a
Sex (% female)	45.8%	72.7%	50%	0.3
APOE ε4 +ve (Frequency % in each group, % with 4/4)	55% (of 118)	36.4% (of 8)	32.7% (of 26)	1
	12.7% (4/4)	0% 4/4		
Years of Education (Mean y, SD)	15.8 (2.6)	15.5 (2.3)		
Baseline MMSE (Mean, SD)	27.4(1.7)	26.6 (1.4)		
Baseline CDR-Global = 0, 0.5 (Frequency %)	19.5%, 80.5%	9.1%, 90.9%		
Baseline CDR-Sum of Boxes (Mean, SD)	1.7 (1.4)	2.1 (1.9)		
GDS scores	2.7 (3.0)	3.4 (8.4)		
Hachinski score (Mean, SD)	0.7 (1.1)	0.8 (1.3)		
Smoker (Mean y, SD)	15.4 (24.2)	9.4 (16.3)		
Any Parkinsonian signs at baseline (Frequency %)	44.3%	54.5%		
Delusions	2.9% (of 68)	0% (of 10)		
Hallucinations	1.5% (of 68)	0% (of 10)		

Mann Whitney or χ^2 Pvalue between rpAD NACC and rpAD NPDSC. n.a. not assessable from lack of data.

Table 2

Average (and Standard deviation) of cognitive change in MMSE and CDR-sum of boxes of among all AD and rpAD subjects meeting inclusion/exclusion criteria in NACC dataset

	NACC all AD	rpAD NACC
Initial MMSE	27.3 (1.8)	26.5 (1.4)
Avg total MMSE drop	5.6 (2.1)	7.6 (4.3)
Average MMSE drop/y	1.1 (0.4)	2.5 (1.4)
Initial CDR-SB	2 (1.8)	2.1 (1.9)
Avg total CDR SB change	4.3 (3.6)	7.6 (3.8)
Average CDR change/y	0.9 (0.7)	2.5 (1.3)