Published in final edited form as:
Mov Disord. 2012 August ; 27(9): 1099–1103. doi:10.1002/mds.25026.

Clinical severity of Huntington's disease does not always correlate with neuropathologic stage

Jagan A Pillai[1], **Lawrence A Hansen**[2,3], **Eliezer Masliah**[2,3], **Jody L. Goldstein**[2], **Steven D Edland**[4], and **Jody Corey-Bloom**[2,5]

[1]Center for Brain Health, Cleveland Clinic, Cleveland [2]Department of Neurosciences, University of California, San Diego [3]Department of Pathology, University of California, San Diego [4]Department of Biostatistics, University of California, San Diego [5]VA San Diego Healthcare System

Abstract

Background—Huntington's disease is an inherited neurodegenerative disorder caused by a triplet repeat, CAG expansion mutation. Although CAG repeat length is thought to correlate with pathologic burden and disease severity, considerable variability in clinical phenotype remains. This study examined whether neuropathologic burden at autopsy corresponded with severity of clinical phenotype in Huntington's disease.

Methods—The brains of 24 patients with a clinical and genetic diagnosis of Huntington's disease were analyzed at autopsy. Subjects were stratified on the basis of Vonsattel staging as mild/moderate (Stage 1–2, n=7) or severe (Stage 3–4, n=17). Clinical severity was assessed on the basis of the Mini Mental State Exam (0–30) and two Unified Huntington's Disease Rating Scale functional components, the Independence Scale (10–100) and the Total Functional Capacity (0–13).

Results—The mild/moderate subjects were significantly older, had lower CAG repeat lengths, and greater fixed brain weights than those classified as severe. Patients who were pathologically

Corresponding Author: Jody Corey-Bloom, Department of Neurosciences, University of California San Diego, La Jolla, CA, jcoreybloom@ucsd.edu, Tel: 858.622.5855, Fax: 858.678.0939.

Author Roles:
Jagan A Pillai: 1) A, B,C 2) A, B 3)A
Lawrence A Hansen1) B,C 3) B
Eliezer Masliah 1)
B, 2) C, 3) B
,Jody L. Goldstein 1) B,C 3) B
Steven D Edland 1) A, 2) C, 3) B
Jody Corey-Bloom 1) A, B, C 2) A 3) B
List all authors along with their specific roles in the project and preparation of the manuscript. These may include but are not restricted to: 1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Full Financial Disclosures of all Authors for the Past Year:
Jagan A Pillai: None
Lawrence A Hansen: NIH AG5131
Eliezer Masliah: NIH AG18840, AG5131 and NS057096
Jody L. Goldstein: None
Steven D Edland : NIA AG005131 and AG034439.
Jody Corey-Bloom: UCSD Huntington's Disease Society of America Center of Excellence, UCSD Shiley-Marcos Alzheimer's Disease Research Center, NIH P50 AG 005131
Information concerning all sources of financial support and funding for the preceding twelve months, regardless of relationship to current manuscript must be submitted with the following categories suggested. List sources or "none".

classified as severe at autopsy were, on average, younger at age of onset and death, and less well educated. Despite obvious clinical and pathological differences between mild-moderate and severe Huntington's disease subjects at autopsy, mean Mini Mental State Exam scores of the two groups prior to death were surprisingly similar. Correlations between Vonsattel stage and functional assessment scores prior to death were low and not statistically significant.

Conclusions—Our results suggest that the extent of striatal changes in Huntington's disease may not always correlate with clinical disease severity measured by Unified Huntington's Disease Rating Scale functional scales.

Keywords

Autopsy study; Huntington's disease; Independence scale; Total Functional Capacity; Unified Huntington's Disease Rating Scale; Vonsattel staging

Introduction

Huntington's disease (HD) is an autosomal-dominant disorder characterized clinically by changes in movement, cognition, and behavior. There is an unstable expansion of CAG (trinucleotide) repeats that underlies the disease with the gene, located on chromosome 4 (4p16.3), encoding the 350 kDa protein huntingtin (1, 2). Neuropathological changes, presumably secondary to mutated huntingtin protein, are most prominently noted in the striatum of HD patients. The distinct topographic changes noted in HD have lead to a grading system of striatal degeneration that was described by Vonsattel and colleagues and is widely used as a research tool (3,4). The aim of the present study was to assess whether degree of pathological burden in HD, as assessed by Vonsattel staging at autopsy, corresponds to severity of clinical phenotype in HD close to death.

Methods

This is an autopsy series of 24 well-characterized HD patients (10 males, 14 females; ages 35 to 83 years at death) from one academic medical center. Most subjects had been diagnosed by a senior neurologist with expertise in movement disorders and had received extensive neurologic evaluations, including cognitive and functional testing, as part of their ongoing care in our HD Center. For the purposes of the current analyses, clinical assessment included the Mini Mental State Examination (MMSE) and two Unified Huntington Disease Rating Scale (UHDRS) functional components, the Independence Scale (IS scores, 10–100, lower scores suggestive of increased disability) and the Total Functional Capacity (TFC scores, 0–13, lower scores suggestive of increased disability) and UHDRS total motor score (5). DNA from the HD patients was isolated from peripheral blood white cells and the number of CAG repeats associated with the IT15 gene was determined by PCR by a standard protocol at some point during clinical follow up.

Autopsy, including brain weight, was performed within 24 hours of death. Neuropathological assessment was performed in all cases by one observer (L.A.H.) blinded to clinical diagnosis. The right hemisphere was frozen and the left hemisphere fixed in 10% formalin for histological examination. Sampling for histological studies included neocortical areas (midfrontal cortex—Brodmann area (BA) (BA8/46), superior temporal gyrus (BA38), inferior parietal lobule (BA39/40), motor cortex in the watershed area (BA4/1,2,3), anterior cingulate gyrus (BA24) and calcarine cortex (BA17/18)), hippocampus, entorhinal cortex, the basal forebrain with amygdala and lentiform nucleus, basal ganglia with nucleus accumbens, thalamus with subthalamic nucleus, midbrain at the level of the third nerve, rostral pons, mid-medulla with hypoglossal nucleus and inferior olivary nucleus, cerebellar vermis and cerebellar cortex with dentate nucleus. Additional sections were taken of

macroscopic lesions (e.g., infarcts, hemorrhages, or mass lesions) for histologic characterization. Depending upon the histologic findings, immunohistochemical studies were performed to characterize the pathology using antibodies to ubiquitin, glial fibrillary acidic protein, and isotype-specific forms of tau and β-amyloid. In cases with white matter pathology, the nature of this pathology was confirmed with additional histochemical methods, Luxol fast blue and Bielschowsky silver stains. The neuropathological burden in HD brains was stratified on the basis of Vonsattel staging as mild/moderate (Stage 1–2) or severe (Stage 3–4) (3,4). Statistical analysis was performed using SPSS to calculate Mann Whitney nonparametric test and Spearman's rank correlation coefficient. The significance level used was $p<0.05$.

Results

The demographic and clinical characteristics of the entire autopsy cohort are presented in Table 1. There were seven subjects identified as Vonsattel stage 1–2 and pathologically classified as mild/moderate. There were 17 subjects identified as Vonsattel stage 3–4 and pathologically classified as severe. One patient with Vonsattel stage 1 HD was noted to have concomitant cerebrovascular disease and one patient with Vonsattel Stage 3 HD was noted to have concomitant mild Alzheimer's disease changes. The clinical, pathologic characteristics of each patient by Vonsattel stage are noted in Table 1. The mild/moderate (Vonsattel stages 1–2) and severe (Vonsattel Stages 3–4) groups did not differ significantly with regard to gender, education, or mean duration from last clinical evaluation to death. The patients with mild/moderate pathology at autopsy had significantly lower mean CAG repeat lengths ($p=0.03$), higher ages at onset ($p=0.03$), older ages at death ($p=0.04$), and larger brain weights ($p=0.01$) as compared to those classified as severe (Table 2). The mild/moderate group had lower mean IS ($p=0.02$) and TFC ($p=0.03$) scores from the severe group. The correlation of each Vonsattel stage (1 to 4) to clinical and pathological variables of interest was next evaluated. There was no correlation between Vonsattel stage and time from last MMSE to death, or time from last functional assessment to death (Table 3). CAG repeat length positively correlated with Vonsattel stage, whereas age at onset of motor symptoms, age at death, and brain weight negatively correlated with Vonsattel stage. There was no correlation between Vonsattel stage and last MMSE, last IS score or last TFC score prior to death. Unfortunately, only 12 of our subjects had UHDRS motor scores documented within two years of death. However, among this subgroup Vonsattel stage correlated highly with last documented UHDRS total motor score (Spearman's rho=0.70, $p=0.01$, individual data not presented). No statistically significant correlations were noted (individual data not presented) between number and nature (psychiatric, medical and surgical) of comorbidities of each subject and their Vonsattel stage, or age at death.

Discussion

This study examined whether the burden of neuropathology, as assessed by Vonsattel staging, corresponded with severity of clinical phenotype in HD. We found that, despite obvious pathological differences between mild-moderate and severe HD subjects at autopsy, cognitive and functional scores just prior to death did not correlate with pathologic severity.

The relationship between pathologic burden at autopsy and CAG repeat length, in addition to younger age at onset and at death, has been described in the literature (6, for a review) and is consistent with the results from our series. On the other hand, only a limited number of autopsy studies have attempted to examine a patient's functional capabilities close to death and their neuropathological severity as assessed by Vonsattel stage (7,8). A retrospective study by Myers et al (7) noted that the mean functional disability rating among HD subjects within each Vonsattel stage one year prior to death negatively correlated with

the severity of the pathology stage. They also noted a wide range of overlapping physical disability scores across different Vonsattel stages consistent with the findings from our study. A large well-described prospective study by Rosenblatt et al (8) found that patients with severe motor impairment and lower MMSE scores generally had higher Vonsattel stage but also noted a poor correlation between the subject's HD Activities of Daily Living (ADL) score and pathology stage. In both of the above series (7,8) the primary aim of the investigation was to identify predictors of neuropathological severity; thus, the relationship between Vonsattel stage and patients' functional abilities were not examined carefully. Both series also used less well-known scales of functional disability for their analyses; thus, no study to date has closely examined the relationship between commonly used UHDRS functional components, the IS and the TFC, with degree of neuropathology. In both observational and treatment trials in HD, TFC has a strong correlation with HD disease progression (9) and is a key functional primary outcome measure. It is therefore important to know whether functional disability as measured by these commonly used UHDRS functional subscales, has a strong correlate with Vonsattel stage, the most commonly used measure of neuropathological disease burden.

Our results show that the pathological grading of the extent of striatal degeneration as put forward by Vonsattel may not always correlate with functional disability as noted by IS and TFC. Significant functional decline was sometimes noted in our HD patient series even when the burden of neuropathology appeared mild; conversely, a severe burden of neuropathology as per Vonsattel stage did not always signify poor functional capability. Of note, cortical changes were not factored into the assessment in the original Vonsattel grading system (6, Vonsattel, Personal communication, 2011) and most autopsy studies, with a few exceptions (eg: 10, 11), have generally emphasized striatal changes in HD. It is therefore possible that the pattern of neurodegeneration beyond the distinctive striatal changes could play a significant role in determining functional status in HD subjects prior to death. It is well known, for example, that not all brain regions are equally affected in all HD subjects. The medial temporal lobe, including the hippocampus, is generally well preserved (10, 11); in addition, other structures, such as the thalamus, are not incorporated in Vonsattel staging (6, 10). Preservation of some of these areas could help maintain higher levels of functional capabilities than expected from the degree of striatal degeneration alone. Furthermore, individual case reports of HD subjects with limited striatal atrophy, but notable cortical atrophy, and significant clinical disability, have been documented at autopsy (12,13) and are consistent with our finding of a poor correlation between Vonsattel stage and functional capacity.

Finally, there is support from multiple neuroimaging studies that the neuropathological changes occurring in HD are significantly more widespread (14, 15, 16) beyond the well-described striatal changes (17, 18, 19, 20). Frontal lobe volumes have been noted to correlate with cognitive measures, such as memory and planning performance (15, 16, 21), and regions, including the thalamus (22), insula (23), white matter (24, 25), and widespread cortices (26, 27), have been associated with cognitive performance in both presymptomatic and early clinically manifest HD. One study by Rosas and colleagues (27) demonstrated a significant association between regional cortical thinning and total functional capacity. Taken together, these studies suggest that variations in cortical and regional brain atrophy can influence the duration and severity of clinical and functional symptoms in HD. A neuropathological grading of disease pathology focused primarily on striatal changes, such as the Vonsattel staging system, is therefore less likely to correlate with functional disability influenced by pathological changes throughout the brain.

It should be pointed out that although the MMSE is widely used by investigators, its heavy emphasis on language and memory may not best capture cognitive domains most affected in

HD, e.g. executive functioning. Increasingly, cognitive instruments such as the Mattis Dementia Rating Scale and the Montreal Cognitive Assessment (MoCA) are being used to track cognitive decline in HD (28). There is an analogous concern about the TFC which, while often easy to administer and follow, was designed to capture early disability and therefore has limited dynamic range, especially in the later stages of HD (9). Additional limitations of our study include lack of MMSE scores just prior to onset of HD symptoms and missing UHDRS motor scores and CAG repeat numbers for some subjects.

Nevertheless, our results support the notion that motor, cognitive and functional disability in HD reflects not only subcortical pathology, but also substantial variability in neuronal dysfunction among both cortical and striatal areas. Interventions to ameliorate and ultimately prevent the development of the HD phenotype should therefore occur early to target neuronal dysfunction in both cortex and striatum (29). Some of the preserved functional capability in the face of severe striatal pathology found in our study could also suggest a degree of cognitive reserve (30) or variability in regional HD gene expression within specific brain areas (21). The advent of better functional and structural imaging in these neurodegenerative conditions holds promise for integrating clinical information on functional and cognitive status with the progress of neurodegenerative pathology.

References

1. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993; 72(6):971–983. [PubMed: 8458085]
2. Cattaneo E, Zuccato C, Tartari M. Normal huntingtin function: an alternative approach to Huntington's disease. Nat Rev Neurosci. 2005; 6(12):919–930. [PubMed: 16288298]
3. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol. 1985; 44(6):559–577. [PubMed: 2932539]
4. Vonsattel JP. Huntington disease models and human neuropathology: similarities and differences. Acta Neuropathol. 2008; 115(1):55–69. [PubMed: 17978822]
5. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord. 1996; 11(2):136–142. [PubMed: 8684382]
6. Vonsattel, JP.; Keller, C.; Amaya, MDP. Neuropathology of Huntington’s disease. In: Duyckaerts, C.; Litvan, I., editors. Handbook of Clinical Neurology, Vol 89 (3rd series) The Dementias. 2008. p. 599-617.
7. Myers RH, et al. Clinical and neuropathologic assessment of severity in Huntington's disease. Neurology. 1988; 38(3):341–7. [PubMed: 2964565]
8. Rosenblatt A, Abbott MH, Gourley LM, et al. Predictors of neuropathological severity in 100 patients with Huntington's disease. Ann Neurol. 2003; 54(4):488–493. [PubMed: 14520661]
9. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. Huntington Study Group. Neurology. 2000 Jan 25; 54(2):452–8. [PubMed: 10668713]
10. Halliday GM, McRitchie DA, Macdonald V, Double KL, Trent RJ, McCusker E. Regional specificity of brain atrophy in Huntington's disease. Exp Neurol. 1998; 154(2):663–672. [PubMed: 9878201]
11. de la Monte SM, Vonsattel JP, Richardson EP Jr. Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. J Neuropathol Exp Neurol. 1988; 47(5):516–525. [PubMed: 2971785]
12. Mizuno H, Shibayama H, Tanaka F, et al. An autopsy case with clinically and molecular genetically diagnosed Huntington's disease with only minimal non-specific neuropathological findings. Clin Neuropathol. 2000; 19(2):94–103. [PubMed: 10749290]
13. Caramins M, Halliday G, McCusker E, Trent RJ. Genetically confirmed clinical Huntington's disease with no observable cell loss. J Neurol Neurosurg Psychiatry. 2003; 74(7):968–970. [PubMed: 12810795]

14. Starkstein SE, Brandt J, Bylsma F, Peyser C, Folstein M, Folstein SE. Neuropsychological correlates of brain atrophy in Huntington's disease: a magnetic resonance imaging study. Neuroradiology. 1992; 34(6):487–489. [PubMed: 1436456]
15. Jernigan TL, Salmon DP, Butters N, Hesselink JR. Cerebral structure on MRI, Part II: Specific changes in Alzheimer's and Huntington's diseases. Biol Psychiatry. 1991; 29(1):68–81. [PubMed: 1825793]
16. Backman L, Robins-Wahlin TB, Lundin A, Ginovart N, Farde L. Cognitive deficits in Huntington's disease are predicted by dopaminergic PET markers and brain volumes. Brain. 1997; 120 (Pt 12):2207–2217. [PubMed: 9448576]
17. Aylward EH, Li Q, Stine OC, et al. Longitudinal change in basal ganglia volume in patients with Huntington's disease. Neurology. 1997; 48(2):394–399. [PubMed: 9040728]
18. Bamford KA, Caine ED, Kido DK, Plassche WM, Shoulson I. Clinical-pathologic correlation in Huntington's disease: a neuropsychological and computed tomography study. Neurology. 1989; 39(6):796–801. [PubMed: 2524678]
19. Harris GJ, Aylward EH, Peyser CE, et al. Single photon emission computed tomographic blood flow and magnetic resonance volume imaging of basal ganglia in Huntington's disease. Arch Neurol. 1996; 53(4):316–324. [PubMed: 8929153]
20. Aylward EH, Anderson NB, Bylsma FW, et al. Frontal lobe volume in patients with Huntington's disease. Neurology. 1998; 50(1):252–258. [PubMed: 9443488]
21. Brandt J, Bylsma FW, Aylward EH, Rothlind J, Gow CA. Impaired source memory in Huntington's disease and its relation to basal ganglia atrophy. J Clin Exp Neuropsychol. 1995; 17(6):868–877. [PubMed: 8847393]
22. Kassubek J, Juengling FD, Ecker D, Landwehrmeyer GB. Thalamic atrophy in Huntington's disease covaries with cognitive performance: a morphometric MRI analysis. Cereb Cortex. 2005; 15(6):846–853. [PubMed: 15459079]
23. Peinemann A, Schuller S, Pohl C, Jahn T, Weindl A, Kassubek J. Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: a neuropsychological and voxel-based morphometric study. J Neurol Sci. 2005; 239(1):11–19. [PubMed: 16185716]
24. Beglinger LJ, Nopoulos PC, Jorge RE, et al. White matter volume and cognitive dysfunction in early Huntington's disease. Cogn Behav Neurol. 2005; 18(2):102–107. [PubMed: 15970729]
25. Rosas HD, Tuch DS, Hevelone ND, et al. Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. Mov Disord. 2006; 21(9):1317–1325. [PubMed: 16755582]
26. Rosas HD, Hevelone ND, Zaleta AK, Greve DN, Salat DH, Fischl B. Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. Neurology. 2005; 65(5):745–747. [PubMed: 16157910]
27. Rosas HD, Salat DH, Lee SY, et al. Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity. Brain. 2008; 131(Pt 4):1057–1068. [PubMed: 18337273]
28. Mickes L, Jacobson M, Peavy G, Wixted JT, Lessig S, Goldstein JL, Corey-Bloom J. A comparison of two brief screening measures of cognitive impairment in Huntington's disease. Mov Disord. 2010; 25(13):2229–2233. [PubMed: 20721924]
29. Cepeda C, Wu N, Andre VM, Cummings DM, Levine MS. The corticostriatal pathway in Huntington's disease. Prog Neurobiol. 2007; 81(5–6):253–271. [PubMed: 17169479]
30. Nithianantharajah J, Barkus C, Vijiaratnam N, Clement O, Hannan AJ. Modeling brain reserve: experience-dependent neuronal plasticity in healthy and Huntington's disease transgenic mice. Am J Geriatr Psychiatry. 2009; 17(3):196–209. [PubMed: 19454847]
31. Hodges A, Strand AD, Aragaki AK, Kuhn A, Sengstag T, Hughes G, Elliston LA, Hartog C, Goldstein DR, Thu D, Hollingsworth ZR, Collin F, Synek B, Holmans PA, Young AB, Wexler NS, Delorenzi M, Kooperberg C, Augood SJ, Faull RL, Olson JM, Jones L, Luthi-Carter R. Regional and cellular gene expression changes in human Huntington's disease brain. Hum Mol Genet. 2006; 15(6):965–77. [PubMed: 16467349]

Mov Disord. Author manuscript; available in PMC 2013 August 01.

Table 1

Clinical and pathologic characteristics of each patient by Vonsattel stage

Case	Vonsattel stage	Gender	Brain weight (gms)	CAG	Age at onset (yrs)	Age at death (yrs)	Additional pathology to HD
1	1	m	1162	n/a	47	60	
2	1	m	1230	43	43	55	
3	1	F	914	41	52	68	
4	1	f	1044	40	63	82	
5	1	f	1390	40	62	83	Cerebrovascular disease
6	2	F	1254	n/a	56	73	
7	2	m	1010	45	41	42	
8	3	f	990	45	51	58	
9	3	m	948	n/a		76	Mild Alzheimer changes
10	3	f	1144	42	55	67	
11	3	f	1032	44	48	65	
12	3	f	1152	47	47	54	
13	3	m	1140	50	25	37	
14	3	f	806	44	37	56	
15	3	f	826	44	45	56	
16	3	m	1012	51	29	39	
17	4	f	774	n/a	24	47	
18	4	m	1118	n/a	33	46	
19	4	m	946	54	37	52	
20	4	m	958	61		35	
21	4	f	982	43	40	53	
22	4	m	884	43	43	58	
23	4	f	920	43	44	55	
24	4	f	744	44	53	67	

m=male; f=female; gms=grams; yrs=years; HD=Huntington's disease

Table 2

Differences between combined pathologic groups, mean [Range]

	Mild/Moderate (Stage 1 & 2)	Severe (Stage 3 & 4)	P value*
Brain Weight (gms) (n=24)	1165.7 [914–1390]	963.3 [744–1152]	P=0.01
Education (yrs) (n=24)	15 [12–19]	12.3 [6–18]	n.s.
CAG repeat length (n=19)	41.8 [40–45]	46.8 [42–61]	P=0.03
Age at onset (yrs) (n=22)	53 [41–63]	41 [24–65]	P=0.03
Age at death (yrs) (n=24)	66.1 [42–83]	53.9 [35–76]	P=0.04
Time from last MMSE assessment to death (yrs) (n=19)	2.1 [0–5]	2.7 [0–5]	n.s.
Last MMSE prior to death (n=19)	23.7 [15–28]	24 [20–30]	n.s.
Independence Scale score at time of last MMSE (n=19)	72 [55–100]	50.5 [10–90]	p=0.02
Functional Capacity Scale score at time of last MMSE (n=19)	6.0 [2–12]	4.0 [2–11]	n.s
Time from last functional assessment to death (yrs) (n=22)	1.5 [0–3]	1.4 [0–3]	n.s.
Last Independence Scale score (n=22)	60 [20–90]	34.2 [10–60]	P=0.02
Last Total Functional Capacity score (n=22)	4.4 [0–9]	1.4 [0–5]	P=0.03

*Mann Whitney non-parametric test

n.s. not significant

Table 3

Correlations between Vonsattel stages (1 to 4) and clinical/pathological variables

	Spearman's rho	P value
CAG repeat length	0.05	P=0.02
Gender	− 0.01	n.s.
Age at onset (yrs)	−0.50	P=0.02
Age at death (yrs)	−0.50	P=0.01
Brain weight (gms)	−0.51	P=0.01
Time from last MMSE to death (yrs)	0.40	n.s.
Last MMSE prior to death	−0.30	n.s.
Time from last functional assessment to death (yrs)	−0.29	n.s.
Last Independence scale score	−0.38	n.s.
Last Total Functional Capacity score	−0.30	n.s.

n.s. not significant