Journal of Huntington's Disease 3 (2014) 209–217
DOI 10.3233/JHD-140111
IOS Press

Research Report

The Co-Occurrence of Alzheimer's Disease and Huntington's Disease: A Neuropathological Study of 15 Elderly Huntington's Disease Subjects

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Abstract.
Background: Dementia is a common feature in both Huntington's disease (HD) and Alzheimer's disease (AD), as well as in the general elderly population. Few studies have examined elderly HD patients with dementia for neuropathologic evidence of both HD and AD.
Objective: We present neuropathological findings in a retrospective case series of 15 elderly HD patients (ages 60–91 years), 11 of whom had prominent clinical dementia.
Methods: Post-mortem brain tissue was examined and stained for evidence of both HD and AD including Vonsattel grading and *Htt*-repeat expansion, Bielskowsky, *tau*, β amyloid, and TDP43 immunostaining.
Results: Mean age at death was 76.8 years, mean disease duration was 18.6 years, and mean CAG repeat expansion was 42. Evidence of AD in addition to HD pathology was present in 9 of 11 (82%) patients with prominent dementia, suggesting that AD may be more commonly co-occurring with HD than previously appreciated. Two patients had only HD as the basis of dementia and four patients did not have prominent dementia. One patient with marked parkinsonian features was not L-dopa responsive and had no substantia nigra Lewy bodies at autopsy.
Conclusions: Our study suggests that AD may frequently contribute to cognitive decline in elderly HD patients which complicates the assessment and management of such individuals. Further study is needed to determine if there is a higher incidence of AD in persons with HD compared to the general population. In addition, our series includes one HD patient whose clinical features masqueraded as Parkinson's disease but was not responsive to levodopa therapy.

Keywords: Huntington's disease, Alzheimer's disease, dementia, parkinsonism

INTRODUCTION

Huntington's disease (HD) is a familial neurodegenerative disease characterized by progressive motor, coordination, cognitive and behavioral symptoms. HD is a dominantly inherited disease caused by a triplet repeat expansion in the huntingtin gene on chromosome 4p. HD onset has been typically documented when patients start to manifest HD-associated movement disorders, although subtle cognitive abnormalities are now appreciated in pre-manifest and early

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ISSN 1879-6397/14/$27.50

stages of HD [1, 2]. Cognitive deficits in HD typically involve reduced attention, verbal fluency, processing speed, executive function and impaired judgment with relatively intact memory [3]. This is in contrast to the typical major cognitive deficit in Alzheimer's disease, namely early and progressive marked memory loss [4]. Severe cognitive deficits causing dementia in HD have been typically attributed to late stage HD, however a few studies have suggested that AD and HD pathology can co-occur [5–10].

HD onset is typically in the 4th to 5th decade of life while AD onset is typically later, in the 7th to 9th decade of life. However, the improved ability to diagnose HD with genetic testing has led to increased recognition of late onset HD cases in the 7th decade of life and later [11, 12]. Prevalence of HD is estimated at 2.7 per 100,000 worldwide,[13] but as high as 12.3 per 100,000 in the UK [11]. AD is far more common than HD, and prevalence in North America is estimated to be 6.4% (6,400/100,000) in people 60 years of age and older, and expected to increase as the elderly population increases [14, 15]. Based on these prevalences, it is likely that independent co-occurrence of AD in elderly HD patients could occur. Alternatively, HD may increase the risk of developing AD, particularly in the elderly HD population.

We present a case series of 15 anecdotally chosen elderly HD patients with neuropathological analysis for both AD and HD, several of whom had reported clinical dementia. In addition, we included a HD patient of special interest whose clinical course masqueraded as Parkinson's disease, but was not responsive to levodopa therapy. To our surprise, AD pathology was co-existent in 9 of the 11 patients with dementia, higher than what would be expected for patients of their age group, suggesting that AD may be a cause of dementia in elderly HD patients more frequently than previously appreciated. Further study is needed to determine whether this co-occurrence of HD and AD is only due to the combined prevalences of these two neurodegenerative diseases, or if there is increased risk of developing AD in the elderly HD population.

METHODS

Fifteen HD patients who died at 60 years of age or older, many with clinical dementia, were ascertained from a collection of postmortem neuropathology studies performed at the University of Washington. CAG repeat expansion within the HD gene was genotyped by the University of Washington Department of Laboratory Medicine by standard methods in 11 subjects. Because this was a retrospective neuropathology study, we were not able to control clinical dementia evaluations, and only one individual had formal neuropsychological testing. Neurologists evaluated all of the patients, and mental status was determined by review of medical records, which included collateral information from family members. Three subjects were seen outside of the University of Washington Medical Center (UWMC) system. The determination of whether or not the patient had prominent dementia was made by medical record review and interview of family members. Prominent dementia was defined as more than the usual difficulty with attention, multitasking and behavior seen in HD. This was a subjective determination because only one patient (#8) had formal neuropsychological testing. The senior author (TDB) of this study personally examined twelve of the patients.

Neuropathology methods: All but one (patient #2) of the autopsies was performed at UWMC over a span of 33 years. For each case, post mortem examination was performed after informed written consent was obtained from the patient's legal next of kin according to the patient's wishes and according to protocols approved by the Institutional Review Board of the University of Washington. After immersion fixation in 10% neutral buffered formalin for approximately two weeks, each brain underwent standard diagnostic neuropathological examination which included brain weight and photographic documentation (except for the oldest cases) and gross examination of the whole brain, coronal slices of the cerebrum, and axial sections of the brainstem and cerebellum. The degree of striatal atrophy was specifically assessed in each case and incorporated into the Vonsattel grade [5]. Each brain underwent standard sampling for neurohistologic analysis from multiple anatomic regions including cerebral cortex, neostriatum, hippocampus, amygdala, brainstem, and cerebellum; sampled tissues were submitted for standard paraffin processing and histology. Paraffin sections were cut at 5 μm thickness and subjected to histochemical and immunohistochemical stains, which routinely included a triple stain of hematoxylin, eosin, and luxol fast blue (H&E/LFB) in addition to Bielschowsky silver stain on frontal and parietal cortex sections and congo red stain for amyloid on occipital cortex sections. Immunostains were performed on selected sections at the time of the autopsy or retrospectively for this study to evaluate for astrogliosis (rabbit anti-

GFAP; DAKO, 1 : 20,000), huntingtin intranuclear and cytoplasmic inclusions (mouse anti-huntingtin, clone EM48; Millipore, 1 : 100), TDP-43 redistribution (rabbit anti-TDP-43; Proteintech, 1 : 5000), β-amyloid (Aβ) plaques (mouse anti-β amyloid, clone 6E10; Covance, 1 : 5000), and neurofibrillary tangles (mouse anti-tau, clone TAU-2; Sigma-Aldrich, 1 : 30,000).

Complete neuropathologic evaluation included assessment of HD neuropathology according to the Vonsattel grading system, which combines measures of neostriatal atrophy grossly and astrogliosis and neuron loss microscopically. Gross Vonsattel grading [5] was performed in the oldest cases retrospectively according to written descriptions and photographs where available. Microscopic neostriatal pathology was assessed retrospectively for every case as part of this study using H&E/LFB and GFAP IHC. Characterization of pathologic intranuclear and cytoplasmic huntingtin protein inclusions was performed in frontal and occipital cortex, striatum, and cerebellum using anti-mutant huntingtin IHC. In addition, each case was retrospectively assessed for Alzheimer's disease pathology according to the 2012 NIA-AA Guidelines for the Neuropathologic Assessment of Alzheimer's disease [16, 17]. Specifically, immunostains for Aβ plaques were performed and assessed in cortex, hippocampus, striatum, midbrain, and cerebellum to determine Thal Aβ plaque distribution [18]. Thal phase was combined with standard Braak and Braak staging of neurofibrillary tangle distribution using Bielschowsky silver stains and anti-tau IHC and CERAD neuritic plaque density grading using Bielschowsky silver stains to arrive at an NIA-AA recommended ABC score for AD neuropathology [19, 20]. Amyloid angiopathy in the occipital cortex was assessed as absent, mild (leptomeningeal vessels only), moderate (involvement of penetrating cortical arterioles), and severe (extensive involvement of parenchymal arterioles with evidence of perivascular involvement) by examining Congo Red stained sections. TDP-43 redistribution from the nucleus to cytoplasmic inclusions was assessed in frontal cortex and hippocampus with IHC. In some of the oldest cases some or all of the paraffin tissue blocks were not available for retrospective staining.

Statistical analysis was performed using STATA 12.1 software.

RESULTS

Fifteen HD patients who died at 60 years of age or older were ascertained for postmortem neuropathology analysis, and are summarized in Table 1. Eleven of these patients were reported to have prominent dementia on clinical exam. The mean age of onset of HD motor symptoms in our case series was 58.0 ± 15.8 years old ($n = 14$), ranging from 30 to 82 years. The mean age at death was 76.8 ± 10.1 years old ($n = 15$), ranging from 60 to 91. The mean duration of symptoms was 18.6 ± 10.4 years ($n = 14$), ranging from 3 to 43 years. Because all subjects died over the age of 60 years and mean age at death was 76.8 years we have referred to them as "elderly", although not all qualify as "late onset HD" because 7 subjects had onset of symptoms before age 60. The average size CAG repeat expansion within the HD gene (*IT15*) was 42 ± 2 ($n = 11$), ranging from 40 to 46. The average brain weight was $1{,}110.4 \pm 156.1$ grams.

Consistent with the diagnosis of HD in all of our patients, Huntingtin intranuclear inclusions were found in all 11 subjects where this staining was available (Fig. 1a). The Vonsattel stage in our cohort ranged from 1 to 4 [5]. Based on clinical exam, 11 of the 15 patients were classified as demented. Only one patient (patient # 8) had formal neuropsychological testing at age 58. Neuropsychological evaluation was obtained in this patient due to recent cognitive decline causing early retirement from a career in aeronautical engineering, and revealed significant deterioration in all aspects of cognitive function. He was not noted to have motor symptoms at the time of neuropsychological evaluation. His evaluation included the Halstead Reitan Neuropsychological Battery, Wechsler Adult Intelligence Scale - Revised, Wide Range Achievement Test – Revised and Wechsler Memory Scale - Revised. Profound deficits were found in all aspects of memory, including visual and verbal memory, and delayed recall. Abstraction, reasoning and problem-solving were significantly reduced, as well as sensory perception and motor skills. Throughout the examination, the patient was reported as confused and disorganized. This individual's neuropathology was consistent with both advanced HD (VS stage 3/4) and AD (see Table 1).

Nine of the 11 (82%) individuals classified as clinically demented met neuropathologic criteria for AD. Five of the nine met NIA-AA criteria based on their ABC score for neuropathologic changes of AD (composite score based on amyloid plaque (Thal) and neurofibrillary tangle (Braak) distribution and neuritic plaque density (CERAD)) (Table 1, Fig. 1b–d) [16–20]. Four others lacked Thal phase data but met AD criteria based on NIA-Reagan criteria (Braak and CERAD data). Two of the 4 individuals who were not considered clinically demented (patient #12 age 85 and

Table 1
Summary of demographic and neuropathologic findings

Patient #	Sex	Onset	Death	Duration	CAG	BW (grams)	Neuritic Plaques	NFT (Braak)	CAA	Thal Stage	TDP-43	Huntingtin[2]	ABC Score	VS Stage	Dementia[3]
1	M	75	85	10	40	1150	Frequent	VI	Moderate	5	H, D	FC, ST	A3, B3, C3	2/4	Yes
2[1]	F	NA	83	NA	NA	1060	Frequent	V	Marked	NA	NA	NA	NA	1/4	Yes
3	F	79	91	12	41	NA	Moderate	V	None	3	None	FC, ST	A2, B3, C2	1/4	Yes
4	F	60	78	18	41	1125	Frequent	VI	Moderate	4	None	FC, ST	A3, B3, C3	3/4	Yes
5	F	39	66	27	NA	NA	Frequent	V	None	NA	NA	NA	NA	2–3/4	Yes
6	M	45	61	16	NA	NA	Frequent	V	NA	5	NA	FC, ST	A3, B3, C3	2/4	Yes
7	F	30	60	30	NA	1180	Frequent	V	NA	NA	NA	NA	NA	2/4	Yes
8[4]	M	56	71	15	43	1000	Frequent	V	Moderate	4	H	FC, ST	A2, B3, C3	3/4	Yes
9	F	56	80	24	46	920	Sparse	I	None	1	None	FC, ST	A1, B1, C1	3/4	Yes
10	F	44	87	43	45	1020	None	I	Moderate	0	H, D	FC, ST	A0, B1, C0	3/4	Yes
11	F	60	83	23	40	900	Frequent	V	None	NA	NA	NA		1/4	Yes
12	F	75	85	10	41	1250	Frequent	V	Moderate	3	None	FC, ST	A2, B3, C3	2/4	No
13	M	63	71	8	40	1390	None	I	None	0	None	FC, OC, ST	A0, B0, C0	2/4	No
14	F	82	85	3	40	1000	Moderate	III	None	3	None	FC, ST	A2, B2, C2	1/4	No
15	M	48	66	18	44	1330	None	I	None	0	None	FC, ST	A0, B1, C0	4/4	No
Mean		58 ± 15.8	76 ± 10.1	18.6 ± 10.4	42 ± 2	1110 ± 156									

CAG: Repeat Number; BW: Brain Weight; CAA: Congophilic Amyloid Angiopathy; NFT: Neurofibrillary tangles; VS: Vonsattel Stage; H: Hippocampus; D: Dentate; FC: Frontal Cortex; FC: ST: Striatum; OC: Occipital Cortex; NA: not available. [1]Sib of #1. Study courtesy of McLean Hospital Brain Bank. [2]immunohistochemistry for Huntingtin intranuclear inclusions. [3]based on retrospective review of clinical records. [4]individual with neuropsychological testing available.

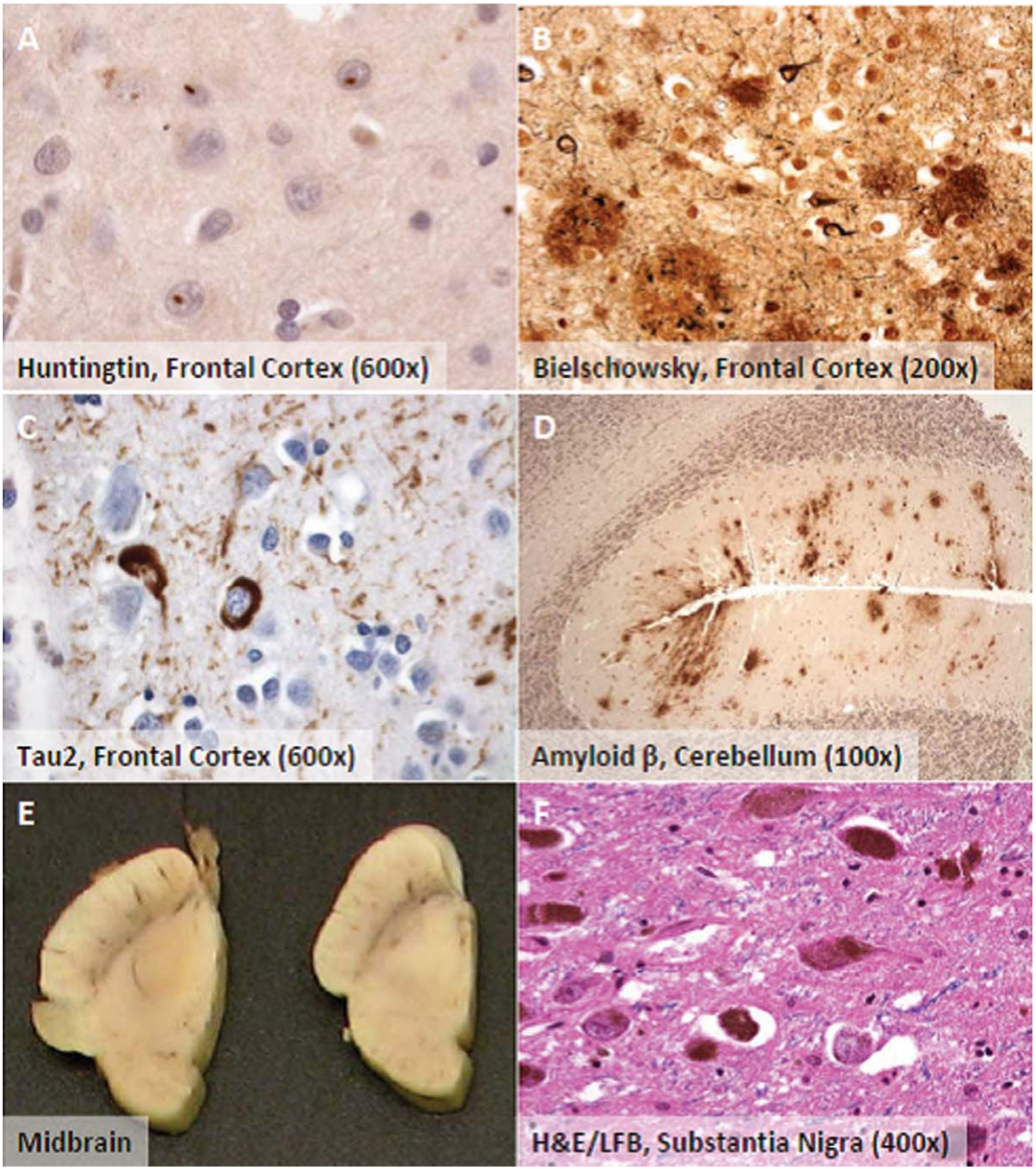

Fig. 1. (A) Mutant huntingtin immunohistochemistry (EM48, 600x) in frontal cortex sections reveals characteristic neuronal intranuclear inclusions as well as scattered cytoplasmic and extracellular huntingtin inclusions. (Patient #15). (B) Bielschowsky silver stain (200x) reveals classic frontal cortex neurofibrillary tangles and neuritic plaques, which are critical components of the "B" and "C" score in the new NIA-AA criteria. The density of neuritic plaques in this patient was considered CERAD "frequent" which corresponds to an NIA-AA AD pathology score of C3 (Patient #1). (C) Immunostains for tau (Tau2, 600x) from a frontal cortex section adjacent to that in Fig 1B decorate neurofibrillary tangles as well as scattered tau neurites and are assessed in hippocampus and frontal and occipital cortex in order to assign a Braak stage ("B" score). Neurofibrillary tangles in the frontal lobe indicate at least a Braak and Braak stage V of VI and correspond to an NIA-AA score of B3 (Patient #1). (D) Amyloid β immunostains (6E10, 100x) reveal classic molecular layer plaques in cerebellar cortex, indicative of the highest Thal amyloid phase "A" score (phase V; A3) (Patient #6). (E) In this HD patient (#15) with parkinsonism there is mild to moderate pallor of the substantia nigra, as can be seen in these consecutive axial sections through the midbrain of this patient. (F) H&E-LFB immunostaining (400x) of substantia nigra depicted grossly in Fig 1E demonstrates near normal density of pigmented dopaminergic neurons with rare melanophages (upper right) indicative of mild neuron dropout (Patient #15).

Table 2
Summary of demographics and neuropathologic findings in individuals with clinical dementia and without reported dementia

	Dementia ($n = 11$)*	No Dementia ($n = 4$)
Age at Onset HD	54.4 ± 15.4, $n = 10$	67 ± 14.9
Age at Death	76.8 ± 10.7	76.8 ± 9.7
Duration HD (years)	21.8 ± 9.9, $n = 10$	9.8 ± 6.2
CAG repeat size	42.3 ± 2.4, $n = 7$	41 ± 2
Brain Weight (grams)	1044.4 ± 103.6, $n = 8$	1242.5 ± 171.5
Thal stage (0–5)	3.1 ± 0.8, $n = 7$	1.5 ± 1.7
Braak stage (0–6)	4.5 ± 1.8	2.5 ± 1.9
Vonsattel stage (0–4)	2.1 ± 0.8	2.3 ± 1.3

*n is specified if information was not available in all 10 individuals with clinical dementia.

patient #14, also age 85) also met neuropathologic criteria for AD based on NIA-Reagan criteria and had at least intermediate AD neuropathologic change based on the new NIA-AA guidelines. Moderate to frequent neuritic plaques were found in 9 of the 11 patients with clinical dementia and 1 of the 5 patients who did not meet neuropathologic criteria for AD. Age at HD onset, death, duration of HD, CAG repeat expansion size, brain weight and Vonsattel stage among individuals in our case series with and without clinical dementia are summarized in Table 2. Statistical significance could not be assessed given our small sample size and non-random ascertainment of these cases, but there was a trend in later onset and shorter disease duration of HD in individuals without clinical dementia. On average those with dementia had a much longer duration of symptomatic HD (21.8 ± 9.9 years) compared to those without dementia (9.8 ± 6.2 years). In addition, there was a trend toward lower brain weight (1044 ± 103 grams vs. 1242 ± 171 grams) and higher Braak and Thal staging in individuals with clinical dementia. Transactivation-responsive DNA-binding protein 43 (TDP-43) staining was performed in 10 of the 14 cases, and was present in two cases that did meet AD criteria, one that did not and absent in seven others (Table 1).

Patient #15 was of special interest because of a clinical course of Huntington's disease notable for marked Parkinsonism with bradykinesia, rigidity, dystonia and hypophonia. This patient was evaluated by three neurologists, including a movement disorder specialist, who found this patient to have many features typical for Parkinson's disease. However, this patient's Parkinsonism was unresponsive to maximum dopaminergic therapy of 700 mg levodopa per day. Postmortem examination confirmed HD with Vonsattel stage 4 but, while there was mild to moderate pallor of the substantia nigra (Fig. 1E), only mild dopaminergic neuron loss was identified in the midbrain with rare associated melanophages (Fig. 1F). Lewy bodies were not identified in pigmented nuclei in midbrain, pons, and medulla nor in amygdala or cingulate and frontal cortex. Huntingtin intranuclear inclusions were also not seen in dopaminergic neurons even though they were present in abundance in striatal and cortical samples from this patient.

CONCLUSIONS

HD is a hereditary neurodegenerative disease that can include significant cognitive decline [3]. By late stage HD, most patients have some level of cognitive impairment, and many are demented. Dementia in late stage HD has been typically attributed to the presence of HD. However AD is common in the elderly population. The prevalence of AD in North America is estimated to be 6.4% in people 60 years of age and older, and is expected to increase [14, 15]. It is possible that AD may be coincident with HD based on the high prevalence of AD alone. Our case series of elderly Huntington's disease patients with postmortem examination of neuropathologic features of both AD and HD provides a unique opportunity to examine the possible coincidence of both neurodegenerative processes. Although this series of HD patients was anecdotally selected rather than systematically or randomly (and does not intend to propose a population prevalence), 9 of the 11 HD patients with clinical dementia met neuropathologic criteria for AD, which is more than one would expect based upon prevalence of AD in the general population. Therefore, these findings hint that AD may be a common cause of or contributor to dementia in elderly HD patients. Two of the 11 patients with clinical dementia did not meet criteria for AD, confirming that dementia can be due to advanced HD alone. Although this case series was not large enough for statistical significance, CAG repeat expansion size and Vonsattel stage did not correlate with clinical dementia in our HD patients (Table 2). However, earlier onset and longer duration of HD trended toward association

with development of clinical dementia in HD. It may be that longer duration of symptomatic HD provides time for the development of AD pathology. It is of note that the presence of AD pathology was not associated with earlier death.

Formal neuropsychological testing confirming dementia was available in only one patient in our series (patient # 8). Cognitive abnormalities typically associated with HD are reduced attention, verbal fluency, processing speed, executive function and impaired judgment and often referred to as subcortical dementia [21–23]. These abnormalities differ from the profound memory deficits typically seen in Alzheimer's disease, which are often referred to as cortical dementia [24]. However, neuropsychological testing in our patient also revealed features of both cortical and subcortical dementias. Interestingly, these cognitive deficits preceded onset of motor symptoms in this patient. Further study with neuropsychological testing and neuropathology correlation of systematically ascertained HD patients with dementia is necessary to determine whether HD patients with co-occurring AD may have a different cognitive profile compared to HD patients without AD.

Of note, patient #14 had a very late onset of HD symptoms at age 82 without prominent dementia and a relatively short duration of disease of 3 years before death. Although she had a moderate burden of neuritic plaques and Braak stage 3 and would not have met criteria for AD pathology previously, her ABC score merits classification as intermediate neuropathological changes of AD according to the new NIA-AA guidelines, which is considered adequate explanation of cognitive impairment or dementia and can be diagnosed as Alzheimer's disease (Table 1). Of course, pathologic changes of Alzheimer's disease including neuritic plaque burden in the elderly population can be present despite absence of significant antemortem dementia [25, 26].

Patient #15 had severe parkinsonism that was unresponsive to levodopa, and was not found to have Lewy body pathology. Parkinsonism in HD is typically associated with the Westphal variant of juvenile HD, with severe bradykinesia and rigidity, but two reports describe adult onset HD with marked parkinsonism, including levodopa-responsive parkinsonism [27, 28]. Because PD is a common disease, some HD cases could have parkinsonism due to co-occurrence of HD and PD. However, our case suggests parkinsonism was caused by HD pathology, given the absence of levodopa-responsiveness and absence of alpha-synuclein pathology. Although alpha-synuclein has been identified in huntingtin inclusions in HD mouse models and post-mortem brain tissue, Lewy bodies have not been reported in HD, including HD patients with primarily akinetic rigid motor symptoms [29]. We looked, but did not find, intranuclear or cytoplasmic huntingtin-immunopositive inclusions in dopaminergic neurons in this particular case. The mild changes in the substantia nigra alone are not likely to explain the marked parkinsonian features seen in this case.

TDP-43 has been found in pathologic inclusions in multiple neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia, AD and HD [30–32]. We found variable presence of TDP-43 in HD patients with and without dementia, supporting prior studies that have identified TDP-43 in huntingtin intracellular inclusions. However, our limited case series did not suggest an association between the presence of TDP-43 and clinical dementia.

There have been only 4 previously published anecdotal cases reporting co-occurrence of AD and HD pathology. Myers et al. reported a case with age at death at 77, Moss et al. reported a case with age at death at 81, Reyes et al. reported a case with age at death at 68, and McIntosh et al. reported a case with age at death at 54 [6, 8–10]. It is unclear whether AD pathology tends to co-occur in late-onset HD patients more frequently than earlier onset cases. Both early and late onset HD cases have been reported to have co-occurrence of AD (including this study), suggesting that AD changes can occur earlier in HD patients compared to AD onset in the general population [9, 10]. Vonsattel et al found 18 cases of coexisting HD and AD which represented 2% of an entire series of 866 HD brains and 5% of the 361 cases over age 65 years at death [33]. This did not appear to be a greater than expected occurrence of AD for the older age group. No details of the coexisting AD/HD cases were presented.

It also remains unknown whether the HD disease process increases the risk of developing AD. It is interesting to note that in our small sample, the average length of disease course was longer in those with AD pathology compared to those without, despite similar ages at autopsy. This could suggest that prolonged HD related pathogenic processes increases the risk of developing AD pathology. In a case series of 27 HD autopsy cases (ages 34–75, with duration of illness 2–7 years), none of the individuals fulfilled criteria for AD but several cases had mild AD pathology [7]. The author of this study suggested that these individuals might have developed AD if they had longer duration of symptomatic illness. Vonsattel et al briefly noted that

13% of 1250 HD brains showed mild AD pathologic changes insufficient to meet neuropathological criteria for a diagnosis of AD and those with mild AD changes were older (mean 72 years) than those without (mean 57 years) [33].

The neuropathologic characteristics of these two neurodegenerative diseases are distinct. However, both are diseases of protein aggregation. Also, recent work suggests that defects in mitochondrial function may underlie pathogenic pathways in multiple neurodegenerative diseases, including HD and AD [34, 35]. Amyloid deposition and neurofibrillary tangles are the defining features of AD pathologically, however the confluence of upstream inciting genetic/environmental factors with attendant processes such as inflammation and oxidative stress are many. One could speculate that a neurotoxic environment secondary to HD pathology initiates further neurodegenerative pathologic cascades of the "AD type" leading to cortical neuronal injury and concomitant deposition of amyloid and tau. Further study is needed to assess the incidence of AD in HD patients, and whether other factors such as ApoE allele status may modify the risk of developing dementia in HD.

The present study was retrospective, patient selection was undoubtedly skewed and clinical cognitive evaluation was incomplete. Nevertheless, our neuropathological series of elderly HD patients clearly documents the relatively common co-occurrence of these two neurodegenerative diseases, and suggests that dementia in late stage HD can be caused by co-existing AD as well as late stage HD. This could have significant clinical implications for pharmacological and behavioral therapy interventions. It is of interest that a small study of 21 HD patients randomized to 8 months treatment with rivastigmine (maximum dose 3 mg twice a day) showed a trend in improvement in cognition, based on performance on the Mini Mental Status Exam [36]. The patients in this study were neither clinically demented nor elderly (age 38 to 66 years, mean 53). Additionally, identifying possible pathogenic relationships between HD and AD may have implications to treatment targeted at cognitive dysfunction in HD. A higher prevalence of AD associated cortical pathology in HD patients may warrant trials of novel neuroprotective therapies originally targeted to AD patients. Further study with neuropathologic correlation of more systematically ascertained and evaluated HD patients with dementia is necessary to determine the prevalence of co-occurrence of AD and HD and the approach to management in this increasingly important population (36).

ACKNOWLEDGMENTS

Supported by Department of Veterans Affairs Research and Fellowship funds, NIH grant P50AG05136 (UW ADRC) and HDSA Center of Excellence grant. We would like to thank Ms. Aimee Schantz for administrative assistance and Ms. Kim Howard for excellent technical support.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

REFERENCES

[1] Tabrizi SJ, Scahill RI, Owen G, Durr A, Leavitt BR, Roos RA, Borowsky B, Landwehrmeyer B, Frost C, Johnson H, Craufurd D, Reilmann R, Stout JC, Langbehn DR, Investigators T-H. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. Lancet Neurol. 2013;12:637-49.

[2] Stout JC, Jones R, Labuschagne I, O'Regan AM, Say MJ, Dumas EM, Queller S, Justo D, Santos RD, Coleman A, Hart EP, Durr A, Leavitt BR, Roos RA, Langbehn DR, Tabrizi SJ, Frost C. Evaluation of longitudinal 12 and 24 month cognitive outcomes in premanifest and early Huntington's disease. J Neurol Neurosurg Psychiatry. 2012;83:687-94.

[3] Papoutsi M, Labuschagne I, Tabrizi SJ, Stout JC. The cognitive burden in Huntington's disease: Pathology, phenotype, and mechanisms of compensation. Mov Disord. 2014;29:673-83.

[4] Salmon DP, Kwo-on-Yuen PF, Heindel WC, Butters N, Thal LJ. Differentiation of Alzheimer's disease and Huntington's disease with the Dementia Rating Scale. Arch Neurol. 1989;46:1204-8.

[5] Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol. 1985;44:559-77.

[6] Myers RH, Sax DS, Schoenfeld M, Bird ED, Wolf PA, Vonsattel JP, White RF, Martin JB. Late onset of Huntington's disease. J Neurol Neurosurg Psychiatry. 1985;48:530-4.

[7] Jellinger KA. Alzheimer-type lesions in Huntington's disease. J Neural Transm. 1998;105:787-99.

[8] McIntosh GC, Jameson HD, Markesbery WR. Huntington disease associated with Alzheimer disease. Ann Neurol. 1978;3:545-8.

[9] Reyes MG, Gibbons S. Dementia of the Alzheimer's type and Huntington's disease. Neurology. 1985;35:273-7.

[10] Moss RJ, Mastri AR, Schut LJ. The coexistence and differentiation of late onset Huntington's disease and Alzheimer's disease. A case report and review of the literature. J Am Geriatr Soc. 1988;36:237-41.

[11] Evans SJ, Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. J Neurol Neurosurg Psychiatry. 2013;84:1156-60.

[12] Lipe H, Bird T. Late onset Huntington Disease: Clinical and genetic characteristics of 34 cases. J Neurol Sci. 2009;276:159-62.

[13] Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: A systematic review and meta-analysis. Mov Disord. 2012;27:1083-91.
[14] Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol. 2011;7:137-52.
[15] Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB. Prevalence of dementia in the United States: The aging, demographics, and memory study. Neuroepidemiology. 2007;29:125-32.
[16] Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT. National Institute on A, Alzheimer's A. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach. Acta Neuropathol. 2012;123: 1-11.
[17] Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. 2012;8:1-13.
[18] Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology. 2002;58:1791-800.
[19] Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82:239-59.
[20] Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L, The Consortium to. Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991;41:479-86.
[21] Paulsen JS. Cognitive impairment in Huntington disease: Diagnosis and treatment. Curr Neurol Neurosci Rep. 2011;11:474-83.
[22] Peavy GM, Jacobson MW, Goldstein JL, Hamilton JM, Kane A, Gamst AC, Lessig SL, Lee JC, Corey-Bloom J. Cognitive and functional decline in Huntington's disease: Dementia criteria revisited. Mov Disord. 2010;25:1163-9.
[23] Ho AK, Sahakian BJ, Brown RG, Barker RA, Hodges JR, Ane MN, Snowden J, Thompson J, Esmonde T, Gentry R, Moore JW, Bodner T, Consortium N-H. Profile of cognitive progression in early Huntington's disease. Neurology. 2003;61: 1702-6.
[24] Rosser AE, Hodges JR. The Dementia Rating Scale in Alzheimer's disease, Huntington's disease and progressive supranuclear palsy. J Neurol. 1994;241:531-6.
[25] Erten-Lyons D, Woltjer RL, Dodge H, Nixon R, Vorobik R, Calvert JF, Leahy M, Montine T, Kaye J. Factors associated with resistance to dementia despite high Alzheimer disease pathology. Neurology. 2009;72:354-60.
[26] Price JL, McKeel DW Jr, Buckles VD, Roe CM, Xiong C, Grundman M, Hansen LA, Petersen RC, Parisi JE, Dickson DW, Smith CD, Davis DG, Schmitt FA, Markesbery WR, Kaye J, Kurlan R, Hulette C, Kurland BF, Higdon R, Kukull W, Morris JC. Neuropathology of nondemented aging: Presumptive evidence for preclinical Alzheimer disease. Neurobiol Aging. 2009;30:1026-36.
[27] Racette BA, Perlmutter JS. Levodopa responsive parkinsonism in an adult with Huntington's disease. J Neurol Neurosurg Psychiatry. 1998;65:577-9.
[28] Reuter I, Hu MT, Andrews TC, Brooks DJ, Clough C, Chaudhuri KR. Late onset levodopa responsive Huntington's disease with minimal chorea masquerading as Parkinson plus syndrome. J Neurol Neurosurg Psychiatry. 2000;68:238-41.
[29] Albin RL, Reiner A, Anderson KD, Penney JB, Young AB. Striatal and nigral neuron subpopulations in rigid Huntington's disease: Implications for the functional anatomy of chorea and rigidity-akinesia. Ann Neurol. 1990;27:357-65.
[30] Schwab C, Arai T, Hasegawa M, Yu S, McGeer PL. Colocalization of transactivation-responsive DNA-binding protein 43 and huntingtin in inclusions of Huntington disease. J Neuropathol Exp Neurol. 2008;67:1159-65.
[31] Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey LF, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ, Lee VM. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 2006;314:130-3.
[32] Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, Mann D, Tsuchiya K, Yoshida M, Hashizume Y, Oda T. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun. 2006;351:602-11.
[33] Vonsattel JP KC, Del Pilar Amaya M. Neuropathology of Hungtington's Disease. In: Duyckaerts C LI, editors. Handbook of Clinical Neurology - Dementias. Elsevier. 2008; p. 599-618.
[34] Dupuis L. Mitochondrial quality control in neurodegenerative diseases. Biochimie. 2014;100:177-83.
[35] Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. J Pharmacol Exp Ther. 2012;342:619-30.
[36] de Tommaso M, Specchio N, Sciruicchio V, Difruscolo O, Specchio LM. Effects of rivastigmine on motor and cognitive impairment in Huntington's disease. Mov Disord. 2004;19:1516-8.
[37] Bird TD, Lipe HP, Steinbart EJ. Geriatric neurogenetics: Oxymoron or reality? Arch Neurol. 2008;65:537-9.