Published in final edited form as:
Arch Neurol. 2009 February ; 66(2): 201–207. doi:10.1001/archneurol.2008.534.

Rapidly Progressive Neurodegenerative Dementias

Keith A. Josephs, MST, MD[1], **J. Eric Ahlskog, MD, PhD**[1], **Joseph E. Parisi, MD**[2], **Bradley F. Boeve, MD**[1], **Brian A. Crum, MD**[1], **Caterina Giannini, MD**[2], and **Ronald C. Petersen, MD, PhD**[1]

[1]Department of Neurology, Mayo Clinic, Rochester, Minnesota

[2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota

Abstract

Background—Neurodegenerative dementias are typically characterized by an insidious onset and a relatively slowly progressive course. Less common are patients with a rapidly progressive course to death.

Objective—To characterize patients with a neurodegenerative disease and a rapidly progressive course to death.

Setting—Tertiary Care Medical Center.

Design/Methods—Using a text word search for “rapid” and “dementia” in the same sentence, the Mayo Clinic Medical Records Linkage system was used to identify all patients evaluated between 1/1/00−9/30/07 with brain autopsy (N=96). Of these 96, we included only those with disease duration of <4 years to death and with histological diagnosis of a neurodegenerative disease.

Results—We identified 22 cases (10 males). Although 36% were Creutzfeldt-Jakob disease (CJD), the rest included frontotemporal lobar degenerative with motor neuron degeneration (FTLD-MND; 23%); a tauopathy (progressive supranuclear palsy or corticobasal degeneration; 18%); diffuse Lewy body disease (DLBD; 14%) or Alzheimer's disease 9%. All CJD cases died ≤12 months after onset while the others had illness duration of >12 months. Notably, all three DLBD patients, but no others, initially experienced a transient postoperative- or illness-associated encephalopathy, then relative normality for two years, before a rapidly progressive dementia and decline to death in 4−12 months.

Conclusions—Based on this cohort, although CJD is the most likely cause of a rapidly progressive neurodegenerative dementia, FTLD-MND, DLBD, tauopathies and Alzheimer's disease can also cause a rapidly progressive dementia. If illness duration is beyond 12-months, a non-CJD neurodegenerative disease may be more likely the diagnosis, than CJD.

INTRODUCTION

The term dementia implies that there is cognitive and or behavioral impairment that significantly affects ones activities of daily living[1]. Dementia however is an umbrella term that

Address all correspondence to: Keith A. Josephs, MST, MD Department of Neurology Mayo Clinic Rochester MN 55905 Tele: (507) 538−1038 Fax: (507)-538−6012 Email: josephs.keith@mayo.edu.

Disclosure Statement: DSK has been a consultant to GE HealthCare, GlaxoSmithKline and Myriad Pharmaceuticals, has served on a Data Safety Monitoring Board for Neurochem Pharmaceuticals, and is an investigator in a clinical trial sponsored by Elan Pharmaceuticals. BFB is an investigator in a clinical trial sponsored by Myriad Pharmaceuticals. RCP has been a consultant to GE Healthcare and has served on a data safety monitoring board in a clinical trial sponsored by Elan Pharmaceuticals.

This study will be presented at the 133rd Annual Meeting of the American Neurological Association, Salt Lake City, Utah; September 2008.

encompasses many different etiologies, including neurodegenerative, metabolic, vascular and infectious diseases.

Individual neurodegenerative diseases have relatively specific characteristic clinical features[2] and are histologically characterized by varying degrees of neuronal loss, gliosis, and usually with abnormal protein deposition. Histological features ultimately define each neurodegenerative disease. The most common neurodegenerative disorders that present with dementia are Alzheimer's disease (AD), diffuse Lewy body disease (DLBD) and frontotemporal lobar degeneration (FTLD). In these conditions, dementia typically is insidious in onset, progressing very slowly and with a total disease duration exceeding five years[3, 4].

More rapidly progressive dementias have been observed with prion diseases, notably Creutzfeldt-Jakob disease (CJD)[5], where illness duration typically is less than one year. We have however occasionally encountered rapidly progressive, ultimately fatal dementias, with clinical features typical of other neurodegenerative diseases, except for the temporal course. Therefore, the aim of this study was to characterize autopsy-confirmed cases of neurodegenerative diseases with rapidly progressive dementia, and to compare them with autopsy confirmed cases of CJD.

DESIGN AND METHODS

Subject selection

Using a text word search for “rapid” and “dementia” in the same sentence, the Mayo Clinic Medical Records Linkage system was used to identify all possible rapidly progressive dementia patients evaluated at our institution between January 1, 2000 and September 30th, 2007 who had also undergone brain autopsy examination at our institution and had received a pathological diagnosis. A total of 96 cases were identified. The medical records of all 96 cases were reviewed blinded to the neuropathological diagnoses by a neurodegenerative specialist (KAJ). Of these 96 cases, only cases with total disease duration of less than four years to death, and a histologically confirmed diagnosis of a neurodegenerative disease were included in the study. Cases that had undergone pathological examination elsewhere with only a mailed or faxed pathological report were excluded (N=3).

Clinical data was abstracted in all cases that met our inclusion and exclusion criteria including demographic features, first clinical features, and initial and final diagnoses prior to death. Disease onset was defined as the month that the patient's family noticed the first neurological symptom that could be associated with a degenerative process. The presence or absence of rapid eye movement sleep behavior disorder (RBD), severe fluctuations[6], Parkinsonism (at least two of tremor, bradykinesia, rigidity or postural instability), hallucinations and delusions, and motor neuron disease, as well as the results of laboratory, cerebrospinal fluid (CSF), electroencephalogram (EEG) and results from neuroimaging studies were recorded. Rapid eye movement sleep behavior disorder was considered positive if the behavior met diagnostic criteria B for REM sleep behavior disorder defined as abnormal wild flailing movement occurring during sleep with sleep related injuries or movements that are potentially injurious or disruptive[7]. Given recent reports of anti-thyroperoxidase (TPO), anti–microsomal, and paraneoplastic antibodies being associated with rapidly progressive dementias, thyroid antibody levels and paraneoplastic testing results were also recorded.

Neuropathology

Neuropathological examination was performed by one of two board certified neuropathologists (JEP and CG) unblinded to the clinical diagnoses. Consensus between both pathologists was performed in the event a case was complex (N=1). In all cases we sampled frontal, temporal, parietal and occipital cortex, amygdala, hippocampus and cingulate gyrus, nucleus basalis,

basal ganglia, thalamus, midbrain, pons, medulla and cerebellum. All cases underwent histological examination with hematoxylin and eosin, as well as modified Bielschowsky silver stain. Immunohistochemistry with antibodies to tau (Clone AT8, 1:3750; Endogen, Woburn, MA), beta-amyloid (Clone 6F3D, 1:20; Novocastra, UK), alpha-synuclein (LB509, 1:25; Zymed, South San Francisco, CA), ubiquitin (Polyclonal, 1:100; Dako, Carpinteria, CA), neurofilament (Clone 2F11, 1:800; Dako, Carpinteria, CA), TDP-43 (1:2000; ProteinTech Group, Chicago, IL) and prion protein (3F4 1:50; Dako, Carpinteria, CA) were completed. All pathological diagnoses were made based on previously published criteria[8-14]. Special attention was paid to the presence of any other pathology, including secondary neurodegenerative diseases (TDP-43 positive inclusions, Lewy bodies, Alzheimer's type pathologies), amyloid angiopathy, vascular pathologies of any sort, and argyrophilic grain disease. All CJD cases underwent confirmation by western blot for PrP at the National Prion Disease Pathology Surveillance Center in Cleveland, Ohio.

Statistics

Statistical analyses were performed utilized the JMP computer software (JMP software version 7.0.0; SAS Institute Inc, Cary, NC) with α set at 0.05. Kruskal-Wallis test was used to compare age at onset across the different pathological diagnostic groups.

RESULTS

We identified 22 cases that met our inclusion and exclusion criteria (Table 1) of which 10 were male. Of these 22 cases, the most common pathological diagnosis was CJD (8/22; 36%). We also found five cases (23%) with a pathological diagnosis of FTLD with motor neuron degeneration (FTLD-MND); four cases (18%) with a tauopathy (progressive supranuclear palsy (PSP) = 2 and corticobasal degeneration (CBD) = 2), three cases (14%) with DLBD and two cases (9%) with AD. The time from disease onset to first neurological evaluation of all 22 cases was on average 7.5 months.

Histological findings are shown in Table 2. Almost all, except those with CJD, had a secondary neuropathology, which included Alzheimer's type pathologies[10, 15], vascular pathologies, amyloid angiopathy or argyrophilic grain disease[16]. However, there were no cases with focal gliosis, peri-vascular cuffing or microglial aggregates suggestive of a secondary, immune-mediated (paraneoplastic) process. Lewy bodies were absent from the non-DLBD cases and abnormalTDP-43 immunoreactive lesions were not identified in any case except for those with FTLD-MND. All FTLD-MND cases showed TDP-43 immunoreactive lesions in brainstem cranial nerve XII nuclei or spinal cord anterior horn cells with variable extramotor TDP-43 immunoreactive inclusions.

The age of onset of all 22 cases ranged from 33 to 85 years and was significantly different across the groups (P=0.04), with the DLBD group the oldest (median 81 years) and the FTLD-MND group the youngest (median 50 years). There appeared to be a bimodal distribution of total illness duration, with the CJD cases all dying ≤ 12 months after onset, while the non-CJD neurodegenerative diseases all had illness durations >12 months.

Remarkably, all three DLBD patients had experienced a transient postoperative- or illness-associated confusional state with apparent complete recovery, which preceded the dementia onset by approximately two years. Among these patients, once the dementia phase ensued, the progression to death was rapid, occurring over 4, 11 and 12 months, respectively. Thus, these patients had a triphasic course with the encephalopathy, then an asymptomatic or minimally-symptomatic 2-year interlude, and finally the rapid dementing phase. The total duration from the initial transient confusional state to death was 2.5 to 3 years. This temporal pattern was quite consistent. Patient 14 experienced two weeks of acute confusion after coronary artery

bypass grafting, then apparently recovered. He subacutely became demented two years later, dying four months after dementia onset. Patient 15 developed an acute confusional state after a benign colonic polyp resection, which slowly resolved over three months. Then 2 years later he developed a rapidly progressive dementia dying 11 months later. Patient 16 was hospitalized for herpes simplex keratitis/cellulitis and experienced a one week episode of confusional psychosis. This abated, but approximately 2 years later she developed a rapidly progressive dementia, dying 12 months later. This unusual triphasic temporal course was not observed in any of the other neurodegenerative diseases.

Certain clinical clues that are often used to predict the neurodegenerative diagnosis were not very reliable in this cohort. Parkinsonism was common across all groups, present in 15 of the 22 cases, including all three DLBD and all four tauopathies. Psychosis (visual hallucinations and delusions) had been recorded at the time of the dementia onset in six patients: two DLBD, two CJD, and two AD. Severe fluctuations over hours were documented in three cases, two with DLBD, the other AD. Motor neuron disease was documented in three cases, one with CJD and two with FTLD-MND. Rapid eye movement sleep behavior disorder was documented in three cases, one with DLBD, the other two with AD. Myoclonus was a specific marker in our series, documented in six patients, all with CJD. Parenthetically, two CJD patients also had choreoathetoid movements and apraxia.

Four of the 14 non-CJD neurodegenerative diseases had been accurately diagnosed in life; two with DLBD and two with FTLD-MND. In a fifth case with pathologically confirmed PSP, the initial differential diagnosis did include PSP whereas the final clinical diagnosis was CJD. In six cases, the final clinical diagnosis was within the spectrum of typical mimickers; especially those in the FTLD spectrum of disorders. Creutzfeldt-Jakob disease was considered the initial or final diagnosis in three of the non-CJD neurodegenerative diseases. In contrast, all CJD were correctly diagnosed prior to death.

Electroencephalography was inconsistently helpful in establishing the correct diagnosis. Periodic atypical triphasic waves, sharp waves, or epileptogenic discharges were noted in four CJD cases. In three of the remaining four CJD cases, the EEG showed excess slow waves, whereas the EEG was normal in one CJD case. All three DLBD patients had atypical triphasic waves on EEG, intermittent in two and semi-periodic in the other. No EEG abnormalities were identified in the other neurodegenerative diseases.

Similarly, the CSF results had limited diagnostic utility. Among the 15 patients undergoing a CSF examination, elevated protein was recorded in seven including one with DLBD, four with CJD and two with AD; none had abnormal cell counts or glucose measurements. Neuron specific enolase was measured in 14 patients and was abnormal (NSE>35ng/ml) in six of the eight CJD patients (median NSE =101.8ng/ml; range 39.4−204ng/ml) and one DLBD patient (NSE =35.2ng/ml). It was mildly elevated (NSE=20−35ng/ml) in the other two CJD patient (NSE =29.1ng/ml; 31.7ng/ml), as well as in two FTLD-MND patients (23.9ng/ml; 22.8ng/ml). The neuron specific enolase level was normal (NSE <20ng/ml) in the other three tested patients (one with CBD and two with AD). Measurement of 14−3−3 protein by sandwich immunochemiluminometric assay was elevated in three of six patients with CJD and normal in the five other neurodegenerative cases where it was analyzed.

MR brain imaging was primarily diagnostic in the CJD cases where diffusion-weighted MR sequences were abnormal in all six of the CJD patients where this was performed. This included diffusion or fluid attenuated inversion recovery (FLAIR) abnormalities of cortical gyral hyperintensities in five patients, diffusion abnormalities within the striatum in four, of which two also showed thalamic abnormalities. Varying degrees of grey matter atrophy were apparent in all groups, but with limited diagnostic utility. Severe frontal lobe atrophy was apparent in

two FTLD-MND patients and left greater than right frontoparietal atrophy in one CBD patient. All other neurodegenerative cases had mild or mild to moderate generalized patterns of atrophy. Single photon emission computed tomography was performed in five patients, similarly with modest diagnostic utility. Among the three with FTLD-MND, frontal hypoperfusion was apparent in two and left anterior medial temporal lobe hypoperfusion in the other. One CBD patient showed reduced uptake in frontoparietal regions while the other showed just frontal hypoperfusion.

Blood work in these patients was not very elucidating, although one AD patient had paraneoplastic type 1 anti-neuronal nuclear (ANNA-1/anti-Hu) and P/Q type calcium channel antibodies, with electromyographic findings also consistent with Lambert-Eaton syndrome. One PSP patient had acetylcholine receptor binding and striated muscle antibodies. Thyroperoxidase antibodies were elevated in four cases, two with CJD, one with PSP, and one with AD. Anti-microsomal antibodies (reference range<1:100) were completed in two patients in this cohort and were elevated in both; one with CJD (1:1600), the other PSP (1:6400).

DISCUSSION

Creutzfeldt-Jakob disease is a prime diagnostic consideration among rapidly progressive neurodegenerative dementias. Among our 22 cases, those with the most aggressive course did indeed have CJD, and illness duration was a distinguishing factor. Thus patients with a dementia progressing to death in < one year all had CJD pathology, whereas a clinical course > one year was always associated with a non-CJD neurodegenerative diagnosis in this series. Obviously, variant CJD has a more protracted course but that condition is extremely rare in the USA[17].

All three DLBD cases had an unusual temporal course, however, that might be confused with CJD. Their terminal dementing phase was ≤12 months. However, in all, this was preceded by a transient encephalopathy lasting weeks to a few months, followed by approximately two years of a presumably asymptomatic or minimally symptomatic interlude. This triphasic course may be unique to DLBD since it was documented in all three of these cases and none of the others in our series.

Other authors have noted that neurodegenerative diseases account for less than 5% of rapidly progressive dementias[18]. We suspect however that the frequency will vary depending upon how one defines rapid, which in our series was defined as onset to death in < four years.

Recognition of CJD is aided by other clinical clues, which were apparent in our series: myoclonus, periodic complexes on EEG and FLAIR and diffusion weighted abnormalities on MRI,[19, 20]. Although an elevated CSF neuron specific enolase[21] is also a clinical clue to CJD, we observed an elevated neuron specific enolase level in one of our DLBD cases, whereas it was mildly elevated in two CJD case. In our series, none of our non-CJD neurodegenerative cases had an abnormal 14−3−3 protein level and hence a larger cohort is needed to determine if 14−3−3 might be a more specific marker of CJD than the neuron specific enolase when the differential diagnosis includes other neurodegenerative diseases.

If CJD can be excluded in the differential diagnosis of a rapidly progressive neurodegenerative dementia, then certain clinical clues and test results may suggest the specific diagnosis. Although findings from ours series require replication, suggestive diagnostic findings surfaced. Among our non-CJD neurodegenerative cases, a young age of onset, around age 50, was most suggestive of FTLD-MND. Conversely, an older age of onset, around age 80, characterized our DLBD cases. Our DLBD patients also uniquely had atypical triphasic waves on EEG, not seen in the other neurodegenerative cases. Unlike CJD however, there was no periodicity to the EEG abnormalities, as previously reported in a few DLBD cases[22]; however, one of our

DLBD cases did have a semi-periodic pattern. Thus, within the first year after disease onset, EEG abnormalities in the context of a rapidly progressive dementia are more suggestive of CJD if there are periodic complexes, while after the first year, atypical triphasic waves, even if they are semi-periodic, may be more indicative of DLBD.

Lower motor neuron disease findings have diagnostic significance, pointing to FTLD-MND if CJD can be excluded. In fact, a rapid course to death is typical of FTLD-MND[23]. In contrast to more typical FTLD with disease durations around 7–8 years,[4, 24] mean disease durations of 2.3 years have been reported in FTLD-MND[23]. Thus, the evaluation should include careful screening for anterior horn cell disease and electromyography when appropriate.

Brain imaging of our cases was not very elucidating, beyond the FLAIR and diffusion weighted MRI abnormalities typical of CJD. We did not find any pattern of grey matter atrophy to be predictive of rapid progression, whereas patterns of regional atrophy were not very specific in pinpointing a specific neurodegenerative diagnosis. In general, a pattern of predominantly frontal or frontotemporal atrophy is more suggestive of FTLD-MND[25], while asymmetric frontoparietal atrophy may be slightly more suggestive of underlying CBD[26]. The same can be said for the patterns of hypoperfusion on single photon emission computer tomography images.

In nearly all the non-CJD neurodegenerative cases, mixed pathologies were apparent (Table 2). It is possible that these combined neuropathologies contributed to the rapid clinical course; this included mainly superimposed Alzheimer pathology, amyloid angiopathy and argyrophilic grain disease. Notably, amyloid angiopathy plus AD pathology has previously been reported to be associated with a rapidly progressive dementia[27]. Alzheimer's disease pathology and amyloid angiopathy may also have been playing a role in the rapid progression of our DLBD cases since all three DLBD cases had Braak stage IV pathology[10], and two cases had mild-moderate amyloid angiopathy. Although both AD and DLBD have been reported to occasionally mimic the rapid course of CJD, there was no mention of whether a secondary pathology was also present in those cases[28].

The four tauopathy cases in our series were the most perplexing. Other than the time course, they presented no differently than typically observed CBD or PSP, where disease duration is approximately 7 years for each[4]. These cases also did have secondary pathologies, including Alzheimer type pathology, vascular disease or argyrophilic grain disease which may be playing a role in the rapid progression. However, the AD stages were not advanced, the vascular changes was not severe, although one case did have a microinfarct, and generally argyrophilic grain disease is not a marker of aggressive neurodegenerative disease[29]. A much larger cohort is needed to do any sort of comparison between these and more typical tauopathies.

Theoretically, the rapid clinical course in some of these non-CJD neurodegenerative cases could have been secondarily facilitated by immuno-mediated processes directed at the central nervous system. However, extensive serological testing including paraneoplastic antibodies, as well as CSF in most patients did not disclose any consistent evidence for that. One patient did have paraneoplastic antibodies and conceivably this may have contributed; however this stands as an exception. Furthermore, neuropathological examination did not show any focal gliosis, perivascular cuffing or microglial aggregates suggestive of an immune-mediated (paraneoplastic) process.

This study should not be used to determine any kind of prevalence of these diseases since using the word “rapid” may not have captured 100% of the cases. In addition, a larger sample size is required to test some the of hypothesis that we have generated based on results from this study.

In conclusion, outside the United Kingdom and France where variant CJD may be found[17], rapidly progressive neurodegenerative dementias surviving beyond a year may more likely represent a non-CJD neurodegenerative disease, although long surviving sporadic CJD cases with disease duration greater than 12 months has been described[30]. In addition, the terminal phase of cases with late-life DLBD may mimic CJD.

ACKNOWLEDGEMENT

KAJ is supported by the NIH Roadmap Multidisciplinary Clinical Research Career Development Award Grant (K12/NICHD)-HD49078. Co-authors on this study are also supported by NIH grants P50-AG16574 and U01-AG06786, as well as the generous support of the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation.

REFERENCES

1. American Pyschiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th Ed) (DSM IV). American Psychiatric Association; Washington DC: 1994.
2. Knopman DS, Boeve BF, Petersen RC. Essentials of the proper diagnoses of mild cognitive impairment, dementia, and major subtypes of dementia. Mayo Clin Proc 2003;78:1290–1308. [PubMed: 14531488]
3. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord 2002;16:203–212. [PubMed: 12468894]
4. Josephs KA, Petersen RC, Knopman DS, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology 2006;66:41–48. [PubMed: 16401843]
5. Masters CL, Harris JO, Gajdusek DC, et al. Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. Annals of neurology 1979;5:177–188. [PubMed: 371520]
6. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 2004;62:181–187. [PubMed: 14745051]
7. Sateia, M. The International Classification of Sleep Disorders. Vol. 2nd ed.. American Academy of Sleep Medicine; Westchester: 2005.
8. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479–486. [PubMed: 2011243]
9. Hauw JJ, Daniel SE, Dickson D, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 1994;44:2015–2019. [PubMed: 7969952]
10. Braak H, Braak E. Evolution of the neuropathology of Alzheimer's disease. Acta Neurol Scand Suppl 1996;165:3–12. [PubMed: 8740983]
11. Kretzschmar HA, Ironside JW, DeArmond SJ, Tateishi J. Diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Arch Neurol 1996;53:913–920. [PubMed: 8815857]
12. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124. [PubMed: 8909416]
13. Dickson DW, Bergeron C, Chin SS, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. J Neuropathol Exp Neurol 2002;61:935–946. [PubMed: 12430710]
14. Josephs KA, Parisi JE, Knopman DS, et al. Clinically undetected motor neuron disease in pathologically proven frontotemporal lobar degeneration with motor neuron disease. Arch Neurol 2006;63:506–512. [PubMed: 16606762]
15. Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol 1997;56:1095–1097. [PubMed: 9329452]

16. Braak H, Braak E. Argyrophilic grains: characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes. Neurosci Lett 1987;76:124–127. [PubMed: 2438598]
17. Liras A. The variant Creutzfeldt-Jakob Disease. Risk, uncertainty or safety in the use of the blood and blood derivatives? Int Arch Med 2008;1:9. [PubMed: 18573217]
18. Geschwind MD, Haman A, Miller BL. Rapidly progressive dementia. Neurol Clin 2007;25:783–807. vii. [PubMed: 17659190]
19. Zerr I, Schulz-Schaeffer WJ, Giese A, et al. Current clinical diagnosis in Creutzfeldt-Jakob disease: identification of uncommon variants. Annals of neurology 2000;48:323–329. [PubMed: 10976638]
20. WHO. Human transmissible spongiform encephalopathies. Wkly Epidemiol Rec 1998;73:361–365. [PubMed: 9844549]
21. Sanchez-Juan P, Green A, Ladogana A, et al. CSF tests in the differential diagnosis of Creutzfeldt-Jakob disease. Neurology 2006;67:637–643. [PubMed: 16924018]
22. Haik S, Brandel JP, Sazdovitch V, et al. Dementia with Lewy bodies in a neuropathologic series of suspected Creutzfeldt-Jakob disease. Neurology 2000;55:1401–1404. [PubMed: 11087793]
23. Josephs KA, Knopman DS, Whitwell JL, et al. Survival in two variants of tau-negative frontotemporal lobar degeneration: FTLD-U vs FTLD-MND. Neurology 2005;65:645–647. [PubMed: 16116138]
24. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: clinicopathological correlations. Annals of neurology 2006;59:952–962. [PubMed: 16718704]
25. Whitwell JL, Jack CR Jr. Senjem ML, Josephs KA. Patterns of atrophy in pathologically confirmed FTLD with and without motor neuron degeneration. Neurology 2006;66:102–104. [PubMed: 16401855]
26. Josephs KA, Whitwell JL, Dickson DW, et al. Voxel-based morphometry in autopsy proven PSP and CBD. Neurobiol Aging 2008;29:280–289. [PubMed: 17097770]
27. Greenberg SM, Vonsattel JP, Stakes JW, et al. The clinical spectrum of cerebral amyloid angiopathy: presentations without lobar hemorrhage. Neurology 1993;43:2073–2079. [PubMed: 8413970]
28. Tschampa HJ, Neumann M, Zerr I, et al. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2001;71:33–39. [PubMed: 11413259]
29. Togo T, Isojima D, Akatsu H, et al. Clinical features of argyrophilic grain disease: a retrospective survey of cases with neuropsychiatric symptoms. Am J Geriatr Psychiatry 2005;13:1083–1091. [PubMed: 16319301]
30. Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Annals of neurology 1999;46:224–233. [PubMed: 10443888]

TABLE 1

Demographic and clinical features

Case #	Sex	Age at onset	Total Disease duration (years)	Presenting symptoms at the time of dementia onset	Additional symptoms during the rapidly progressive clinical course	Final clinical diagnosis before death	Pathological diagnosis
1	F	72	0.67	Personality change	Limb apraxia and myoclonic jerks	CJD	CJD
2	F	51	0.33	Personality change, dysarthria, poor attention, hypersomnolence, and restless leg movements in sleep	Limb apraxia, myoclonic jerks and choreoathetoid movements	CJD	CJD
3	F	80	0.25	Speech difficulties and loss of episodic memory	Myoclonic jerks and excessive startle	CJD	CJD
4	M	61	1.0	Cognitive and behavioral changes and balance difficulties	Worsening of balance with falls, delusions and reduplicative para-amnesia	CJD	CJD
5	F	41	0.25	Body spasms, speech difficulties and abnormal involuntary arm movements	Worsening of balance with falls, myoclonic jerks and choreoathetoid movements	CJD	CJD
6	F	68	0.42	Loss of episodic memory	Worsening of balance with falls myoclonic jerks and hallucinations	CJD	CJD
7	F	73	0.17	Cognitive decline, balance difficulties and excessive startle	Worsening of balance with falls and stereotypical rubbing of the bed sheet.	CJD	CJD
8	M	56	1.0	Cognitive and behavioral changes and difficulties with gait	Urinary incontinence, ataxia myoclonic jerks and fasciculations	CJD	CJD
9	F	67	3.5	Difficulties with gait	Impaired attention, aphasia and parkinsonism	Dementia NOS	FTLD-MND
10	M	33	2.0	Personality change	Impaired judgment and planning	FTD	FTLD-MND
11	F	48	2.0	Behavioral changes and dysarthria	Cognitive changes and paranoia	FTD vs. AD	FTLD-MND
12	F	52	2.5	Paranoid behaviors and dysarthria	Cognitive changes	FTD-MND	FTLD-MND
13	F	50	2.0	Personality change	Aphasia and dysarthria	FTD-MND	FTLD-MND
14	M	85	2.5*	Memory loss, difficulty putting words together and wandering at night	Incontinence of urine, reduced personal hygiene, fluctuations and RBD	DLB	DLBD
15	M	72	3.0*	Increasingly confused and disoriented, agitated, word finding difficulties and hallucinations	Fluctuations throughout the daytime, shuffling gait, falls	DLB	DLBD
16	F	81	3.0*	Increasingly confused with short term memory loss	Hallucinations, parkinsonism	CJD	DLBD
17	F	79	3.5	Word finding pauses in speech	Cognitive impairment, dystonia and apraxia of limb movement	CBD	Tauopathy (PSP)
18	M	83	1.5	Gait difficulties with falls and choreoathetoid movements	Cognitive impairment and apraxia of speech	CJD	Tauopathy (PSP)
19	M	54	3.5	Personality change	Parkinsonism and stiffness of muscles	FTD	Tauopathy (CBD)
20	M	63	3.5	Cognitive problems with confusion and obsessive behaviors	Parkinsonism and stiffness of muscles	FTDP	Tauopathy (CBD)
21	M	72	3.0	Impaired judgment and confusion	Fluctuating course, RBD and hallucinations	Dementia NOS	AD
22	M	74	1.2	Gait difficulties, cognitive impairment and light headedness on standing	Hallucinations and RBD	DLB	AD

AD = Alzheimer's disease; CJD= Creutzfeldt-Jakob disease; FTD = Frontotemporal dementia; FTDP = Frontotemporal dementia with parkinsonism; FTD-MND = frontotemporal dementia with motor neuron disease; FTLD-MND = frontotemporal lobar degeneration with motor neuron degeneration; DLB = dementia with Lewy bodies; DLBD = Diffuse Lewy body disease; PSP = progressive supranuclear palsy; CBD = corticobasal degeneration; RBD = rapid eye movement sleep behavior disorder

• Total disease duration is based on the time of onset being recognized as the transient postoperative- or illness- associated confusion, and not as the time of onset of the dementia.

Arch Neurol. Author manuscript; available in PMC 2009 October 20.

TABLE 2

Secondary pathologies co-occurring with the primary diagnoses

Primary neuropathological diagnosis	*Brain weight	Braak and Braak neurofibrillary tangle stage10	NIA Reagan criteria for AD15 (probability)	Amyloid angiopathy	AGD	Vascular pathologies
CJD (N=8)	1185 [1034−1412]	Braak stage 0 (N=8)	Low probability (N=8)	None	None	None
FTLD-MND (N=5)	1228 [1042−1302]	Stage VI (N=1) Stage IV (N=1) Stage II (N=1) Stage I (N=2)	High probability (N=1) Low probability (N=4)	Mild (N=2)	(N=1)	Mild cranial arteriolosclerosis (N=2) Mod. cranial arteriolosclerosis with cribiform change, white matter pallor and rarefaction (N=1)
DLBD (N=3)	1291 [1216−1398]	Stage IV (N=3)	Intermediate probability (N=3)	Mild (N=1) Mod. (N=1)	(N=1)	Mod. cranial arteriolosclerosis with cribiform change, white matter pallor and rarefaction (N=1)
CBD & PSP (N=4)	1426 [1344−1508]	Stage III (N=2)	Low probability (N=4)	None	(N=2)	Mild cranial arteriolosclerosis (N=1) Mod. cranial arteriolosclerosis with cribiform change, white matter pallor and rarefaction (N=2) Remote hemorrhagic infarct, focal left lateral putamen, microscopic
AD (N=2)	1477 [1372−1582]	Stage VI (N=1) Stage V (N=1)	High probability (N=2)	Mod. (N=1) Severe (N=1)	None	Mod. cranial arteriolosclerosis with cribiform change, patchy white matter pallor and rarefaction (N=2)

AD = Alzheimer's disease; CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; DLDB = diffuse Lewy body disease; FTLD-MND = frontotemporal lobar degeneration with motor neuron disease; PSP= progressive supranuclear palsy

*= Median [range]; NIA = National Institute of Health; Mod = moderate