Rapidly Progressive Neurodegenerative Dementias

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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.

Design, Setting, and Patients: 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 January 1, 2000, and September 30, 2007, with brain autopsy (N=96) at a tertiary care medical center. Of these 96 patients, we included only those with disease duration of less than 4 years to death and with histological diagnosis of a neurodegenerative disease.

Main Outcome Measures: Rapidly progressive dementia with death sooner than 4 years after onset and pathological diagnosis at our institution of a neurodegenerative disease.

Results: We included 22 patients (10 men). Although 8 cases (36%) had Creutzfeldt-Jakob disease (CJD), the rest had frontotemporal lobar degeneration with motor neuron degeneration (5 cases [23%]), a tauopathy (progressive supranuclear palsy or corticobasal degeneration) (4 cases [18%]), diffuse Lewy body disease (3 cases [14%]), or Alzheimer disease (2 cases [9%]). All of the patients with CJD died 12 months or sooner after onset, whereas the others had an illness duration longer than 12 months. Notably, all of the 3 patients with diffuse Lewy body disease but no others initially experienced a transient postoperative or illness-associated encephalopathy, then relative normality for 2 years, and finally a rapidly progressive dementia and decline to death in 4 to 12 months.

Conclusions: Based on this cohort, although CJD is the most likely cause of a rapidly progressive neurodegenerative dementia, frontotemporal lobar degeneration with motor neuron degeneration, diffuse Lewy body disease, tauopathies, and Alzheimer disease can also cause a rapidly progressive dementia. If illness duration is beyond 12 months, a non-CJD neurodegenerative disease may be more likely than CJD to be the diagnosis.

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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 patients with possible rapidly progressive dementia who were evaluated at our institution between January 1, 2000, and September 30, 2007, who had undergone brain autopsy examination at our institution, and had received a pathological diagnosis. A total of 96 cases were identified. The medical records of the 96 cases were reviewed by a neurodegenerative specialist (K.A.J.) blinded to the neuropathological diagnoses. Of these 96 cases, only those with total disease duration of less than 4 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 were abstracted in all of the 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 in which 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, severe fluctuations,8 parkinsonism (≥2 of the following: tremor, bradykinesia, rigidity, or postural instability), hallucinations and delusions, and motor neuron disease as well as the results of laboratory, cerebrospinal fluid (CSF), electroencephalographic (EEG), and neuroimaging studies were recorded. Rapid eye movement sleep behavior disorder was considered positive if the behavior met diagnostic criteria B for rapid eye movement 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 antithyroid peroxidase, antimicrosomal, and paraneoplastic antibodies being associated with rapidly progressive dementias, thyroid antibody levels and paraneoplastic testing results were also recorded.

NEUROPATHOLOGICAL EXAMINATION

Neuropathological examination was performed by 1 of 2 board-certified neuropathologists (J.E.P. and C.G.) unblinded to the clinical diagnoses. Consensus between both pathologists was performed in the event that a case was complex (n = 1). In all of the 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 of the cases underwent histological examination with hematoxylin-eosin as well as modified Bielschowsky silver stain. Immunohistochemistry with antibodies to tau (clone AT8 with a titer of 1:3750; Endogen, Woburn, Massachusetts), β-amyloid (clone 6F3D with a titer of 1:20; Novocastra Laboratories, Newcastle upon Tyne, England), α-synuclein (clone LB509 with a titer of 1:25; Zymed Laboratories, Inc, South San Francisco, California), ubiquitin (polyclonal with a titer of 1:100; Dako North America, Inc, Carpinteria, California), neurofilament (clone 2F11 with a titer of 1:800; Dako North America, Inc), TDP-43 (with a titer of 1:200; ProteinTech Group, Inc, Chicago, Illinois), and prion protein (clone 3F4 with a titer of 1:50; Dako North America, Inc) was performed in the event that a case was complex (n = 1). In all of the pathological diagnoses were made based on previously published criteria.12,13 Special attention was paid to the presence of any other pathological finding, including secondary neurodegenerative diseases (TDP-43–positive inclusions, Lewy bodies, Alzheimer-type pathological findings, α-synucleinopathy, vascular pathological findings of any sort, and argyrophilic grain disease. All of the CJD cases underwent confirmation by Western blot for prion protein at the National Prion Disease Pathology Surveillance Center, Cleveland, Ohio.

RESULTS

We identified 22 patients (10 of whom were men) who met our inclusion and exclusion criteria (Table 1). Of these 22 cases, the most common pathological diagnosis was CJD (8 cases [36%]). We also found 5 cases (23%) with a pathological diagnosis of FTLD with motor neuron degeneration (MND), 4 cases (18%) with a tauopathy (2 with progressive supranuclear palsy [PSP] and 2 with corticobasal degeneration [CBD]), 3 cases (14%) with DLBD, and 2 cases (9%) with AD. The time from disease onset to first neurological evaluation of all of the 22 cases was on average 7.5 months.

Histological findings are shown in Table 2. Almost all cases, except those with CJD, had a secondary neuropathological finding, which included Alzheimer-type pathological findings,10,15 vascular pathological findings, amyloid angiopathy, or argyrophilic grain disease.16 However, there were no cases with local gliosis, perivascular cuffing, or microglial aggregates suggestive of a secondary, immunomodulated (paraneoplastic) process. Lewy bodies were absent from the non-DLBD cases and abnormal TDP-43 immunoreactive lesions were not identified in any case except for those with FTLD-MND. All of the 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 at onset for all of the 22 cases ranged from 33 to 85 years and was significantly different across the groups (P = .04), with the DLBD group being the oldest (median age, 81 years) and the FTLD-MND group being the youngest (median age, 50 years). There appeared to be a bimodal distribution of total illness duration, with patients with CJD all dying 12 months or sooner after onset and the patients with non-CJD neurodegenerative diseases all having illness durations longer than 12 months.

Remarkably, all of the 3 patients with DLBD had experienced a transient postoperative or illness-associated confusional state with apparent complete recovery, which preceded the dementia onset by approximately 2 years. Once the dementia phase ensued among these patients, the progression to death was rapid, occurring in 4, 11, and 12 months. 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 3.0 years. This temporal pattern was quite consistent. Patient 14 experienced 2 weeks of acute confusion after coronary artery bypass grafting, then apparently recovered. He subsequently became demented 2 years later, dying 4 months after the confusional state.

STATISTICAL ANALYSIS

Statistical analyses were performed with JMP software version 7.0.0 (SAS Institute Inc, Cary, North Carolina) with α set at .05. Kruskal-Wallis test was used to compare age at onset across the different pathological diagnostic groups.
after dementia onset. Patient 15 developed an acute confusional state after a benign colonic polyp resection, and the confusional state slowly resolved over 3 months. He developed a rapidly progressive dementia 2 years after that and died 11 months later. Patient 16 was hospitalized for herpes simplex keratitis and cellulitis.
rienced a 1-week episode of confusional psychosis. This abated, but she developed a rapidly progressive dementia approximately 2 years after that and died 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 of the groups; it was present in 15 of the 22 cases, including all of the 3 patients with DLBD and all of the 4 patients with tauopathies. Psychosis (visual hallucinations and delusions) had been recorded at the time of dementia onset in 6 patients: 2 with DLBD, 2 with CJD, and 2 with AD. Severe fluctuations over hours were documented in 3 patients, 2 with DLBD and 1 with AD. Motor neuron disease was documented in 3 patients, 1 with CJD and 2 with FTLD-MND. Rapid eye movement sleep behavior disorder was documented in 3 patients, 1 with DLBD and 2 with AD. Myoclonus was a specific marker in our series; it was documented in 6 patients, all of whom had CJD. Parenthetically, 2 patients with CJD also had choreoathetoid movements and apraxia.

Four of the 14 patients with non-CJD neurodegenerative diseases had been accurately diagnosed in life, 2 with DLBD and 2 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 6 patients, 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 3 of the patients with non-CJD neurodegenerative diseases. In contrast, all of the patients with CJD had correct diagnoses prior to death.

Electroencephalography was inconsistently helpful in establishing the correct diagnosis. Periodic atypical triphasic waves, sharp waves, or epileptogenic discharges were noted in 4 CJD cases. The EEG showed excess slow waves in 3 of the remaining 4 CJD cases, whereas the EEG was normal in 1 CJD case. All of the 3 DLBD cases had atypical triphasic waves on EEG, intermittent in 2 and semiperiodic 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 levels were recorded in 7, including 1 with DLBD, 4 with CJD, and 2 with AD; no patients had abnormal cell counts or glucose levels. Neuron-specific enolase levels were measured in 14 patients and were abnormal (>35 ng/mL) in 6 of the 8 patients with CJD (median, 101.8 ng/mL; range, 39.4-204.0 ng/mL) and 1 patient with DLBD (35.2 ng/mL). They were mildly elevated (20-35 ng/mL) in the other 2 patients with CJD (29.1 ng/mL and 31.7 ng/mL) as well as in 2 patients with FTLD-MND (23.9 ng/mL and 22.8 ng/mL). The neuron-specific enolase level was normal (<20 ng/mL) in the other 3 tested patients (1 with CBD and 2 with AD). Levels of 14-3-3 protein measured by sandwich immunochromiluminometric assay were elevated in 3 of 6 patients with CJD and normal in the 5 patients with other neurodegenerative diseases in whom they were analyzed.

Magnetic resonance imaging of the brain was primarily diagnostic in the CJD cases; diffusion-weighted magnetic resonance sequences were abnormal in all of the 6 patients with CJD in whom this was performed. This included diffusion-weighted or fluid-attenuated inversion recovery abnormalities of cortical gyral hyperintensities in 5 patients and diffusion-weighted abnormalities within the striatum in 4 patients, of whom 2 also showed thalamic abnormalities. Varying degrees of gray matter atrophy were apparent in all groups but had limited diagnostic utility. Severe frontal lobe atrophy was apparent in 2 patients with FTLD-MND, and left-greater-than-right frontoparietal atrophy was present in 1 patient with CBD. All of the other

| Table 2. Secondary Pathological Findings Co-occurring With the Primary Diagnoses |

<table>
<thead>
<tr>
<th>Primary Neuropathological Diagnosis</th>
<th>Brain Weight, Median (Range), g</th>
<th>Braak and Braak Neurofibrillary Tangle Stage (Patients, No.)</th>
<th>Probability of NIA Reagan Criteria for AD (Patients, No.)</th>
<th>Amyloid Angiopathy (Patients, No.)</th>
<th>Patients With AGB, No.</th>
<th>Vascular Pathological Findings (Patients, No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CJD (n=8)</td>
<td>1186 (1034-1412)</td>
<td>0 (8)</td>
<td>Low (8)</td>
<td>None</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>FTLD-MND (n=5)</td>
<td>1228 (1042-1302)</td>
<td>VI (1); IV (1); II (1); I (2)</td>
<td>High (1); low (4)</td>
<td>Mild (2)</td>
<td>1</td>
<td>Mild cranial arteriolosclerosis (2); moderate cranial arteriolosclerosis with cribiform change, white matter pallor, and rarefaction (1)</td>
</tr>
<tr>
<td>DLBD (n=3)</td>
<td>1291 (1216-1398)</td>
<td>IV (3)</td>
<td>Intermediate (3)</td>
<td>Mild (1); moderate (1)</td>
<td>1</td>
<td>Moderate cranial arteriolosclerosis with cribiform change, white matter pallor, and rarefaction (1)</td>
</tr>
<tr>
<td>CBD and PSP (n=4)</td>
<td>1426 (1344-1558)</td>
<td>0 (2); III (2)</td>
<td>Low (4)</td>
<td>None</td>
<td>2</td>
<td>Mild cranial arteriolosclerosis (1); moderate cranial arteriolosclerosis with cribiform change, white matter pallor, and rarefaction (2); remote hemorrhagic infarct, focal left lateral putamen, microscopic (1)</td>
</tr>
<tr>
<td>AD (n=2)</td>
<td>1477 (1372-1582)</td>
<td>VI (1); V (1)</td>
<td>High (2)</td>
<td>Moderate (1); severe (1)</td>
<td>0</td>
<td>Moderate cranial arteriolosclerosis with cribiform change, patchy white matter pallor, and rarefaction (2)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; AGB, argyrophilic grain disease; CBD, corticobasal degeneration; CJD, Creutzfeld-Jakob disease; DLBD, diffuse Lewy body disease; FTLD-MND, frontotemporal lobar degeneration with motor neuron degeneration; NIA, National Institute on Aging; PSP, progressive supranuclear palsy.
neurodegenerative cases had mild or mild to moderate generalized patterns of atrophy. Single-photon emission computed tomography was performed in 5 patients and similarly had modest diagnostic utility. Among the 3 patients with FTLD-MND, frontal hypoperfusion was apparent in 2 and left anterior medial temporal lobe hypoperfusion was present in the other. One patient with CBD showed reduced uptake in frontoparietal regions, whereas the other showed just frontal hypoperfusion.

Blood work in these patients was not very elucidating, although 1 patient with AD had paraneoplastic type 1 antineuronal nuclear (ANNA-1/anti-Hu) and P/Q-type calcium channel antibodies, with electromyographic findings also consistent with Lambert-Eaton syndrome. One patient with PSP had acetylcholine receptor binding and striated muscle antibodies. Thyroperoxidase antibody levels were elevated in 4 patients, including 2 with CJD, 1 with PSP, and 1 with AD. Measurements of antimicrosomal antibodies (reference range titer, <1:100) were completed in 2 patients and were elevated in both, one with CJD (titer, 1:1600) and the other with PSP (titer, 1:6400).

**COMMENT**

Creutzfeldt-Jakob disease is a prime diagnostic consideration among rapidly progressive neurodegenerative dementias. Among our 22 cases, those with the most agressive course did indeed have CJD, and illness duration was a distinguishing factor. Thus, patients with a dementia progressing to death in less than 1 year all had CJD pathological findings, whereas a clinical course longer than 1 year was always associated with a non-CJD neurodegenerative diagnosis in this series. Variant CJD obviously has a more protracted course, but that condition is extremely rare in the United States.

All of the 3 DLBD cases had an unusual temporal course, however, that might be confused with CJD. Their terminal dementing phase was 12 months or shorter. However, in all, this was preceded by a transient encephalopathy lasting weeks to a few months, followed by approximately 2 years of a presumably asymptomatic or minimally symptomatic interlude. This triphasic course may be unique to DLBD as it was documented in all of the 3 DLBD cases and no others in our series.

Other investigators have noted that neurodegenerative diseases account for less than 5% of rapidly progressive dementias. We suspect, however, that the frequency will vary depending on how one defines rapid, which in our series was defined as onset to death in less than 4 years.

Recognition of CJD is aided by other clinical clues that were apparent in our series: myoclonus, periodic complexes on EEG, and fluid-attenuated inversion recovery and diffusion-weighted abnormalities on magnetic resonance imaging. Although an elevated CSF neuron-specific enolase level is also a clinical clue to CJD, we observed an elevated neuron-specific enolase level in 1 of our DLBD cases, whereas it was mildly elevated in 2 CJD cases. In our series, no non-CJD neurodegenerative cases had an abnormal 14-3-3 protein level; hence, a larger cohort is needed to determine whether 14-3-3 protein might be a more specific marker of CJD than 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 our series require replication, suggestive diagnostic findings surfaced. Among our non-CJD neurodegenerative cases, a young age at onset (around age 50 years) was most suggestive of FTLD-MND. Conversely, an older age at onset (around age 80 years) characterized our DLBD cases. Our patients with DLBD also uniquely had atypical triphasic waves on EEG, not seen in the other neurodegenerative cases. Unlike CJD, there was no periodicity to the EEG abnormalities as previously reported in a few DLBD cases; however, one of our DLBD cases did have a semiperiodic 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, whereas after the first year, atypical triphasic waves (even if they are semiperiodic) 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. In contrast to more typical FTLD with disease durations around 7 to 8 years, a mean disease duration of 2.3 years has been reported in FTLD-MND. 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 fluid-attenuated inversion recovery and diffusion-weighted magnetic resonance imaging abnormalities typical of CJD. We did not find any pattern of gray matter atrophy to be predictive of rapid progression, and 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, whereas asymmetric frontoparietal atrophy may be slightly more suggestive of underlying CBD. The same can be said for the patterns of hypoperfusion on single-photon emission computed tomographic images.

In nearly all of the non-CJD neurodegenerative cases, mixed pathological findings were apparent (Table 2). It is possible that these combined neuopathological findings contributed to the rapid clinical course; this included mainly superimposed Alzheimer pathological findings, amyloid angiopathy, and argyrophilic grain disease. Notably, amyloid angiopathy plus AD pathological findings were previously reported to be associated with a rapidly progressive dementia. Alzheimer disease pathological findings and amyloid angiopathy may also have been playing a role in the rapid progression of our DLBD cases as all of the 3 DLBD cases had Braak stage IV pathology and 2 cases had mild or 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 pathological finding was also present in those cases.

The 4 tauopathy cases in our series were the most perplexing. Other than the time course, they presented no dif-
ferently than typically observed CBD or PSP, where disease duration is approximately 7 years for each. These cases also did have secondary pathological findings, including Alzheimer-type pathological findings, 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 were not severe (although 1 case did have a microinfarct), and generally argyrophilic grain disease is not a marker of aggressive neurodegenerative disease. 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 immunomediated 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 immunomediated (paraneoplastic) process.

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

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

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Study supervision: Giannini.

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REFERENCES


New Initiatives: Clinical Trials and Videos

We have embarked on 2 new initiatives: Clinical Trials and video presentations. We welcome manuscripts that describe double-blind, randomized, placebo-controlled clinical trials as our primary area of interest. Open-label studies will also receive our special attention. We plan on expediting the review process and time to publication and to include them online ahead of print as these studies are time sensitive and of direct benefit to our patients. We hope you will take advantage of this new initiative. Please refer to the Instructions for Authors when submitting a Clinical Trials paper, including the requirement to register the trial with an accepted clinical trials site.

We plan to utilize videos as part of published papers that highlight and provide convincing information about the observational and visual features of a patient’s neurologic findings. Please refer to Instructions for Authors for instructions on submitting video presentations.