Cognitive Deficits Associated With a Recently Reported Familial Neurodegenerative Disease

Familial Encephalopathy With Neuroserpin Inclusion Bodies

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Background: We recently discovered an autosomal dominant disease causing a progressive dementia. The disease is caused by a point mutation in the gene coding for the serine protease inhibitor (ie, serpin) neuroserpin. The mutation results in an unstable neuroserpin protein that readily aggregates into intraneuronal inclusions that we identify as Collins bodies. The bodies are distributed throughout the cerebral hemispheres but are significantly more numerous in the cortex and the substantia nigra. We have named the disease familial encephalopathy with neuroserpin inclusion bodies (FENIB).

Objectives: To describe the cognitive and neurophysiological changes exhibited by individuals with FENIB and to correlate the phenotypic expression of the disease with the neuropathological findings.

Design: Multiple case studies using neuropsychological assessment, electroencephalography (EEG), magnetic resonance imaging (MRI), and single-photon emission computed tomographic (SPECT) studies of family members were performed. Using these measures, we also compared family members in whom the mutation is present with family members in whom the mutation was absent to control for nonspecific familial factors.

Subjects: Nine individuals (5 women, aged 31-64 years; 4 men, aged 43-67 years) from 2 generations of family members related to the first reliably identified individual with symptoms of this disease. Symptoms, by self-report and reports of other family members, ranged from asymptomatic to severe dementia. Six of the 9 individuals carried the disease mutation.

Results: All subjects with the mutation demonstrated some cognitive changes, with the greatest demonstrated by subjects older than 40 years. The changes included restricted attention, concentration, and response regulation functions, reduced controlled oral fluency (word-list generation), and restricted visuospatial organization. In general, recall memory was not as affected as other cognitive domains. The most severely affected subject demonstrated global dementia with prominent frontal lobe features. Findings on SPECT showed anomalies limited to frontal areas in the less affected subjects and more global, patchy areas of hypoperfusion in the more severely affected subjects. The 3 oldest and most affected subjects demonstrated slowing on EEG findings. The MRI findings were noncontributory except in the 2 most severe cases, which showed global cortical atrophy.

Conclusions: Cognitive changes in mildly to moderately affected subjects were characterized by deficits in frontal and frontal-subcortical area–dependent processes. Continued progressive deterioration of cerebral functions with relative sparing of recall memory suggests a unique dementia associated with this disease.

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Dementia is associated with a variety of degenerative brain processes that lead to distinct patterns of cognitive and behavioral decline. Occasionally, individuals demonstrate unusual patterns of cognitive decline or may lack the pathophysiology of known diseases, raising the question of an idiopathic or previously unknown debilitating process. We have been observing a family in upstate New York in which a number of individuals have an unusual dementia associated with the presence of neuronal inclusion bodies (Collins bodies) that are composed primarily of neuroserpin, a brain-specific serine protease inhibitor (serpin).

In 1989, the brain of a 65-year-old man with an unusual dementia characterized by odd behaviors and cognitive deficits suggestive of Huntington disease was brought for autopsy at the State University of New York Upstate Medical University, Syracuse. Neuropathological examination disclosed the presence of round, 5- to 30-µm eosinophilic inclusions of a previously unknown type detected with...
SUBJECTS AND METHODS

SUBJECTS

Nine volunteer subjects (5 women, aged 31-64 years; 4 men, aged 43-67 years) from 2 generations of family members were studied. Genotyping indicated that 6 subjects carried the gene for the mutation, whereas 3 did not. Subjects’ symptoms, by self-report and reports of other family members, ranged in severity from asymptomatic to severe dementia. Subjects who were described as asymptomatic by other family members were usually in their fourth and fifth decades of life. One 67-year-old man was described as asymptomatic and subsequently found to be free of the disease mutation. Subjects who demonstrated symptoms noticeable to themselves and/or to other family members were older than 50 years. All subjects were in relatively good physical health. Only 1 of the 9 subjects recruited presented with obvious marked dementia during the clinical interview. That subject, a 64-year-old woman, was unable to undergo testing on many of the neuropsychological measures, and therefore her neuropsychological test results were not included in the statistical comparison.

TEST INSTRUMENTS

Neuropsychological Assessment

Each subject was administered a 3- to 4-hour battery of neuropsychological measures in accordance with published testing guidelines. The psychometric tests used have been standardized to age-specific populations unless otherwise noted. The tests evaluated a broad range of neuropsychological functions and are listed in Table 1.

Magnetic Resonance Imaging

Cross-sectional T1- and T2-weighted magnetic resonance imaging (MRI) scans of the brain were acquired using a 1.5-T magnetic resonance imaging (MRI) scanner (Siemens Medical Systems, Inc, Iselin, NJ) to detect the presence of morphologic brain changes.

Single-Photon Emission Computed Tomography

Cross-sectional images of regional cerebral blood flow (rCBF) in the brain were acquired by means of single-photon emission computed tomography (SPECT) over 20 minutes using a 3-head scanner (Triad; Trionix, Twinsburg, Ohio) to detect γ-radiation emitted from intravenously administered technetium Te 99m bicisate. Three-dimensional images of brain rCBF were reconstructed from the acquired data. Before the injection of the tracer, subjects lay quietly in a dimly lit room for about 10 minutes and were instructed to relax. They received no instructions to perform any cognitive tasks during the administration of the tracer.

Electroencephalography

The electroencephalographic (EEG) recordings were made using a digital acquisition system (Grass-Telefactor, a division of Astro-Med, Inc, West Warwick, RI) using 21 recording channels and a 10-20 electrode placement system. Subjects underwent testing in awake and drowsy conditions that included photic stimulation and hyperventilation.

ANALYSIS

Results of MRI, SPECT, and EEG were interpreted by physicians in the Departments of Radiology, Division of Nuclear Medicine, and Neurology, respectively, State University of New York Upstate Medical University, according to standard protocols. The results of those measures were binomially classified as indicating the absence or presence of abnormalities. The MRI, EEG, and SPECT findings of subjects carrying the mutation were compared with the findings of those who did not using the Fisher exact test.

Neuropsychological tests were scored according to the guidelines provided in their respective test manuals. On most measures, subject test scores were obtained using the normative data from normally distributed age-specific general populations provided in the test manuals. In most cases, neuropsychological test scores were converted to standard scores (mean, 100; SD, 15). Some tests assessing frontal lobe–dependent functions, including alternating hand movements, reciprocal motor programs, and repeating graphomotor patterns (cursive m’s and n’s), were not readily converted to standard scores. This was also true for some language tests (subtests of the Boston Diagnostic Aphasia Examination). Those test results were classified instead on a 4-point scale of impairment. The Stoop color-word interference test scores were not standardized, and instead raw error scores were used for the between-group comparison.

We computed z-score comparisons between the mean standardized test scores of the mutation-present family members and the mean scores of the population on which the tests were normed (mean score, μ=100) to determine statistically significant differences between the affected subjects and the general population. Significant z scores indicate significantly lower mean scores in the mutation-present group compared with the general population.

We also compared the scores of the mutation-present family members with the mutation-absent family members to control for possible nonspecific familial factors. Because of the small and unequal subject group sizes, Aspin-Welch 1-tailed t tests were used to compare the test scores of mutation-present and mutation-absent groups. Post hoc power analyses of comparisons that reached or approached significance were completed using an online power calculator available from the Department of Statistics, University of California–Los Angeles.7

The possibility of a familial dementia was raised after postmortem examination of a second family mem-

hematoxylin-eosin stain (Figure 1). The inclusions, which we later named Collins bodies, were found scattered throughout the cerebral cortex and subcortical structures but not in white matter. Their most significant concentrations were in the deeper cortical layers (primarily pyramidal layers III-V), the insular cortex, the cingulate gyrus, and the substantia nigra (pars compacta). The cerebellum appeared to be spared.3

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ber, who had also exhibited unusual behavior, showed a similar distribution of Collins bodies. Investigation of the family confirmed that other members had experienced similar neuropsychological problems. Affected family members were described by their relatives as demonstrating perseveration, poor judgment, lack of insight, memory difficulties, and eventual loss of daily living skills. Other neurologic manifestations, including tremor, myoclonus, limb dyspraxia, and cogwheel rigidity, were seen in the most severely affected individuals.

Further investigation revealed that another affected family member, a 55-year-old woman, had previously undergone neuropsychological testing in 1990. At the time of testing, she was described as restless and fidgety, with impaired attention and response regulation and marked perseveration. Her word finding was restricted on an object-naming measure, and her visuomotor functioning was grossly impaired. Although her visual learning and memory were impaired, she demonstrated intact verbal learning and memory. She received a diagnosis of dementia, but Alzheimer disease was ruled out because of her relatively intact attention and concentration (Wechsler Memory Scale−Revised Attention/Concentration Index), oral fluency to generate lists of words beginning with particular letters (f, a, and s), and word-list learning (California Verbal Learning Test). Near significance was found on measures of visuospatial reasoning (Wechsler Adult Intelligence Scale−Revised [WAIS-R] Performance IQ, P = .07). The z scores were not obtained on the Stroop Color-Word Interference Test, which measures inhibition of an impulsive tendency to read words rather than to perform an alternative response, because subject performance was not normally distributed. Nonetheless, the performance of the mutation-present group was clinically impaired, particularly in the more severely affected subjects who demonstrated marked difficulty inhibiting their automatized reading response.

Table 2 shows statistically significant z scores that indicate areas of impaired neuropsychological functioning in the mutation-present group. Significant deficits were found on measures of attention and concentration (Wechsler Memory Scale−Revised [WAIS-R] Performance IQ, P = .05), and word-list learning (California Verbal Learning Test). Near significance was found on measures of visuospatial reasoning (Wechsler Adult Intelligence Scale−Revised [WAIS-R] Performance IQ, P = .07). The z scores were not obtained on the Stroop Color-Word Interference Test, which measures inhibition of an impulsive tendency to read words rather than to perform an alternative response, because subject performance was not normally distributed. Nonetheless, the performance of the mutation-present group was clinically impaired, particularly in the more severely affected subjects who demonstrated marked difficulty inhibiting their automatized reading response.
Table 2. Areas of Impaired Neuropsychological Functioning*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mutation-Present Group (n = 5)</th>
<th>Mutation-Absent Group (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Score</td>
<td>z Score†</td>
</tr>
<tr>
<td>Attention/concentration index (WMS-R)</td>
<td>79.4 (22.2)</td>
<td>-3.07</td>
</tr>
<tr>
<td>Oral fluency (f, a, and s)</td>
<td>73.0 (12.5)</td>
<td>-4.02</td>
</tr>
<tr>
<td>WAIS-R performance IQ</td>
<td>91.4 (10.9)</td>
<td>-1.28</td>
</tr>
<tr>
<td>WMS-R visual reproductions 1</td>
<td>92.4 (4.1)</td>
<td>1.13</td>
</tr>
<tr>
<td>CVLT trials 1-5</td>
<td>88.4 (12.8)</td>
<td>-1.73</td>
</tr>
<tr>
<td>CVLT immediate recall</td>
<td>79.0 (17.1)</td>
<td>-3.13</td>
</tr>
<tr>
<td>CVLT delayed recall</td>
<td>85.0 (15.0)</td>
<td>-2.23</td>
</tr>
<tr>
<td>Stroop Color-Word Interference Test</td>
<td>7.6 (79.3)</td>
<td>Not normally distributed</td>
</tr>
</tbody>
</table>

*Scores are standard scores (standardized using age-appropriate normative data where mean = 100 and SD = 15) except on the Stroop Color-Word Interference Test, for which number of errors are reported. All means for standardized test scores have a 95% confidence interval of ± 13.15 for the mutation-present group and ± 16.99 for the mutation-absent group. Neuropsychological measures are described in the “Results” section. WMS-R indicates Wechsler Memory Scale–Revised; WAIS-R, Wechsler Adult Intelligence Scale–Revised; and CVLT, California Verbal Learning Test.
†Derived by comparing study group with age-appropriate norms.
‡Significant at the level of .05, 1-tailed tests.

Table 3. Between-Group Comparisons of Neuropsychological Test Scores*

<table>
<thead>
<tr>
<th>Measure</th>
<th>t†</th>
<th>P Value</th>
<th>Power, 1 − β‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/concentration index (WMS-R)</td>
<td>2.5</td>
<td>.02§</td>
<td>.31</td>
</tr>
<tr>
<td>Oral fluency (f, a, and s)</td>
<td>2.4</td>
<td>.03§</td>
<td>.67</td>
</tr>
<tr>
<td>WAIS-R performance IQ</td>
<td>1.8</td>
<td>.07</td>
<td>.81</td>
</tr>
<tr>
<td>WMS-R visual reproductions 1</td>
<td>1.6</td>
<td>.08</td>
<td>.51</td>
</tr>
<tr>
<td>CVLT trials 1-5</td>
<td>0.26</td>
<td>.40</td>
<td>.62</td>
</tr>
<tr>
<td>CVLT immediate recall</td>
<td>0.11</td>
<td>.46</td>
<td>.39</td>
</tr>
<tr>
<td>CVLT delayed recall</td>
<td>0.01</td>
<td>.50</td>
<td>.27</td>
</tr>
<tr>
<td>Stroop Color-Word Interference Test</td>
<td>-1.73</td>
<td>.08</td>
<td>.11</td>
</tr>
</tbody>
</table>

*Neuropsychological measures are described in the “Results” section. Abbreviations are defined in the first footnote to Table 1.
†Indicates difference between mutation-absent and mutation-present group means.
‡Power to detect significant difference between group means was computed for each individual test using an n of .05 for a 1-tailed unequal variance t test. An effect size of 15 points (approximately 1 SD for the standardized scores) was used for all tests except the Stroop test, for which power was computed using the observed difference between means for the effect size.
§Significant at the level of .05, 1-tailed tests.

COMMENT

The cognitive deficits that accompany FENIB are qualitatively unique when compared with the patterns of progressive decline associated with other dementia processes. The FENIB-affect ed subjects consistently demonstrated deficits in areas associated with frontal lobe processes. Subjects carrying the gene mutation who were initially described as asymptomatic demonstrated mostly intact cognition, with the exception of restricted attention, concentration, and oral fluency, ie, an inability to generate lists of words beginning with particular letters (f, a, and s). Because the frontal lobes and related frontal-subcortical structures are regions of the brain that are intimately associated with attention,12 the subjects’ attend-

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tion deficits suggest that the accumulation of Collins bodies primarily affects frontal and frontal-subcortical areas during the early stages of the disease process. Deficits in oral fluency also implicated frontal areas, because oral fluency is also dependent on intact frontal lobe functioning. The findings of SPECT perfusion deficits in the frontal lobes in the mildly affected subjects with FENIB also indicated frontal lobe involvement early in the course of the disease.

As the disease progresses, cognitive deficits become more global in nature, presumably because of an increased accumulation of Collins bodies. In addition to restricted attention and fluency, the more affected subjects demonstrated impaired visuospatial organization. The most severely affected subjects demonstrated more marked deficits in frontal lobe–related areas of attention, concentration, mental control, working memory, and response regulation, and they exhibited impaired verbal and visual reasoning and restricted expressive and receptive language. Finally, the most significantly affected subject demonstrated severe dementia with prominent frontal features (eg, perseveration, stereotypic behavior, stimulus-bound behavior, and motor restlessness). Of note is that the most affected subjects demonstrated some sparing of recall memory when provided structure to assist in their recall such as cues or forced-choice recognition.

The findings of frontal lobe–related cognitive deficits and marked accumulation of Collins bodies in the substantia nigra in FENIB suggest similarities to Parkinson disease, which is characterized by the accumulation of Lewy bodies and neurodegeneration in this same region. Likewise, the early manifestation of attention, concentration, and fluency deficits and the subsequent emergence of restricted visuoconstructual reasoning (indicated by lower WAIS-R Performance IQ scores) in FENIB are qualitatively similar to cognitive deficits described for Parkinson disease. However, the marked motor involvement and cognitive slowing that typically accompany Parkinson dementia are not primary characteristics of FENIB. Hence, the 2 diseases can be clearly differentiated.

Furthermore, the dementia associated with FENIB is qualitatively distinct from dementia of the Alzheimer type (DAT) and from other “cortical” dementias (ie, dementias with a characteristic decline of cortically dependent functions such as language, reasoning, and memory). The relative sparing of recall memory and the lack of significant word-finding difficulty on testing, both of which are hallmarks of early DAT, are spared in the early stages of FENIB and indicate that it is clinically distinct from DAT. The neurophysiological changes underlying the differences between FENIB and other dementing processes directly affecting the cortex are not clear, since many
of these disorders also have characteristic cortical inclusions. One possible explanation may be that in FENIB the inclusions (i.e., Collins bodies) are found mostly in the deeper cortical layers (III-V).

A number of frontotemporal dementias have been described, some of which are associated with chromosome 17q21.6-18 Although different frontotemporal dementia syndromes have been described, common characteristics among them include middle-age onset, cognitive deficits associated with frontal lobe functioning, memory deficits, and Parkinson-like motor involvement. Although FENIB shares a number of these characteristics, its histopathologic features and molecular genetics make it distinct from other frontotemporal dementia syndromes.

Age appears to play a vital role in the clinical manifestations of FENIB, although age differences did not achieve statistical significance because of our limited sample size. We assume that the emergence of cognitive deficits correlates with the deposition of neuroserpin as Collins bodies in the brain. Generally, problems are not noticeable by other family members until the affected individuals reach their fifth or early sixth decade of life. Conversely, neuropsychological testing demonstrates changes at an earlier age. For example, in our study, 2 mutation-present subjects in their early fourth decades of life showed cognitive deficits. In one subject, the changes were subtle and were restricted to limited learning of a word list with intact learning on other memory tasks, whereas the other showed more notable cognitive decline. As an individual ages, the disease becomes clinically recognizable; the 2 mutation-present subjects in their fifth decade of life showed marked deficits, whereas the subject in his sixth decade of life was clearly demented, and the oldest subject, who was in her seventh decade of life, was nearly unable to undergo testing. The late onset of FENIB thus conforms to the general pattern of neurodegeneration caused by aberrant protein processing and tissue deposition. Because neurons are nondividing cells, the damage appears to be cumulative and irreversible.

The question of familial factors unrelated to the gene mutation that may have influenced subjects' cognition in our study was raised by our finding that mutation-present and mutation-absent family members demonstrated impaired learning on a word-list learning test. The finding of impaired performance by the control group on that measure indicated that the low scores of the mutation-present family members on that measure could be attributed to nonspecific or familial factors other than FENIB. Thus, caution must be taken when interpreting cognitive deficits of FENIB without adequate control subjects.

Recently, other occurrences of FENIB have been described in which the patients present with epilepsy and dementia.20-22 The findings of FENIB in unrelated families suggest that neuroserpin may play a more widespread role in dementia than previously known. Further study of individuals carrying the gene mutation in the family that we have been observing and in others as they may be discovered will provide better understanding of the progression of cognitive loss secondary to the accumulation of neuroserpin in the brain. Technological advances suggest that measures to quantify neuroserpin concentrations will become available, such as the development of MRI spectroscopy protocols. New means of evaluating the presence of neuroserpin in the brain will allow researchers to correlate neuroserpin accumulation with physiological and neuropsychological measures to provide further understanding of the disease process and its effects on cognition.

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