Incidence and Causes of Nondegenerative Nonvascular Dementia
A Population-Based Study

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Background: Information on the incidence of nondegenerative and nonvascular dementia is limited.

Design: We used the records-linkage system of the Rochester Epidemiology Project to ascertain incident cases of dementia in Rochester, Minn, from January 1, 1990, through December 31, 1994. To define causes of dementia, we reviewed all diagnoses, imaging study results, laboratory test results, and clinical courses, as recorded historically in the patient dossier.

Results: We found 560 incident cases of dementia, and 60 of them (10.7%) had onset before the age of 70 years (younger-onset group). Forty-three cases (7.7%) were due to nondegenerative nonvascular causes and represented 30.0% of the total in the younger-onset group, but only 5.0% of the total in the older-onset group (aged 70-99 years). The most common nondegenerative nonvascular causes were cancer with or without brain metastases (n=13), chronic alcoholism (n=7), and chronic mental illness (n=11). There were no cases of dementia due to normal-pressure hydrocephalus, subdural hematoma, hypothyroidism, vitamin B12 deficiency, or neurosyphilis. There were 2 individuals with acute confusion due to subdural hematoma and 1 with hypothyroidism whose cognition normalized with therapy.

Conclusions: Nondegenerative nonvascular causes were more common than expected in patients with a younger onset of dementia. None of the patients with dementia reverted to normal with treatment of the putative reversible cause.

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The incidence of dementia increases with advancing age.1,2 Alzheimer disease (AD), vascular dementia, and dementia with Lewy bodies are the 3 most common disorders among individuals with onset in their 70s and 80s. Along with other less common degenerative disorders, such as progressive supranuclear palsy and frontotemporal lobar degeneration, degenerative and vascular diseases dominate the spectrum of dementia. However, dementia can also be a manifestation of several other diseases of the central nervous system or of other body organs.3-5 Because nondegenerative nonvascular (NDNV) causes of dementia are less common than AD, vascular dementia, or dementia with Lewy bodies, and because the diagnosis of NDNV causes often requires extensive medical examinations and longitudinal follow-up, the NDNV causes of dementia have not been studied extensively in population-based surveys.

We studied the incidence of specific causative subtypes of dementia with a focus on NDNV causes using the records-linkage system of the Rochester Epidemiology Project.2,6,7

Methods

Case Ascertainment

We ascertained incident cases of dementia from January 1, 1990, through December 31, 1994, using the records-linkage system of the Rochester Epidemiology Project, as described previously.2,6,7

We searched these indexes for 132 specific codes from the Hospital Adaptation of the International Classification of Diseases that might indicate dementia.6 These codes specifically included an exhaustive list of neurological diagnoses associated with dementia, such as subdural hematoma and communicating hydrocephalus, in addition to primary dementia diagnoses such as AD and vascular dementia. To increase the likelihood of capturing individuals with undetected early dementia, the indexes were searched for the study interval and for the 6 years following the last year of the study interval. Cases of dementia identified in the 6 subsequent years were then reviewed for evidence of dementia onset in the 1990 to 1994 period.
Mental Disorders, Fourth Edition

imaging and judged to be critical. Dementia with Parkinson disease was defined by the presence of an extrapyramidal disorder clearly postdated the onset of dementia. We required that the imaging studies occurred in the time window between 1 year before and 3 years after the onset of dementia to avoid considering imaging lesions that clearly postdated the onset of dementia. 

All medical records of each potential case were screened by a specifically trained nurse abstractor. The study behavioral neurologists (D.S.K. or R.C.P.) confirmed the presence of dementia, classified the dementia by type, and determined the year of onset.

CLINICAL DIAGNOSTIC CRITERIA

The principal sources of diagnostic information were the medical history, neurological examination results, neuroimaging study results, and laboratory study results as recorded historically in the patient dossier of the records-linkage system (per routine medical care). The diagnostic criteria for dementia of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, were applied retrospectively; however, we were unable to estimate the severity of dementia through our retrospective medical record review. It was impossible to view the actual computed tomographic scans or magnetic resonance images of our patients; however, the primary study neurologists (D.S.K. or R.C.P.) reviewed the radiologists’ written reports of these studies. We required that the imaging studies occurred in the time window between 1 year before and 3 years after the onset of dementia to avoid considering imaging lesions that clearly postdated the onset of dementia.

We defined AD using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria. Vascular dementia was defined by the presence of 1 of the following 2 features: (1) clear evidence for the onset or worsening of dementia within 3 months of a clinical stroke or (2) bilateral gray matter infarcts shown by imaging had at least 1 magnetic resonance image. Thyroid function tests for syphilis if they had been performed within the 3 years preceding the onset of symptoms or any time later. To attribute a dementia-related illness to deficiencies of vitamin B12 or thyroxine, we required that treatment of the disorder result in substantial recovery. If the deficiency was treated but the dementia persisted, we inferred that the metabolic deficiency was not the primary cause of dementia. It remains possible, however, that these conditions contributed to irreversible degenerative or vascular changes in the brain.

DATA ANALYSES

We calculated age- and sex-specific incidence rates for dementia overall and for specific types of dementia through the age of 99 years (centenarians were excluded), after adjusting the denominators for prevalent cases of dementia, as described elsewhere.

There were 560 persons with onset of dementia in Rochester from 1990 to 1994. Most cases were degenerative or vascular. Table 1 presents the age- and sex-specific incidence rates for dementia overall and for NDNV dementia. Forty-three cases (7.7%) were due to NDNV causes, the largest subsets of which were cancer with or without brain metastases (n = 379), chronic alcoholism (n = 2), and chronic psychiatric conditions (n = 11). Table 2 lists the specific causes. Patients with dementia due to an NDNV cause represented 30.0% of all patients with onset before the age of 70 years, but only 5.0% in the older-onset group (aged 70-99 years).

Brain imaging study results were available for 409 (73.0%) of the 560 incident cases. Most studies were computed tomographic; only 33.3% (136/409) of cases with imaging had at least 1 magnetic resonance image. Thyrotropin levels were available for 515 patients (92.0%) within the 3 years preceding the onset of cognitive symptoms or any time later. For 341 of these patients (60.9% of the total), the testing was done at the time of symptom onset or later. Vitamin B12 levels were available in 444 (79.3%) of the patients with dementia, of which 379 (67.7%) were obtained at symptom onset or after. In addition, there were 291 (52.0%) subjects with rapid plasma reagin serological results.

No subjects with dementia had normal-pressure hydrocephalus. The diagnosis was suspected in 5 patients, leading to shunt placement in 3; none responded to therapy.

Table 1. Age- and Sex-Specific Incidence Rates of Dementia Overall and of Nondegenerative Nonvascular Dementia in Rochester, Minn, 1990 Through 1994

<table>
<thead>
<tr>
<th>Age, y</th>
<th>40-49</th>
<th>50-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75-79</th>
<th>80-84</th>
<th>85-89</th>
<th>90-99</th>
<th>Total</th>
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<tbody>
<tr>
<td>Sex</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women†</td>
<td>8.5</td>
<td>38.1</td>
<td>107.1</td>
<td>271.5</td>
<td>601.3</td>
<td>612.3</td>
<td>2131.4</td>
<td>4257.1</td>
<td>5027.5</td>
<td>556.0</td>
</tr>
<tr>
<td>Men‡</td>
<td>9.2</td>
<td>6.7</td>
<td>148.6</td>
<td>383.6</td>
<td>900.4</td>
<td>1220.0</td>
<td>2898.8</td>
<td>1744.8</td>
<td>5027.5</td>
<td>208.1</td>
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<tr>
<td>Total</td>
<td>8.8</td>
<td>22.9</td>
<td>152.9</td>
<td>321.1</td>
<td>723.3</td>
<td>1290.2</td>
<td>2376.2</td>
<td>3561.7</td>
<td>5005.7</td>
<td>445.8</td>
</tr>
</tbody>
</table>

Nondegenerative Nonvascular Dementia

<table>
<thead>
<tr>
<th>Age, y</th>
<th>40-49</th>
<th>50-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75-79</th>
<th>80-84</th>
<th>85-89</th>
<th>90-99</th>
<th>Total</th>
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<tr>
<td>Sex</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Women†</td>
<td>0.0</td>
<td>19.1</td>
<td>15.3</td>
<td>50.9</td>
<td>75.2</td>
<td>100.5</td>
<td>50.7</td>
<td>83.5</td>
<td>68.9</td>
<td>30.1</td>
</tr>
<tr>
<td>Men‡</td>
<td>9.2</td>
<td>6.7</td>
<td>37.2</td>
<td>127.9</td>
<td>109.4</td>
<td>38.1</td>
<td>318.1</td>
<td>109.1</td>
<td>0.0</td>
<td>39.4</td>
</tr>
<tr>
<td>Total</td>
<td>4.4</td>
<td>13.1</td>
<td>25.3</td>
<td>85.0</td>
<td>89.0</td>
<td>79.0</td>
<td>127.0</td>
<td>90.6</td>
<td>56.9</td>
<td>34.2</td>
</tr>
</tbody>
</table>

*Incidence rates are given per 100,000 person-years. Numbers in parentheses indicate the actual number of cases observed.
†Denominators (in person-years) for women were as follows: 40 to 49 years, 21,801; 50 to 59 years, 15,729; 60 to 64 years, 6533; 65 to 69 years, 5894; 70 to 74 years, 5332; 75 to 79 years, 4973; 80 to 84 years, 3941; 85 to 89 years, 2396; and 90 to 99 years, 1422.
‡Denominators (in person-years) for men were as follows: 40 to 49 years, 21,801; 50 to 59 years, 14,860; 60 to 64 years, 5383; 65 to 69 years, 4693; 70 to 74 years, 3665; 75 to 79 years, 2623; 80 to 84 years, 1572; 85 to 89 years, 917; and 90 to 99 years, 306.
§Four incident cases of dementia (all women with Alzheimer disease) with onset after the age of 99 years were not reported.
No subjects had chronic subdural hematomas as a cause of dementia. However, there were 2 subjects with subacute cognitive impairment, not dementia, preceding the discovery of the chronic subdural hematoma. They both improved following surgical removal of the hematoma, but never fully recovered cognitively and then subsequently experienced dementia. An acute subdural hematoma was diagnosed in 2 other patients. One was due to trauma, and the second was associated with subarachnoid hemorrhage due to a ruptured intracranial aneurysm.

No subjects were diagnosed as having hypothyroid-related dementia. One woman developed acute confusion and had severe hypothyroidism; however, her confusion resolved completely on thyroid replacement therapy. Among patients with dementia, only 5 (1.0%) had thyrotropin levels greater than 20 mIU/L (of 515 with available levels), all of which normalized with therapy without any improvement of the dementia.

There were no patients with dementia due to vitamin B₁₂ deficiency. There were 5 patients (1.1%) with vitamin B₁₂ values of less than 100 pg/mL (<73.8 pmol/L) (of 444 with available levels) and 39 (8.8%) with levels of less than 200 pg/mL (<147.6 pmol/L). Most patients were treated, and their vitamin B₁₂ levels returned to normal without any improvement in the dementia (27 [69.2%] of 39 patients). The remaining 12 subjects experienced vitamin B₁₂ deficiency in the context of their terminal illness, active breast cancer, or alcoholism.

No subjects were diagnosed as having neurosyphilis. There were 5 patients (1.7%) with positive rapid plasma reagin serological results (of 291 ever tested), 4 of whom also had positive fluorescent treponemal antibody determinations. Of these 5 patients, 2 were treated with antibiotics, 1 had a negative cerebrospinal fluid examination result, and 1 had AD at autopsy. The treatment status of the remaining subject who had profound dementia at serological testing could not be determined.

The distribution of dementia subtypes in this geographically defined population varied noticeably with age. The NDNV dementia made a substantial contribution for patients with onset before the age of 70 years. Cancer-related, alcohol-related, and psychiatric or substance abuse causes were the principal NDNV causes. Our findings were similar to findings in other populations.⁴,⁵ However, many of the patients with NDNV dementia are never referred to specialized memory disorder clinics. Therefore, the diseases causing NDNV dementia in this population were different from those found in series of patients with dementia referred to specialized clinics.⁶

Our patients with dementia had high rates of brain imaging and laboratory investigations conducted for routine medical care. There were several patients with suspected normal-pressure hydrocephalus and several with documented subdural hematoma, vitamin B₁₂ deficiency, or hypothyroidism. Hypothyroidism⁷ and vitamin B₁₂ deficiency⁸ are frequent among elderly persons. However, none of these diagnoses were judged clinically to be the principal cause for dementia in our series. The presence of a modest number of cases of vitamin B₁₂ deficiency, hypothyroidism, subdural hematoma, or normal-pressure hydrocephalus suggested that treating physicians in our community were aware of these diagnoses, and that the ascertainment of cases of dementia in this study was sensitive to these conditions. Our findings suggest that, in this population, none of the commonly considered “reversible causes of dementia” were the principal cause of dementia, because dementia did not revert to normal with appropriate treatment. A few patients with a putative reversible cause experienced an acute or subacute confusional state that responded to treatment (and were never classified as having dementia). The concept of reversible causes of dementia should be reconsidered.

### Table 2. Causative Classification of Patients With Nondegenerative Nonvascular Dementia*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Comments</th>
<th>&lt;70</th>
<th>70-99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>Neurologist diagnosed; proved at autopsy</td>
<td>1</td>
<td>(5.6)</td>
</tr>
<tr>
<td>CNS trauma</td>
<td>Severe head injury with posttraumatic amnesia</td>
<td>1</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Anoxic encephalopathy</td>
<td>Documented cardiac arrests with postarrest cognitive impairment</td>
<td>3</td>
<td>(16.7)</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Down syndrome with dementia onset age at 50 y</td>
<td>0</td>
<td>(5.6)</td>
</tr>
<tr>
<td>HIV disease</td>
<td>Known HIV-positive individual; developed progressive multifocal leukoencephalopathy</td>
<td>1</td>
<td>(5.6)</td>
</tr>
<tr>
<td>CNS infection</td>
<td>Dementia with unusual inflammatory changes in meninges; presumed infectious</td>
<td>0</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>Primary or metastatic brain tumors</td>
<td>4</td>
<td>(22.2)</td>
</tr>
<tr>
<td>Systemic tumor</td>
<td>Dementia associated with systemic cancer but with unknown pathogenetic mechanism</td>
<td>0</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>Patient with malignant fibrous histiocytoma; had Lambert-Eaton syndrome; developed dementia; presumed paraneoplastic</td>
<td>1</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Alcohol related</td>
<td>Severe decades-long alcohol abuse with or without concomitant psychiatric diagnoses; developed dementia</td>
<td>4</td>
<td>(22.2)</td>
</tr>
<tr>
<td>Mental illness</td>
<td>Decades-long histories of severe depression or schizoaffective disorder</td>
<td>2</td>
<td>(11.1)</td>
</tr>
<tr>
<td>Total</td>
<td>NA</td>
<td>18</td>
<td>(100.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; NA, data not applicable.

*There were no patients who had the following diagnoses: normal-pressure hydrocephalus (shunt-responsive dementia), vitamin B₁₂-deficiency dementia (dementia that resolved with parenteral vitamin B₂ therapy), hypothyroid dementia (dementia that resolved with thyroid hormone replacement), subdural hematoma (surgical removal of the subdural hematoma resolves dementia), and neurosyphilis (proved by cerebrospinal fluid and response to treatment).

†Data are given as number (percentage) of each group. Percentages are based on column totals and may not total 100 because of rounding.
We are aware of only 1 population-based study of shunt-responsive normal-pressure hydrocephalus that estimated an incidence of 2.2 cases per million per year in the Netherlands. Therefore, our failure to find any shunt-responsive case was not unexpected given the population of Rochester, Minn (total population, 70,745 in 1990). Our 2 cases of chronic subdural hematoma over 37,754 person-years (for those >65 years). This rate is similar to the one reported from 3 district hospitals in North Wales from 1996 to 1999 (8.2 per 100,000).15

There were no definite cases of neurosyphilis in our series. We are unaware of any prevalence estimates of tertiary neurosyphilis in elderly persons. Data from the Centers for Disease Control and Prevention show low rates of late or latent syphilis in Minnesota, especially in older age ranges (STD Surveillance 2000; available at: http://www.cdc.gov/std/stats00/TOC2000.htm). There are other regions in the United States where syphilis is more common and neurosyphilis may make a greater contribution to the burden of dementia. For example, 17 persons with neurosyphilis with neuropsychiatric symptoms were recently described from a university hospital in New Orleans, La, over a 3-year period (only 3 of those persons were >60 years).16

We were surprised by the number of individuals with chronic mental illness in our dementia cohort. There were 9 persons with lifelong histories of schizophrenia or disabling depression who experienced superimposed declines in cognition and functioning and met our criteria for dementia. They represent a challenge in clinical diagnosis. Whether their cognitive decline was an extension of the mental illness or due to a distinct neurodegenerative or covert cerebrovascular disease cannot be determined with confidence.

We found several persons with decades of alcoholism who experienced dementia. The pathological substrate of alcohol-related dementia that cannot be linked to a thiamine deficiency disorder remains uncertain.17 We could not determine whether the appearance of dementia was merely coincidental or was causatively related to alcohol use. One other study of dementia frequency in a clinical series of individuals younger than 60 years reported alcohol-related dementia in 10% of the cases.

One strength of this study was that the persons were drawn from a geographically defined population, and that most patients underwent an adequate examination for their dementia as part of routine care. Documentation was also adequate in most cases to establish the temporal sequence of the dementia-related illness and other medical and neurological conditions. Weaknesses of the study include the retrospective nature of case identification; this may have caused the nondetection of some mild cases of dementia. The distribution of causes must be viewed with caution because the diagnoses were clinical. For some patients, the medical record was incomplete in describing treatment, and some patients lacked adequate laboratory testing or imaging.

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Author Contributions: Study concept and design: Knopman, Petersen, and Rocca. Acquisition of data: Knopman, Petersen, Edland, and Rocca. Analysis and interpretation of data: Knopman, Petersen, Cha, and Rocca. Drafting of the manuscript: Knopman and Rocca. Critical revision of the manuscript for important intellectual content: Knopman, Petersen, Cha, Edland, and Rocca. Statistical analysis: Cha and Rocca.

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15. Fredman A, Eklund S, Månsson T. Incidence of late or latent syphilis in Minnesota, especially in older age ranges (STD Surveillance 2000; available at: http://www.cdc.gov/std/stats00/TOC2000.htm). There are other regions in the United States where syphilis is more common and neurosyphilis may make a greater contribution to the burden of dementia. For example, 17 persons with neurosyphilis with neuropsychiatric symptoms were recently described from a university hospital in New Orleans, La, over a 3-year period (only 3 of those persons were >60 years).