Insidious Cognitive Decline in CADASIL

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Background and Purpose—Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) causes repeated ischemic attacks leading to subcortical vascular dementia. The aim of this study was to characterize cognitive function in subjects with a C475T (R133C) mutation in the Notch3 gene, leading to CADASIL.

Methods—Prestroke (n=13) and poststroke (n=13) mutation carriers and mutation carriers with dementia (n=8) were compared with healthy noncarriers from the same families using a comprehensive set of neuropsychological tests.

Results—Changes in working memory and executive function were observed in the very early phase of the disease before transient ischemic attack (TIA) or stroke. Later, in the poststroke phase, the cognitive impairment concerned also mental speed and visuospatial ability. Finally, the subjects with dementia had multiple cognitive deficits, which engaged even verbal functions, verbal episodic memory, and motor speed. The 2 mutation carrier groups without dementia and the controls could be reliably distinguished using 3 tests that assessed working memory/attention, executive function, and mental speed. Episodic memory was relatively well-preserved late in the disease.

Conclusion—A deterioration of working memory and executive function was already observed in the prestroke phase, which means that cognitive decline may start insidiously before the first onset of symptomatic ischemic episodes.

Key Words: CADASIL ■ neuropsychology ■ vascular diseases ■ small vessel disease

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a generalized small-vessel disease caused by mutations in the Notch3 gene on chromosome 19. The Notch3 gene encodes Notch3 receptor protein that is expressed in adults only on vascular smooth muscle cells (SMC). Mutated Notch3 induces destruction of these SMCs with parallel deposition of granular osmiophilic material (GOM) and fibrosis. These arterial changes result in decreased cerebral blood flow (CBF), especially in the white matter, and consequent periventricular white matter degeneration and lacunar infarcts in deep white matter and basal ganglia. The natural course of CADASIL is variable. Recurrent transient ischemic attacks (TIA) and strokes are the main manifestations. One third of the patients have migraine headache and one fifth have mood disorders, these being mostly depression or anxiety.

The cumulative brain lesions lead to insidious cognitive decline, the progression of which to subcortical dementia is still poorly known. There have been only a few studies focused on the early signs of cognitive decline and compared nondemented mutation carriers with 15 healthy nonmutation carriers from the same kindreds.

Subjects and Methods

Thirty-four subjects from 8 Finnish families were genetically confirmed to carry the same C475T (R133C) mutation in exon 3 of the Notch3 gene on chromosome 19. The Notch3 gene encodes Notch3 receptor protein that is expressed in adults only on vascular smooth muscle cells (SMC). Mutated Notch3 induces destruction of these SMCs with parallel deposition of granular osmiophilic material (GOM) and fibrosis. These arterial changes result in decreased cerebral blood flow (CBF), especially in the white matter, and consequent periventricular white matter degeneration and lacunar infarcts in deep white matter and basal ganglia. The natural course of CADASIL is variable. Recurrent transient ischemic attacks (TIA) and strokes are the main manifestations. One third of the patients have migraine headache and one fifth have mood disorders, these being mostly depression or anxiety.

The cumulative brain lesions lead to insidious cognitive decline, the progression of which to subcortical dementia is still poorly known. There have been only a few studies focused on the early signs of cognitive decline and compared nondemented mutation carriers with 15 healthy nonmutation carriers from the same kindreds.
Notch3 gene. All had typical periventricular white matter changes on T2-weighted magnetic resonance imaging (MRI). The controls (n=15) were genetically confirmed to be negative for the mutation and they showed no pathological findings on MRI. Information about the history of TIA and stroke as well as occurrence of migraine and mood changes was collected through semi-structured interviews of the subjects and close informants as well as from medical files.

The mutation carriers were divided into 3 groups defined by occurrence of clinical ischemic symptoms and dementia. The post-stroke group (n=13) comprised subjects without TIA, stroke, or dementia. The post-stroke group (n=13) included subjects who had experienced at least 1 cerebrovascular ischemic symptom but were not demented. Subjects in the dementia group (n=8) fulfilled the DSM-III-R criteria for dementia and 6 of them had had 1 or more strokes.

Neuropsychological Assessment

The neuropsychological examination included the following tests: similarities, block design, digit symbol, digit span total score, digit span forwards, and digit span backwards from the Wechsler Adult Intelligence Scale-Revised (WAIS-R), letter fluency (FAS), Trail-Making Test, parts A and B (TMTA, TMTB; number of correct responses and log-transformed time score), Luria clock-setting and clock-reading test, Rey–Osterreith memory, digit symbol, digit span total score, digit span backwards, and digit symbol, which are primarily associated with executive function, working memory, and alternation hands.

Six mutation carriers and 4 controls were tested in the late 1980s and early 1990s at the Department of Neurology of Oulu University Hospital. The remaining 28 mutation carriers and 11 controls were examined between 1997 to 1999 at the Department of Neurology of Keski-Pohjanmaa Central Hospital and Turku University Hospital by 2 neuropsychologists (K.A. and M.W.). Of the mutation carriers, 14 had a history of mood changes but none of them had severe depression according to clinical evaluation at the time of the neuropsychological investigation. Nineteen of the 34 mutation carriers and 11 controls were examined between 1997 to 1999 at the Department of Neurology of Keski-Pohjanmaa Central Hospital and Turku University Hospital by 2 neuropsychologists (K.A. and M.W.). Of the mutation carriers, 14 had a history of mood changes but none of them had severe depression according to clinical evaluation at the time of the neuropsychological investigation.

The joint Ethical Committee of Turku University Hospital and University of Turku approved the study.

Statistical Methods

Groups were compared by 1-way ANOVA or with ANCOVA when possible confounding factors (age and education) were included. Sheffe test was used for the post-hoc analysis. Because of the exploratory nature of this study, P<0.05 was regarded as a difference and no correction for multiple testing was performed. Stepwise discriminant analysis with Wilks lambda as criterion was used to find the best combination of tests to separate groups of nondemented mutation carriers and controls. Cross-validation of classification of cases was performed using jack-knife procedure (each case is classified by functions derived from all cases other than that case). All analyses were performed using SPSS version 11.0.

TABLE 1. Demographic Characteristics of Healthy Controls and the 3 Mutation Carrier Groups

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Controls</th>
<th>Prestroke</th>
<th>Poststroke</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (female/male)</td>
<td>15 (5/10)</td>
<td>13 (5/8)</td>
<td>13 (4/9)</td>
<td>8 (3/5)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>39.5±10.8</td>
<td>39.3±11.0</td>
<td>48.7±6.9</td>
<td>54.5±5.8</td>
</tr>
<tr>
<td>Education (y)</td>
<td>12.1±4.3</td>
<td>10.2±3.5</td>
<td>9.3±3.5</td>
<td>6.5±0.9</td>
</tr>
<tr>
<td>Migraine (frequency)</td>
<td>2/15</td>
<td>7/13</td>
<td>9/13</td>
<td>3/8</td>
</tr>
<tr>
<td>Mood change (frequency)</td>
<td>0</td>
<td>5/13</td>
<td>6/13</td>
<td>3/8</td>
</tr>
</tbody>
</table>

Results

Demographics

In Table 1, the demographic data for the 4 groups are presented. The mean age of the poststroke and dementia groups was significantly higher (P<0.001) than that of the control and prestroke groups. The latter 2 groups did not differ from each other. The mean level of education differed significantly (P<0.001) between the dementia group versus control and prestroke and poststroke groups, but there was no significant difference between the latter 3 groups.

Impairment in the Cognitive Performance in Different Phases of the Disease

The prestroke group performed poorer than controls in 3 tests: digit span forward (P<0.05), digit span backward (P<0.001), and Rey–Osterreith memory test (P<0.001). The poststroke CADASIL subjects performed more poorly than poststroke subjects in 4 tests: number correct responses (P<0.01), log time (P<0.01) of TMTB, digit symbol (P<0.001), and the block design test (P<0.01). Unexpectedly, the poststroke group performed almost as well as the controls.

In the dementia group, only 11 of the 21 neuropsychological tests could be administered because of the severity of the cognitive impairment. In 8 of these 11 tests, the dementia group differed from all the other groups. Only in a single test, clock-setting, did the groups not differ from each other. For detailed comparisons between the groups, see Table 2.

Discriminant Analysis

Using all neuropsychological tests, a stepwise discriminant analysis was performed on control, prestroke, and poststroke groups. This analysis resulted in 2 significant discriminant functions (P<0.001) in 3 tests: Rey–Osterreith memory, digit span backwards, and digit symbol, which are primarily associated with executive function, working memory, and mental speed. The first discriminant function explained 79% of the variance and was associated with low performance in 2 tests to approximately the same extent (standardized coefficients 0.63 for Rey–Osterreith memory and 0.69 for digit span backwards). The second discriminant function explained 21% of the variance and was associated with high performance in digit symbol (standardized coefficient −0.74) compared with the performance in Rey–Osterreith memory (0.32) and digit span backwards (0.50). The first discriminant function differentiated the poststroke group from the prestroke and control groups by low level of cognitive perfor-
According to Discriminant Analysis of CADASIL Subjects, poorer performance in the Rey–Osterreith memory test and controls were misclassified as prestroke subjects because of incorrectly classified subjects were compared, 3 of 15 correctly and digit span backwards (P<0.01 and P<0.05, respectively). Among the prestroke subjects, 3 were misclassified (2 were classified as controls because they performed as well as the those in the control group in the Rey–Osterreith memory test; P<0.001). In summary, misclassification of individuals was related to patterns of relative performance as demonstrated by a scatter-plot of all prestroke and poststroke subjects and the controls in terms of the 2 discriminant functions (Figure 1).

**TABLE 2. Neuropsychological Test Results (mean±SD) in Healthy Controls and Prestroke, Stroke, and Dementia Groups of CADASIL Patients**

<table>
<thead>
<tr>
<th>Neuropsychological Tests</th>
<th>Controls</th>
<th>Prestroke</th>
<th>Poststroke</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similarities</td>
<td>21.5±3.4</td>
<td>21.2±3.0</td>
<td>20.9±4.1</td>
<td>→ 8.0±4.9</td>
</tr>
<tr>
<td>FAS letter fluency</td>
<td>44.7±8.6</td>
<td>36.9±12.8</td>
<td>35.8±14.6</td>
<td>→ 10.0±4.2</td>
</tr>
<tr>
<td>Clock-reading, # corr</td>
<td>5.0±0.0</td>
<td>4.9±0.3</td>
<td>4.5±1.0</td>
<td>→ 3.3±0.9</td>
</tr>
<tr>
<td>Clock-setting, # corr</td>
<td>4.7±0.6</td>
<td>4.4±0.8</td>
<td>4.5±0.9</td>
<td>3.8±1.2</td>
</tr>
<tr>
<td>R-O copying</td>
<td>35.2±0.8</td>
<td>33.5±2.0</td>
<td>32.2±4.1</td>
<td>→ na</td>
</tr>
<tr>
<td>Block design</td>
<td>31.9±2.8</td>
<td>36.0±4.4</td>
<td>→ 30.0±5.4</td>
<td>→ 9.9±4.7</td>
</tr>
<tr>
<td>TMTA, log time (sec)</td>
<td>1.5±0.2</td>
<td>1.5±0.2</td>
<td>1.7±0.2</td>
<td>→ 2.5±0.2</td>
</tr>
<tr>
<td>TMTB, # corr</td>
<td>24.0±0.0</td>
<td>23.8±0.8</td>
<td>→ 17.5±6.6</td>
<td>na</td>
</tr>
<tr>
<td>TMTB, log time (sec)</td>
<td>1.9±0.2</td>
<td>2.0±0.2</td>
<td>→ 2.2±0.2</td>
<td>na</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>42.1±10.0</td>
<td>49.0±7.6</td>
<td>→ 28.0±5.3</td>
<td>na</td>
</tr>
<tr>
<td>Digit span, total</td>
<td>14.9±3.8</td>
<td>12.7±2.1</td>
<td>13.4±2.0</td>
<td>→ 7.1±2.8</td>
</tr>
<tr>
<td>Digit span forward</td>
<td>6.9±1.1</td>
<td>→ 6.0±0.9</td>
<td>6.2±0.4</td>
<td>na</td>
</tr>
<tr>
<td>Digit span backward</td>
<td>5.9±1.0</td>
<td>→ 4.7±0.5</td>
<td>4.3±0.8</td>
<td>na</td>
</tr>
<tr>
<td>RAVL learning</td>
<td>49.1±9.3</td>
<td>47.6±7.6</td>
<td>43.2±9.7</td>
<td>na</td>
</tr>
<tr>
<td>RAVL retention</td>
<td>10.9±2.5</td>
<td>9.9±2.3</td>
<td>8.9±2.7</td>
<td>na</td>
</tr>
<tr>
<td>SGRC recall, # corr</td>
<td>8.1±1.4</td>
<td>7.1±1.8</td>
<td>6.8±1.0</td>
<td>→ 4.8±1.0</td>
</tr>
<tr>
<td>SGRC recognition, d-prime</td>
<td>3.3±1.1</td>
<td>3.4±0.9</td>
<td>2.6±0.9</td>
<td>2.3±0.5</td>
</tr>
<tr>
<td>R-O memory</td>
<td>27.7±2.8</td>
<td>→ 20.9±5.6</td>
<td>16.8±6.5</td>
<td>na</td>
</tr>
<tr>
<td>Finger-tapping, dominant</td>
<td>57.8±10.2</td>
<td>60.2±8.2</td>
<td>52.0±8.0</td>
<td>→ 32.8±7.1</td>
</tr>
<tr>
<td>Finger-tapping, nondominant</td>
<td>50.6±7.4</td>
<td>53.0±6.0</td>
<td>48.8±8.1</td>
<td>40.8±14.0</td>
</tr>
<tr>
<td>Finger-tapping, alternating</td>
<td>87.0±13.2</td>
<td>91.0±29.0</td>
<td>84.9±16.7</td>
<td>na</td>
</tr>
</tbody>
</table>

**Table 3. Classification (Original/Cross-Validated) of Subjects According to Discriminant Analysis of CADASIL Subjects Without Dementia and the Controls**

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Controls</th>
<th>Prestroke</th>
<th>Poststroke</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>12/11</td>
<td>3/4</td>
<td>0/0</td>
<td>15</td>
</tr>
<tr>
<td>Prestroke patients</td>
<td>2/3</td>
<td>10/9</td>
<td>1/1</td>
<td>13</td>
</tr>
<tr>
<td>Poststroke patients</td>
<td>0/0</td>
<td>0/1</td>
<td>13/12</td>
<td>13</td>
</tr>
</tbody>
</table>

na indicates not assessed; →, pair-wise difference between the groups; # corr, number of correct responses; R-O, Rey–Osterreith; TMTA, Trail Making Test A; TMTB, Trail Making Test B; RAVL, Rey Auditory Verbal Learning; SGRC, Stockholm Gerontology Research Center.

Discussion

Cognitive decline could be observed very early during the course of CADASIL as shown in the prestroke and poststroke groups. The performance of the prestroke group was poorer than that of the controls in 3 cognitive domains: short-term memory (digit span forwards), working memory (digit span backwards), and executive function (Rey–Osterreith memory), because of poor strategy and planning in completing the task. The cognitive domain, which distinguished prestroke from the poststroke group, was mental slowing as verified by poor results in digit symbol and TMTB time and set-shifting ability (TMTB, number correct responses). This pattern of cognitive decline was also confirmed by the discriminant analysis in which tests of working memory (digit span backwards), executive function (Rey–Osterreith memory),
and mental speed (digit symbol) determined the classification of the prestroke and poststroke subjects and controls.

It was unexpected that motor speed (finger-tapping dominant, nondominant, and alternating hands) did not distinguish the prestroke and poststroke groups from the control group, because motor slowing is considered to be a common symptom in stroke-related dementia disorders. In concordance with other vascular dementias, verbal episodic memory was not significantly impaired in the pre- and poststroke groups compared with the controls. This is in contrast to its early appearance in Alzheimer disease.

The dementia group demonstrated considerable decline in multiple cognitive domains, which is in accordance with the clinical picture of CADASIL. Interestingly, in 3 tests (SGRC word recognition, finger-tapping dominant hand, and clock-setting) there was no difference compared with the other groups, suggesting that episodic memory, motor speed, and visuospatial ability are relatively spared late in the disease development. The cognitive impairment in the dementia group corresponded to early frontal–subcortical vascular dementia, in which episodic memory is relatively well-preserved, showing predominantly difficulties of retrieval and less decline in encoding and storage. This is in agreement with previous research.

Hypothetically, the pattern of cognitive impairment in various phases of CADASIL can be associated with dysfunction in certain brain regions. The early decline in Rey–Osterreith memory and digit span forwards and backwards may reflect a common underlying insufficiency of working memory and executive function. Experimental studies have demonstrated an association between prefrontal structures and working memory capacity. Deterioration of executive function has also been associated with decreased activity in the prefrontal cortex. Concordantly, the cerebral blood flow in frontal white matter is decreased already in the prestroke phase and degeneration of the white matter is already detectable by MRI. In the progression of the disease, white matter lesions were more extended in the periventricular areas. Lacunar infarcts are also seen in deep white matter and in basal ganglia. These changes are in accordance with the more severe of the cognitive impairment in later phases of CADASIL. The frontal involvement became more accentuated in the poststroke subjects, as indicated by poorer performance in tests measuring mental speed (digit symbol) and set-shifting ability (TMTB, number correct). Also in the subjects with dementia, cognitive impairment still showed predominantly frontal–subcortical involvement, whereas cognitive functions associated with posterior regions were less affected. This type of cognitive decline is also seen in other diseases with frontal subcortical involvement, such as other stroke-related dementias, Huntington disease, and multiple sclerosis.

In previous clinical studies of CADASIL, the focus has mostly been on the poststroke and dementia phases of the disease. Of the 2 studies mentioned, Taillia et al showed results concordant with ours. Their 8 symptomatic (TIA, stroke, migraine or seizures) CADASIL patients without dementia had significantly impaired performance in Wisconsin Card Sorting Test, trail-making test, and Rey–Osterreith copying. Two of them showed cognitive decline without having had TIA or stroke. This is in accordance with the results for our prestroke group. In accordance with our study, the decline began with deterioration in tests associated with executive function, attention, and mental speed. However, the results of Trojano et al differ from those of our prestroke subjects. In a 2-year follow-up study, Trojano et al did not find any significant differences in cognitive performance between the controls and 5 asymptomatic CADASIL patients.

In our study, the groups differed significantly with respect to age and length of education. The age difference between the patient groups is explained by the progressive nature of the disease; therefore, the 2 symptomatic groups are older. The difference in years of education was caused by a cohort effect, with the oldest subjects being less educated as compared with the younger ones. However, when age and education were controlled for, the group differences remained unchanged. Importantly, the prestroke group and controls did not differ for age or education, thus supporting our findings of subclinical cognitive impairment in CADASIL without confounding effects of demographic variables. In our material, frequencies of mood change (39%) and migraine (54%) were somewhat higher than reported earlier. However, none of our subjects had depression according to clinical evaluation at the time of the neuropsychological investigation. Although there is some evidence of cognitive impairment in persons with life-long migraine, in our patients, history of migraine or mood change did not significantly associate with cognitive performance. There was also an overrepresentation of men among our subjects (approximately two thirds), which deviates from that generally seen in CADASIL. The dementia group was small and the subjects were severely impaired and not able to perform all the tests. This may limit the power of comparison with the other groups.

In conclusion, our findings indicate that the cognitive decline in CADASIL begins before the first TIA or stroke. It can be detected as an impaired performance in neuropsychological tests of working memory, executive function, and...
mental speed. The most sensitive tests to detect cognitive decline in CADASIL appear to reflect frontal subcortical involvement. Cognitive impairment begins with deterioration of executive functions and working memory/attention in the asymptomatic prestroke phase, an impairment of mental speed and visuospatial ability are seen in the poststroke phase. Finally, multiple deficits of cognition including verbal functions, verbal episodic memory, and motor speed are observed in the patients who fulfill the criteria of dementia.

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References
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