Neuropsychological Profiles Associated with Subcortical White Matter Alterations and Parkinson’s Disease: Implications for the Diagnosis of Dementia

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Abstract

Despite the emergence of a number of new classification systems, the diagnosis of cerebrovascular dementia remains controversial. Also controversial is the significance of periventricular and deep white matter alterations (WMA) as seen on magnetic resonance imaging (MRI). To further clarify this issue, MRI scans were used to regroup patients clinically diagnosed with Alzheimer’s disease (AD) or subcortical ischemic vascular dementia (IVD) into cohorts presenting with either little versus significant WMA on MRI. These two groups were then compared to demented patients diagnosed with idiopathic Parkinson’s disease (PD) using a comprehensive neuropsychological protocol. Neuropsychological assessment failed to distinguish between patients with PD and significant WMA. By contrast, both of these patient groups exhibited disproportionate impairment on tests of executive systems functioning, whereas patients with little WMA showed greater impairment on tests of declarative memory and semantic knowledge. These findings constitute further evidence that the pattern of cognitive impairment associated with significant WMA is distinctly different when compared to AD. These results are discussed within the context of a growing body of literature.

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suggesting that elements of the underlying neuropathologies in AD and IVD are linked. Implications for the diagnosis of dementia are also discussed. © 2000 National Academy of Neuropsychology. Published by Elsevier Science Ltd.

Since magnetic resonance imaging (MRI) became available, there has been much controversy surrounding the clinical diagnosis of cerebrovascular dementia. Equally as controversial is whether periventricular and deep white matter alterations (WMA) as seen on MRI can be associated with a unique pattern of cognitive impairment, and how the presence of MRI WMA can be integrated into the clinical diagnosis of cerebrovascular dementia.

Early reports tended to downplay the clinical significance of WMA (Hendrie, Farlow, Austrom, Edwards, & Williams, 1989). More recent studies, however, have noted that the neuropsychological impairment sometimes seen in association with WMA is similar to other types of “subcortical” dementing illnesses (Giovannetti-Carew, Lamar, Cloud, & Libon, 1997; Corbett, Bennett, & Kos, 1994; Gupta et al., 1988; Kertesz & Clydesdale, 1994; Lafosse et al., 1997; Libon, Scanlon, Swenson, & Coslett, 1990; Libon, Swenson, Malamut, Coslett, & Sands, 1993; Mendez, Cherrier, & Perryman, 1997; Padovani et al., 1995; Pillon et al., 1993; Starkstein et al., 1996; Villardita, 1993).

Libon et al. (1997) studied a large group of ambulatory demented outpatients. WMA were measured using the 40-point leukoaraiosis (LA) scale (Junque et al., 1990; Pujol et al., 1991). When the relationship between WMA and neuropsychological functioning was assessed with multiple regression analyses, a dissociation was found on tests of verbal declarative memory and executive systems functioning such that patients with ischemic vascular dementia (IVD) obtained lower scores and made more perseverations on executive systems tests, but exhibited less forgetting, obtained higher test scores on delayed free/cued recall and recognition test conditions, and made fewer intrusion errors than AD patients. Libon and colleagues (1997) concluded that the pattern of neuropsychological impairment seen in dementia associated with subcortical WMA was more similar to subcortical dementing illnesses, such as PD and Huntington disease, than cortical dementing illnesses such as AD. Similar findings have recently been reported by Doody, Massman, Mawad, and Nance (1998).

The purpose of the present study was to assess the impact of WMA on neuropsychological functioning independent of clinical diagnosis. To accomplish this goal, the LA scale was used as an independent variable to regroup patients who were clinically diagnosed with either AD or IVD into groups presenting with either minimal-mild WMA or significant WMA. These two groups were then compared to patients with PD, a traditional form of subcortical dementia. To our knowledge, such a comparison has not been reported.

Our first prediction was that there would be little, if any, neuropsychological differences between patients with PD and patients with significant WMA. On the other hand, it was our expectation that both of these patient groups could be dissociated from patients with mild WMA. Thus, our second prediction was that the primary neuropsychological deficits in patients with mild WMA would revolve around prominent encoding deficits on tests of declarative memory, and significant impairment in tests of semantic knowledge. By contrast,
patients with PD and patients with significant WMA would exhibit greater impairment on
tests of executive systems and visuoclonstructional functioning.

1. Methods

1.1. Patients

All patients who were clinically diagnosed with either AD or IVD came from the Crozer Chester Medical Center Alexander Silberman Geriatric Assessment Program Center. All patients were examined by a neurologist, neuropsychologist, psychiatrist, geriatrician, and a social worker. An MRI study of the brain and appropriate diagnostic laboratory studies were obtained to evaluate for reversible causes of dementia. A clinical diagnosis was determined at an interdisciplinary team conference. Based on team diagnosis, 42 patients with probable AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) (McKhann et al., 1984) and 34 patients with probable/possible IVD using the California Criteria (Chui et al., 1992) were studied. In addition to WMA, all patients diagnosed with probable IVD (n = 21) had evidence of two or more ischemic strokes based on their history, neurological examination, and/or a T1-weighted MRI study of the brain. Patients diagnosed with possible IVD (n = 13) presented with either evidence of a single stroke without a clear documented relationship to the onset of their dementia, and/or Binswanger’s disease as defined by Chui et al. (1992). AD and IVD patients with cortical CV As on MRI scans were excluded.

Nineteen demented patients with PD were evaluated from the Crozer Chester Medical Center Parkinson’s Disease and Movement Disorders Clinic (CCMC-PDMDC). The diagnosis of dementia secondary to PD was made by a neurologist based on the presence of cognitive impairment; the presence of three of the four cardinal features of PD: rigidity/postural instability, bradykinesia, resting tremor; and an obvious and sustained response to levodopa or dopamine agonists. All PD patients had been followed for several years at the CCMC-PDMDC. All PD patients were assessed with the Unified Parkinson’s Disease Rating Scale and were taking anti-Parkinsonian medication at the time of testing. MRI scans were obtained on only a portion of our PD patients (n = 8). The LA scale for these patients ranged from 0 to 11 with a mean and standard deviation of 6.2 and 3.7, respectively.

Based on a median split of the LA scale, patients who were clinically diagnosed with either AD or IVD were regrouped into groups with either minimal to mild WMA (n = 37: AD = 30, IVD = 7) or significant WMA (n = 39: AD = 5, IVD = 34). There were no differences among the three groups in age, education, and level of dementia as assessed with the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) or level of depression as measured with the Geriatric Depression Scale (GDS; Yesavage, 1987; see Table 1).

Patients were excluded if there was any history of head injury, substance abuse, major psychiatric disorders (including major depression), epilepsy, or B12, folate, or thyroid deficiency. This information was gathered from a knowledgeable family member.
1.2. Neuropsychological Assessment

The following domains of neuropsychological functioning were assessed:

1.2.1. Motor functioning

Motor functioning was assessed with the Halstead-Reitan Finger Tapping Test (Martivilalta, Reitan, & Wolfson, 1985). Output was calculated based on seven test trials. The dependent variable was the output averaged across each hand.

1.2.2. Executive systems functioning

Executive systems functioning was assessed with the Boston Revision of the Wechsler Memory Scale-Mental Control subtest (WMS-MC; Cloud et al., 1994; Lamar, Giovannetti, & Libon, 1999). In addition to the three tasks that comprise the standard WMS-MC subtest (i.e., counting from 20 to 1, reciting the alphabet, and adding serial 3s; Wechsler, 1945), the Boston Revision of the WMC-MC subtest includes four additional tasks: reciting the months of the year forward and backward, an alphabet rhyming task, which requires patients to identify letters that rhyme with the word “key,” and an alphabet visualization task, which requires patients to provide all block printed letters that contain curved lines. Patients were allowed to work as long as necessary on these tasks provided they were working meaningfully.

The dependent variables derived from this test were two separate accuracy indices (AcI) derived from four of the automatized tasks (i.e., WMS-MC Automatized Index: counting 20–1, alphabet, serial 3s, and months forward) and the three nonautomatized tasks (i.e., WMS-MC Nonautomatized Index: months backward, alphabet rhyming, and alphabet visualization). These AcI were based on the following algorithm: \[ \text{AcI} = (1 - \frac{\text{falsepositive + misses}}{\text{numberpossiblecorrect}}) \times 100. \] This algorithm yielded a percentage score ranging from 0 to 100, such that patients obtaining a score of 100% correctly identified all targets and made no false positive responses or misses. Composite scores assessing performance on both the automatized and nonautomatized mental control tasks were calculated by averaging the AcI for all respective tasks for each patient.

Executive systems functioning was also assessed with tests of letter word list generation (WLG; letters F, A, and S; Spreen & Strauss, 1998) and the Goldberg

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild WMA</th>
<th></th>
<th>Significant WMA</th>
<th></th>
<th>PD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.8 (5.5)</td>
<td>79.0 (6.6)</td>
<td>75.6 (7.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>12.1 (2.5)</td>
<td>11.3 (3.0)</td>
<td>12.0 (4.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>21.4 (3.9)</td>
<td>20.7 (4.4)</td>
<td>21.9 (3.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS</td>
<td>6.0 (3.7)</td>
<td>6.6 (4.6)</td>
<td>6.5 (3.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA scale</td>
<td>4.2 (2.7)</td>
<td>15.4 (5.5)</td>
<td>6.2 (3.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: WMA = periventricular and deep white matter alterations; PD = Parkinson’s disease; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; LA = leukoaraiosis.
Graphical Sequences Test-Dementia Version (GST-D; Goldberg, 1986; Goldberg & Tucker, 1979; Lamar et al., 1997). On the letter WLG test, patients were given 60 seconds to generate words, excluding proper nouns, beginning with a specified letter. The dependent variable was the number of responses summed across each letter. On the GST-D, patients were asked to draw or write easily recognizable geometric objects, shapes, and letters. At various times throughout the test patients are required to switch their mode of output, that is, instead of drawing geometric shapes such as circles, squares, and triangles, subjects were required to write sentences using the words circle, square, and triangle, and so forth. The dependent variable was the total number of perseverations made throughout the test.

1.2.3. Language/semantic functioning

Language/semantic functioning was assessed with the 60-item version of the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) and a test of category WLG (“animals”; Giovannetti-Carew et al., 1997; Monsch et al., 1994). The dependent variable derived from the BNT was the number of correct responses. On the animal WLG test, patients were given 60 seconds to generate exemplars. Three dependent variables were derived from the animal WLG task: the total number of responses excluding perseverations and intrusion errors generated in 60 seconds, the total association index (AI), and the percent of all responses that are semantically clustered (PERCENT). The AI and PERCENT indices are special scoring techniques that measure the semantic integrity between successive responses on the animal WLG. High scores on these measures are believed to reflect generally intact semantic memory stores. Complete details regarding how the AI and PERCENT indices were scored and derived can be found in Giovannetti-Carew et al. (1997).

1.2.4. Visuoconstructional functioning

Visuoconstructional functioning was assessed by asking patients to draw the face of a clock with hands set for “ten after eleven” to command and copy (Goodglass & Kaplan, 1983). Following procedures described by Libon, Malamut, Swenson, and Cloud (1996), errors related to graphomotor impairment, errors in hand/number placement, and errors related to executive control impairment were scored as either 1 (i.e., present) or 0 (i.e., absent). Separate tallies were computed for each of the three types of errors in both clock-drawing conditions.

1.2.5. Declarative memory

Declarative memory was assessed with the nine-word dementia version of the California Verbal Learning Test (CVLT; Delis, Kramer, Ober, & Kaplan, 1987; Libon, Mattson, et al., 1996). For the present research, four CVLT indices were analyzed: immediate free recall was assessed by tallying the total number of words recalled from List A Trials 1–5; intrusions were measured by calculating the number of cued recall responses that were extra list responses; a savings index was derived by calculating the percent of words recalled on List A Trial 5 that were recalled on the delayed free recall condition; and recognition memory was assessed with the recognition discriminability index. These indices were chosen because previous research with patients with AD and IVD has shown that these indices load on
separate factors and, therefore, appear to assess different aspects of declarative memory (Libon, Mattson, et al., 1996).

1.3. MRI

All MRI scans were conducted on a Siemens 1.5 Tesla machine. Both T1- (TR–500 ms, TE–15 ms) and T2- (TR–4000 ms, TE–90 ms) weighted studies were obtained. The severity of WMA was quantified using the 40-point LA scale described by Junque and colleagues (Junque et al., 1990; Capdevila et al., 1991). This scale divides each hemisphere into five areas: the frontal centrum semiovale, the parietal centrum semiovale, the white matter around the frontal horns, the white matter around the body of the lateral ventricles, and the white matter around the atrium and occipital horns. The severity of WMA was then graded from 0 to 4 and then summed across all 10 areas. LA scores were calculated by a board-certified neuroradiologist who was blind to all clinical information regarding these patients. LA scores obtained from our patients with AD and IVD were normally distributed (kurtosis $\hat{\gamma} = -0.537$, skewness $\hat{\beta} = 0.508$), and ranged from 1 to 26 with a mean and standard deviation of 9.97 and 6.86, respectively. The median and mode of the LA scale were 10.0 and 3.0, respectively. In previous research, the interrater reliability in calculating the LA scale by two board-certified neuroradiologists was very robust ($r = 0.93$, $p < .001$; Libon et al., 1998). Also, the mean and standard deviation for the LA among patients with AD and IVD are similar to patients with PD.

1.4. Statistical Analysis

The effect of group, that is, severity of WMA on neuropsychological functioning was analyzed with a series of multivariate analyses of variance (MANOVAs). In these analyses, the variable group (i.e., mild WMA, significant WMA, PD) was the independent variable,

<table>
<thead>
<tr>
<th>Executive systems functioning test</th>
<th>Mild WMA ($M$) ($SD$)</th>
<th>Significant WMA ($M$) ($SD$)</th>
<th>PD ($M$) ($SD$)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC autom AcI$^a$</td>
<td>97.9 (5.7)</td>
<td>93.3 (10.1)</td>
<td>90.9 (8.5)</td>
<td>$F(2, 83) = 5.14$, $p &lt; .008$</td>
</tr>
<tr>
<td>MC nonautom AcI$^b$</td>
<td>69.6 (16.8)</td>
<td>54.6 (25.6)</td>
<td>52.3 (21.7)</td>
<td>$F(2, 60) = 4.15$, $p &lt; .020$</td>
</tr>
<tr>
<td>Letter ($F, A, S$) WLG$^c$</td>
<td>23.6 (9.5)</td>
<td>16.4 (8.4)</td>
<td>17.7 (9.8)</td>
<td>$F(2, 76) = 5.06$, $p &lt; .009$</td>
</tr>
<tr>
<td>GST-D$^d$</td>
<td>9.9 (7.9)</td>
<td>11.8 (10.9)</td>
<td>17.0 (11.5)</td>
<td>$F(2, 68) = 2.81$, $p &lt; .067$</td>
</tr>
</tbody>
</table>

Note: WMA = periventricular and deep white matter alterations; PD = Parkinson’s disease; MC autom AcI = automatized mental control accuracy index; MC nonautom AcI = nonautomatized mental control accuracy index; WLG = word list generation; GST-D = Graphical Sequences Test-Dementia Version; M = mild; S = significant; ANOVA = analysis of variance.

$^a$ MC autom AcI: WMA-M vs. WMA-S, $t(66) = 2.44$, $p < .017$; WMA-M vs. PD, $t(48) = 3.99$, $p < .001$.

$^b$ MC nonautom AcI: WMA-M vs. WMA-S, $t(44) = 2.84$, $p < .015$; WMA-M vs. PD, $t(39) = 2.87$, $p < .007$.

$^c$ Letter ($F, A, S$) WLG: WMA-M vs. WMA-S, $t(58) = 3.08$, $p < .003$; WMA-M vs. PD, $t(48) = 2.12$, $p < .040$.

$^d$ GST-D: WMA-M vs. PD, $F(2, 72) = 6.92$, $p < .002$. 
and the various neuropsychological variables were the dependent variables. All univariate statistical information is contained in Tables 2 through 5. Because of the large number of follow-up comparisons, significance was set at $p < .01$.

2. Results

2.1. Motor and Executive Systems Functioning

On the finger tapping test, the univariate analysis of variance (ANOVA) failed to reach significance. In addition, none of the follow-up comparisons were significant. With respect to the executive systems tests (Table 2), because some measures were added after the research protocol was initiated, not all patients were administered all of the executive systems tests described above. Thus, each executive systems test was analyzed separately using ANOVA followed by individual $t$-tests. As predicted, on many tests, patients with mild WMA obtained better scores than patients with significant WMA and PD. In addition, there were no differences on any test between patients with significant WMA and PD. This pattern was obtained on the MC-automatized Acl, the MC-nonautomatized Acl, and on the letter ($F,A,S$)

Table 3

<table>
<thead>
<tr>
<th>Visuocnonstructional functioning test (clock drawing)</th>
<th>Mild WMA</th>
<th>Significant WMA</th>
<th>PD</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Command ($a$) (errors)</td>
<td>2.3 (1.1)</td>
<td>3.4 (1.3)</td>
<td>4.1 (1.5)</td>
<td>$F(2, 84) = 12.92$, $p &lt; .001$</td>
</tr>
<tr>
<td>Copy ($b$) (errors)</td>
<td>1.0 (.86)</td>
<td>2.6 (1.6)</td>
<td>3.5 (1.7)</td>
<td>$F(2, 84) = 24.90$, $p &lt; .001$</td>
</tr>
</tbody>
</table>

Note: WMA = periventricular and deep white matter alterations; PD = Parkinson’s disease; ANOVA = analysis of variance; M = mild; S = significant.

$a$ command: WMA-M vs. WMA-S, $t(69) = 3.81$, $p < .001$; WMA-M vs. PD, $t(50) = 5.00$, $p < .001$.

$b$ copy: WMA-M vs. WMA-S, $t(70) = 5.35$, $p < .001$; WMA-M vs. PD, $t(52) = 7.12$, $p < .001$.

and the various neuropsychological variables were the dependent variables. All univariate statistical information is contained in Tables 2 through 5. Because of the large number of follow-up comparisons, significance was set at $p < .01$.

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Table 4

<p>| Naming/semantic knowledge test scores: means and (standard deviations) $b$ |
|---------------------------------------------------|----------|-----------------|----|-------|</p>
<table>
<thead>
<tr>
<th>Naming/semantic functioning test</th>
<th>Mild WMA</th>
<th>Significant WMA</th>
<th>PD</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Naming Test</td>
<td>34.4 (11.1)</td>
<td>34.0 (11.2)</td>
<td>38.8 (11.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Category (animal) WLG</td>
<td>7.5 (2.8)</td>
<td>7.1 (2.9)</td>
<td>8.4 (5.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Category (animal) WLG AF</td>
<td>2.6 (.96)</td>
<td>3.4 (.76)</td>
<td>3.3 (.81)</td>
<td>$F(2, 72) = 6.92$, $p &lt; .002$</td>
</tr>
<tr>
<td>Category (animal) WLG PERCENT</td>
<td>45.0 (31.3)</td>
<td>75.3 (20.2)</td>
<td>66.4 (25.2)</td>
<td>$F(2, 72) = 9.90$, $p &lt; .001$</td>
</tr>
</tbody>
</table>

Note: WMA = periventricular and deep white matter alterations; PD = Parkinson’s disease; WLG = word list generation; AI = association index; PERCENT = percent in cluster index; ANOVA = analysis of variance; M = mild; S = significant.

$a$ WLG AI: WMA-M vs. WMA-S, $t(56) = 3.38$, $p < .001$; WMA-M vs. PD, $t(46) = 2.61$, $p < .012$.

$b$ WLG PERCENT: WMA-M vs. WMA-S, $t(56) = 4.33$, $p < .001$; WMA-M vs. PD, $t(46) = 2.45$, $p < .018$. 
WLG test. On the GST-D, only the PD group made more perseverations than patients with mild WMA.

2.2. Visuoconstruction

The performance on tests of clock drawing (Table 3) was very similar to the results obtained on executive systems tests. The multivariate test for group was highly significant, $F(4, 164) = 12.83, p < .001$, as were both univariate tests. As with performance on tests of executive systems functioning, the drawings produced by patients with mild WMA were superior in all respects when compared to all other patients, but the drawings produced by patients with significant WMA and PD were equally impaired on both the command and copy.

2.3. Naming and Semantic Knowledge

The four dependent variables derived from the BNT and animal WLG test were analyzed in a single MANOVA (Table 4). The multivariate effect for group was significant, $F(8, 136) = 3.24, p < .002$. Only the univariate ANOVAs for the animal WLG AI and PERCENT indices were significant. Follow-up comparisons indicated that there were no differences between patients with significant WMA and PD on either of these measures, but both groups produced higher AIs, suggesting relatively intact semantic knowledge, and generated more words within semantic cluster than patients with mild WMA.

2.4. Memory and Learning

Finally, on the CVLT, the multivariate effect for group was significant, $F(8, 162) = 3.55, p < .001$, as were the univariate comparisons for the savings score, cued recall intrusions, and the delayed recognition discriminability index (Table 5). As on the indices derived from the animal WLG test, there were no differences between patients with significant WMA and PD.
on any of the scores derived from the CVLT, but both of these groups produced better savings and recognition discriminability test scores, indicating some relative capacity to learn and retain new information, than patients with mild WMA.

3. Discussion

3.1. Review of Findings

Despite newly proposed criteria, the clinical diagnosis of cerebrovascular dementia is controversial, and the exact relationship between periventricular and deep WMA and the clinical diagnosis of cerebrovascular dementia, remains unclear (Chui et al., 1992; Roman et al., 1993; Wetterling, Kanitz, & Borgis, 1994). We sought to clarify this problem by reconstituting our patients based on the severity of their WMA using the LA scale, which has previously been shown to be psychometrically reliable and valid (Libon et al., 1998). Using this methodology, three important findings emerged.

First, our neuropsychological protocol failed to distinguish between patients with significant WMA from demented patients with idiopathic PD. Consistent with past research, both of these groups exhibited differentially worse performance on most tests of executive systems functioning and visuoconstruction. By contrast, on tests of memory, these patients made fewer semantic intrusion errors and produced higher savings and recognition memory test scores, suggesting a greater capacity to learn new information.

Second, the neuropsychological profile of patients with minimal to mild WMA was striking with respect to low savings and recognition memory test scores as well as the high number of intrusion errors produced on tests of memory. This test performance is consistent with a primary anterograde amnesia at the encoding level. This group also produced low AI and PERCENT test scores on the animal WLG task. Such findings are suggestive of degraded semantic memory stores.

Third, our methodology underscores the utility of the LA scale as a means to operationally define the severity of WMA in patients with dementia, rather than using a 3–4 ordinal scale, which has been the more common practice. In sum, these findings suggest that the pattern of neuropsychological deficits associated with WMA is similar to other subcortical dementing illnesses such as PD and Huntington disease (Butters et al., 1988; Delis et al., 1991; Hodges, Salmon, & Butters, 1990; Kramer et al., 1988; Massman, Delis, Butters, Levin, & Salmon, 1990; Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992).

3.2. Subcortical WMA and the Clinical Diagnosis of Dementia

The results of the current study indicate that moderate to severe WMA as seen on MRI scans is associated with a pattern of neuropsychological deficits distinctly different from the pattern of neuropsychological impairment often associated with AD. Does this mean that an MRI profile of WMA is sufficient to diagnose the presence of a cerebrovascular dementia? Doody and colleagues (1998) have suggested that the underlying neuropathological mechanisms associated with WMA seen in AD patients might be different when compared to
patients with cerebrovascular dementia. Thus, at the present time the answer to this question is, at best, unclear.

Nolan, Lino, Seligmann, and Blass (1998) described a series of 87 dementia patients who came to autopsy. While alive, 26 of these patients were given a clinical diagnosis of either cerebrovascular dementia or cerebrovascular dementia with AD. Yet, upon autopsy, cerebrovascular disease was not found to be the sole cause of dementia in any of these patients. Seven patients, however, were found to meet criteria for both cerebrovascular dementia and AD.

The clinical diagnosis for cerebrovascular dementia in this series of patients was made based on NINDS-AIREN criteria. These criteria primarily rely on obtaining a history of a temporal relationship between a decline in activities of daily living and cognitive functioning and the occurrence of a stroke. Indeed, from the description provided by the authors, their patients primarily suffered from either large cortical or subcortical lacunar infarction. No mention is made of either the severity, or even the presence of periventricular and deep white matter disease in their patients. In addition, no neuropsychological test data was reported. An assessment of neuropsychological strengths and weaknesses at the time the original clinical diagnosis was made might have been helpful in determining whether the cognitive disabilities that were present were primarily due to cerebrovascular disease or AD.

Victoroff, Mack, Lyness, and Chui (1995) obtained autopsies on 196 patients with dementia. Among this group, 116 patients were diagnosed with probable AD (McKhann et al., 1984). Yet, 100 of these patients (86%) were found to have evidence of other possible dementing disorders, including cerebrovascular disease. Similar to the study of Nolan and colleagues (1998), there is no mention of a relationship between clinical or neuropathological diagnosis and subcortical WMA. In addition, no neuropsychological information is reported.

Bowler, Munoz, Merskey, and Hachinski (1998) studied a group of 122 patients with dementia. Of this group 81% of patients were diagnosed clinically with AD. However, upon autopsy, only 44% of cases had pure AD without any other coexisting causes of dementia.

3.3. MRI—Subcortical WMA, AD, and the Diagnosis of a Mixed Dementia

The findings reported by Victoroff et al. (1995) and Bowler et al. (1998) suggest that large numbers of demented patients might be suffering from a mixed dementing illness. A diagnosis of a mixed dementia is usually applied when a dementing illness is believed to be caused by multiple disease processes. Traditionally, these multiple disease processes have been viewed as independent phenomena. Yet, there is a growing literature to suggest that AD and cerebrovascular dementia may share a common etiology. For example, several studies found an association between the APOE 4 allele and atherosclerosis in patients with both AD and cerebrovascular dementia (Hofman et al., 1997; Slooter et al., 1997, 1998). Zarow, Barron, Chui, and Perlmutter (1997) speculated that there may be a relationship between capillary microangiopathy and production of neurofibrillary tangles and senile plaques in AD. Skoog (1998) believes that AD and cerebrovascular dementia may share similar risk factors and etiologic pathways.
Hachinski (1994) recently argued for a total reappraisal of the concept of “vascular dementia.” Hachinski (1994) suggested that cerebrovascular alterations may, in fact, be the single most prevalent cause of cognitive impairment in the world. Nonetheless, Hachinski (1994) believes that the concept of vascular dementia as an idiopathic cause of dementia may be too generic and nonspecific because of the potential overlap between the causes of cerebrovascular disorders and other disease processes. Moreover, Hachinski (1994) points out that the medical conditions that are associated with cerebrovascular alterations can be identified and treated. For these reasons Hachinski (1994) proposed the term vascular cognitive impairment as a more accurate way to describe the association between neuro-psychology deficits and cerebrovascular alterations. Hachinski (1994) has proposed that greater efforts should be made to identify patients who are at risk for vascular dementia. In so doing, one might be able to describe the precise cognitive impairment associated with specific vascular risk factors and/or vascular alterations as operationalized with neuroimaging techniques. Appropriate preventive measures can then be implemented.

We acknowledge that a weakness of the present research is that not all of our PD patients had MRI studies. Thus, we cannot say with 100% certainty that cerebrovascular alterations did not influence our results. Another weakness of the present research is our lack of neuropathological information regarding our patients. Thus, it is certainly possible that some of our patients for whom we diagnosed as IVD might also meet criteria for AD. We believe, however, that the possibility that patients may meet criteria for IVD as well as AD only serves to enlarge, rather than diminish, the importance of cerebrovascular disease in the diagnosis of dementia for several reasons.

First, the differential patterns of neuropsychological impairment on tests of executive system/visuoconstructional functioning versus tests of declarative memory and semantic knowledge has tremendous clinical importance with respect to treatment and in counseling families on how they should interact with their family member. For example, Ryan et al. (in press) studied a large group of dementia patients diagnosed with either AD or subcortical IVD associated with WMA. They found that, in patients with mild dementia (i.e., MMSE > 22), performance on tests of executive functions was the best predictor of decrements in ADL functioning.

Second, to date, the recruitment of patients to participate in drug trials for the treatment of dementia has tended to focus on whether patients meet a broad criterion such as that proposed by the NINCDS-ADRDA or NINCDS-AIREN consensus panels. If there are significant numbers of patients whose dementia are due to an admixture of neuropathologies, combination therapies might be more appropriate.

In sum, as individuals live well into their 9th decade, the severity and incidence of vascular disease may be expected to rise. Thus, there is a pressing need to disambiguate the relationship between alterations in cognitive state and cerebrovascular disease. Based on the findings reported above, we believe that our results constitute further evidence that cognitive impairment associated with WMA can be viewed within the context of a subcortical dementing syndrome. More important, greater knowledge is necessary regarding how multiple neuropathologies interact with respect to the etiology of dementing syndromes and their corresponding changes in ADL as well as neuropsychological functioning. Therefore, the value of neuropsychological assessment may not be, so much, to merely classify
patients as suffering from one type of dementia versus another; but as a means to assess the relative contributions of various neuropathological substrates in dementia.

References


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