Differential Impact of Lacunes and Microvascular Lesions on Poststroke Depression

Micaela Santos, MD; Gabriel Gold, MD; Enikő Kövari, MD; Francois R. Herrmann, MD, MPH; Vasilis P. Bozikas, MD; Constantin Bouras, MD; Panteleimon Giannakopoulos, MD

Background and Purpose—Previous studies have postulated that poststroke depression (PSD) might be related to cumulative vascular brain pathology rather than to the location and severity of a single macroinfarct. We performed a detailed analysis of all types of microvascular lesions and lacunes in 41 prospectively documented and consecutively autopsied stroke cases.

Methods—Only cases with first-onset depression <2 years after stroke were considered as PSD in the present series. Diagnosis of depression was established prospectively using DSM-IV criteria for major depression. Neuropathological evaluation included bilateral semiquantitative assessment of microvascular ischemic pathology and lacunes; statistical analysis included Fisher exact test, Mann-Whitney U test, and regression models.

Results—Macroinfarct site was not related to the occurrence of PSD for any of the locations studied. Thalamic and basal ganglia lacunes occurred significantly more often in PSD cases. Higher lacune scores in basal ganglia, thalamus, and deep white matter were associated with an increased PSD risk. In contrast, microinfarct and diffuse or periventricular demyelination scores were not increased in PSD. The combined lacune score (thalamic plus basal ganglia plus deep white matter) explained 25% of the variability of PSD occurrence.

Conclusions—The cumulative vascular burden resulting from chronic accumulation of lacunar infarcts within the thalamus, basal ganglia, and deep white matter may be more important than single infarcts in the prediction of PSD. (Stroke. 2009;40:3557-3562.)

Key Words: behavioral neurology ■ brain ischemia ■ cerebral infarct ■ neuropathology

According to the World Health Organization, stroke is the most common severe neurological disorder and the third leading cause of mortality among adults.1 A recent review reported a strikingly high frequency of depressive symptoms in 33% of all stroke survivors at any time during the follow-up.2 In addition, stroke survivors have a 6-fold higher risk for clinically overt depression, even ≥2 years after index stroke compared to age-matched controls.3 Proponents of a neuroanatomical model believe that poststroke depression (PSD) is related to the location of ischemic lesions, whereas supporters of a psychological model maintain that PSD is the result of the psychological adjustment to the neurological deficits and their consequences.4,5 Early animal data in this field revealed an association between the laterality of ischemic damage and both brain catecholamine concentration and behavioral patterns in rats, indicating that ischemic damage may induce depression via the disruption of biogenic amine pathways.6 Later, several neuroimaging studies have suggested a link between PSD and macrovascular lesions in the left frontal lobe, bilateral prefrontal cortex, left anterior and posterior areas, and right occipital lobe.7–10 In a recent study, Hama et al11 reported that the severity of affective depression was associated with left frontal lobe lesions, whereas apathetic depression was mostly related to basal ganglia damage. Other areas that have been recently identified as independent determinants of PSD are the left genu of the internal capsule and bilateral pallidum.12 However, other studies failed to identify such relationships,13,14 and several systematic reviews did not confirm the hypothesis that PSD is influenced by the site of the cerebral lesion.2,4,15 The lack of uniformity in definition and assessment of depression, sampling differences (ie, inpatient vs community-based selection), variable assessment intervals from acute to chronic stroke, and types of lesions considered may explain this discrepancy. We previously performed a neuropathological study to assess the relationship between the development of diffuse or focal macrovascular pathology and the occurrence of clinical depression in the first 2 years after index stroke in elderly
patients without lifetime history of depression.16 Our results did not reveal a significant impact of these neuropathological parameters on PSD occurrence raising further doubts about the validity of the neuroanatomical model in this disorder.

Paralleling the debate on the origin of PSD, the abundant literature on vascular depression pointed to the possible role of small vascular and microvascular chronic pathology in triggering depressive episodes.17–23 In a similar vein, Brodaty et al13 postulated that “depression after stroke may be related to cumulative vascular brain pathology rather than side and severity of single stroke.” This vascular burden in the aging brain depends on the progressive accumulation of lacunes and microvascular lesions that are not or are barely identified with classical neuroimaging methods. To address the role of progressive ischemic damage in PSD, we performed an exhaustive analysis of these lesion types in consecutively autopsied stroke patients with and without major depression after stroke.

Subjects and Methods

Patients

The initial autopsy series included 960 patients who underwent autopsy at the Geriatric Hospital of the University of Geneva between 1996 and 2003. Three criteria were used to define the final sample. First, clinical diagnosis of stroke was based on the presence of focal neurological deficits of acute onset and supportive MRI. Second, patients were included only if the stroke could be confirmed pathologically by the presence of single or multiple cortical macroinfarcts and if poststroke survival was at least 1 month. Third, only cases with first-onset depression <2 years after stroke were considered in the present series. All patients with clinical evidence of concurrent dementia as well as those with substantial Alzheimer disease pathology (Braak stages 4, 5, and 6), Lewy bodies, Pick bodies, α-synuclein, and ubiquitin-positive inclusions, as well as argyrophilic grains were also excluded. From the initial 960 autopsy cases, 125 presented with clinical signs of stroke. In 109 cases, single or multiple macroinfarcts were confirmed (with poststroke survival >1 month). Patients with history of psychiatric disorders such as lifetime history of depression (4 cases), substance abuse/dependence (3 cases), other neurological diseases such as Parkinson disease (8 cases), primary or metastatic brain tumors (4 cases), inflammation (3 cases), or trauma (5 cases), as well as aphasia (10 cases) and dystasia (3 cases), preventing reliable assessment of depression, clinical evidence of DSM-IV dementia,24 and those with substantial Alzheimer disease pathology (Braak stages 4, 5, and 6; 25 cases), Lewy body disease (2 cases), and frontotemporal dementia with ubiquitin-positive inclusions (1 case) were also excluded.

The final series included 41 autopsied stroke cases. Twenty patients had PSD and 21 did not. The overall cognitive status of all cases was assessed using the Clinical Dementia Rating (CDR) scale.25 Among PSD cases, 12 had CDR score 0, 4 had CDR score 0.5, and 4 had CDR score 1. In the non-PSD group, 17 had CDR score 0, 2 had CDR score 0.5, and 2 had CDR score 1. The clinical diagnosis of depression subtypes was established prospectively using DSM-IV criteria for major depression.26 Because the neuroanatomical model of PSD mainly refers to this subtype of depression, and to discuss our findings in the light of previous neuroimaging studies in this field, we decided to exclude cases with minor.26 The occurrence of depressive symptoms was systematically assessed in poststroke survivors by the medical staff, twice per week. In all cases with suspected depression a consultation by a liaison psychiatrist was requested. The liaison psychiatry staff consisted of 2 certified psychiatrists with extensive experience in old age psychiatry. Patients were interviewed for symptoms of major depression. This included the presence of depressed mood, anhedonia, sleep disturbances, weight and appetite loss, decreased energy, low self-esteem, inability to concentrate, suicidal ideation, and anxiety. The clinician also noted the presence of psychomotor agitation or retardation. Each consultation was followed by a written report defining the presence/absence of a DSM-IV diagnosis of mental illness, lifetime occurrence of depression, and treatment proposal. Moreover, all patients with PSD were followed-up by 1 of the liaison psychiatrists during their entire hospital stay. All procedures involving the use of postmortem human brain were conducted with the written consent of the next of kin and were approved by the relevant ethics committee at the University Hospitals of Geneva.

Tissue Processing

Brains obtained at autopsy were fixed in 15% formaldehyde for at least 4 weeks and cut into 1-cm-thick coronal slices and examined for macroscopic vascular lesions including brain infarcts, cerebral hemorrhage, and lacunes (Figure 1A). These latter were defined as small definitive ischemic necrosis, ranging from 1 mm to 1.5 cm, located in the white matter or basal ganglia and thalamus. Macroscopically, they were identified on macroscopic examination and controlled on Luxol van Gieson-stained coronal sections. Histologically, lacunes were recognized as irregular cavities containing parenchymal fragments and lipid-laden or hemosiderin-laden macrophages.27 To assess diffuse white matter and periventricular demyelination, whole coronal sections at the level of the anterior commissure were embedded in paraffin, cut into 20-μm-thick sections, and stained with Luxol van Gieson (Figure 1B). Cortical microinfarcts were defined as small ischemic necroses in the cerebral cortex seen only on histological examination. They tend to occur in the border zone between the 3 main arteries, giving—if widespread—the appearance of “granular cortical atrophy”28 (Figure 1C). To visualize these lesions, 1-cm-thick tissue blocks from the anterior hippocampus, inferior temporal cortex (area 20), frontal cortex (area 9), and parietal cortex (area 40) bilaterally were cut into 20-μm-thick serial sections of ≈3×2 cm. Every 50 sections, 1 section was stained with Globus silver impregnation for a total of 10 sections per area, which were subsequently considered for semiquantitative analysis.29 (Figure 1D). To visualize Alzheimer Disease–type lesions, Pick bodies, ubiquitin-positive inclusions of frontotemporal dementia, argyrophilic grains and Lewy bodies, additional blocks from hippocampus, temporal, frontal, parietal, and occipital cortex were embedded in paraffin, and 12-μm-thick sections were processed with highly specific and fully characterized antibodies to the phosphory-
lation-dependent tau AT8 (1/1000; Innogenetics),30 core amyloid β protein A4 4G8 (1/1000; Signet Laboratories),31 α-synuclein (1/20 000 courtesy of Dr Y. Charnay) and ubiquitin (1/100; Sigma) as previously described.29

Lacunes and cortical microinfarcts were assessed semiquantitatively in 10 sections per area using the following score: 0 (absence of such lesions), 1 (<3 lesions per slide), 2 (3–5 lesions per slide), and 3 (>5 lesions per slide). For each of these lesions, a total score was obtained by adding the scores of each area. The severity of diffuse white matter and periventricular demyelination in each hemisphere was estimated in Luxol van Gieson–stained sections using the following rating scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. Scores for each hemisphere were added to obtain a total score. The same semiquantitative assessment of lacunes and microvascular pathology has already been used in our previous studies with a high inter-rater reliability.32,33 In the present study, 2 independent investigators (E.K. and M.S.), blind to the clinical findings, assessed the severity of vascular pathology with a high inter-rater reliability (κ values ranging from 0.88–0.95 for the severity score of the different neuropathological variables). In case of disagreement between the 2 raters, the final determination was defined in a consensus meeting between both raters.

Statistical Analysis

Group comparisons were conducted using Fisher exact test for dichotomous variables. This procedure is appropriate to examine the significance of the association between 2 binary variables in a 2×2 contingency table, when the sample size is small.34 The Mann-Whitney U test was used for ordinal variables and t tests for continuous variables. Logistic regression was used to evaluate the strength of the association. Most importantly, its presence had no effect on the poststroke survival period. No non-PSD case received psychotropic medication. The distribution of pathologically confirmed microinfarcts was summarized in the Table. Importantly, microinfarct site was not related to the occurrence of PSD for any location (Fisher exact test, probability values ranging from 0.07–1, depending on the site; Table). In contrast to recent neuroimaging data,35 antidepressant medication was not associated with the severity of cortical microinfarcts, periventricular, and deep white matter demyelination. Most importantly, its presence had no effect on the combined lacune score (Mann-Whitney U test, z = -0.121; P = 0.90). Considering the 5 missing values as all untreated (Mann-Whitney U test, z = 0.079; P = 0.94) or all treated (Mann-Whitney U test, z = -0.327; P = 0.74) did not change the lack of association between neuropathological parameters and antidepressant medication.

Regional Distribution of Small Vascular and Microvascular Pathology in PSD Cases

In a first analysis we determined whether the simple presence of small vascular lesions was related to the occurrence of PSD. This proved to be the case for thalamic and basal ganglia lacunes bilaterally, as well as for deep white matter lacunes in the right hemisphere, which significantly occurred

Table. Regional Distribution of Vascular Pathology in PSD Cases

<table>
<thead>
<tr>
<th>Side</th>
<th>PSD, N (%)</th>
<th>Non-PSD, N (%)</th>
<th>t Test</th>
<th>Fisher Exact, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>21</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Age at stroke, yr</td>
<td>77.2±9.9</td>
<td>77.7±11.1</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Poststroke survival, yr</td>
<td>2.8±3.4</td>
<td>5.4±7.6</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Macroinfarcts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal lobe Left</td>
<td>2 (10)</td>
<td>8 (38)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>6 (30)</td>
<td>5 (24)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Parietal lobe Left</td>
<td>5 (25)</td>
<td>9 (43)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>11 (55)</td>
<td>11 (52)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe Left</td>
<td>4 (20)</td>
<td>4 (19)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8 (40)</td>
<td>8 (38)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Occipital lobe Left</td>
<td>1 (5)</td>
<td>6 (29)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>3 (15)</td>
<td>7 (33)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia Left</td>
<td>7 (35)</td>
<td>2 (10)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>4 (20)</td>
<td>2 (10)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Lacunes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus Left</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>4 (20)</td>
<td>0 (0)</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia Left</td>
<td>13 (65)</td>
<td>6 (29)</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8 (40)</td>
<td>2 (10)</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Deep white matter Left</td>
<td>5 (25)</td>
<td>4 (20)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8 (40)</td>
<td>2 (10)</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Demyelination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periventricular Left</td>
<td>5 (25)</td>
<td>5 (24)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Deep white matter Left</td>
<td>15 (75)</td>
<td>16 (76)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>15 (75)</td>
<td>15 (71)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Cortical microinfarcts Left</td>
<td>7 (35)</td>
<td>5 (24)</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>11 (55)</td>
<td>11 (52)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

PSD, poststroke depression; non-PSD, without poststroke depression; DF, Degree of freedom.
Lacune Score Impact on PSD Occurrence

Using the semiquantitative ischemic scores described, we were also able to explore the relationship between the severity of lacunes and microvascular pathology and the presence of PSD as the scores provide more information than the simple recording of the presence or absence of lesions. This analysis confirmed that basal ganglia and thalamic lacunes were the best neuropathological correlates of PSD; the higher the lacunar scores in these areas, the greater the risk of PSD (Mann-Whitney U test, z = -3.129; P = 0.002 for basal ganglia and for thalamic lacunes). Interestingly, semiquantitative severity scores for white matter lacunes were also related to the occurrence of PSD (Mann-Whitney U test, z = -2.211; P = 0.03). This was not the case for microinfarcts nor for diffuse or periventricular white matter demyelination (Mann-Whitney U test, z = -0.425, probability values of 0.67, z = -0.705, 0.48, and z = 0.087, 0.93, respectively). The combined brain lacune score (thalamic plus basal ganglia plus deep white matter) was strongly related to the occurrence of PSD (P < 0.001) and explained 25% of the variability of this occurrence. In multivariate models adjusting for CDR scores, there was no significant association between this variable and occurrence of PSD (P = 0.87 for CDR 0.5 vs CDR 0, P = 0.94 for CDR 1 vs CDR 0). In regression models, basal ganglia and thalamic lacunes explained 20% of the variability in PSD occurrence, whereas deep white matter lacunes added an extra 5%. Importantly, the combined brain lacune score distinguished stroke cases with PSD from those without PSD with only minimal overlap (Figure 2).

Discussion

The present data reveal a significant relationship between the presence of lacunes and the occurrence of PSD, providing strong evidence that biological factors are an important determinant of PSD. Four limitations should, however, be taken into account. First, and as is the case for all neuropathological studies, autopsy-related biases cannot be formally ruled out. Similarly, the exclusion of patients with severe aphasia may also decrease the representativeness of our cohort. However, one should consider that the study hospital covers the entire Geneva catchment area and is characterized by unusually high autopsy rates ranging from 25% to 32%. Second, the temporal relationship between lacune formation and PSD cannot be established on the basis of postmortem observations. We thus cannot exclude that lacune formation may have taken place in part during the relatively short poststroke survival period resulting in a lacune score that does not precisely reflect the vascular burden at the time of the index stroke. Third, the number of autopsy cases with PSD was not sufficient to determine whether the location of microvascular lesions and lacunes modulated their effect on mood and affect. Thus, it is still conceivable that the presence of microvascular lesions in neocortical areas predominantly involved in mood regulation and associated behaviors (ie, cingulate and orbitofrontal cortex) may increase the risk for PSD. Finally, lacunes were assessed with a semiquantitative severity scale without taking into account their volume. Interestingly, a very recent study demonstrated that the volume of lacunes in cases with hereditary vascular pathology can be evaluated using appropriate MRI sequences. Future studies comparing the present findings with volumetric MRI measurements of subcortical lacunes could be of interest to further explore our hypothesis.

Despite the fact that lacunes are found in 10% to 30% of elderly individuals with 6% of newly affected cases annually, their clinical significance is still unclear. They are thought to be clinically silent in the majority of elderly cases but they can also affect cognition, particularly in the presence of associated Alzheimer disease neuropathology, via the possible disruption of subcortical-frontal circuits. Most previous neuroimaging studies reported a close link between small subcortical infarcts and PSD without making an explicit mention of lacunes. Only 1 case report pointed to the link between lacunar infarcts of the left internal capsule and depression. Our findings indicate that lacunes in the basal ganglia and thalamic nuclei can increase the risk of clinically overt major depression in the poststroke period, possibly via the interruption of the monoaminergic routes that connect the brain stem with the cerebral cortex. Moreover, the severity of lacune formation in deep white matter was an independent correlate of PSD in the present series implying that progressive damage of cortico-cortical circuits may also contribute to the pathogenesis of this disorder.

Four additional observations support the relevance of lacunes in the context of PSD pathogenesis. Their effect on depression persisted after adjustment for the presence of modest cognitive decline (CDR scores 0.5–1). Moreover, the described relationship seems to be specific to lacunes because both macroinfarcts and microvascular lesions such as cortical microinfarcts or gliosis did not determine the occurrence of major depression after stroke. Macroinfarcts in basal ganglia were more frequent in PSD compared to non-PSD cases, but
this difference did not reach statistical significance. Although this may be related to the relatively limited sample size, it is important to note that these results are consistent with a previous autopsy study of 95 cases, for which we also reported no relationship between the presence of microinfarcts in this area and PSD. The combined lacune score, which takes into account the global severity of lacune formation both in deep white matter and subcortical nuclei, revealed only limited overlap between patients with and without depression. Most importantly, this score predicts 25% of the variability in the occurrence of PSD. Although this percentage may appear modest, one should keep in mind that it is comparable or superior to what has been reported for widely used neuropathological staging systems such as Braak NFT and Aβ staging in Alzheimer Disease. This percentage is also clearly higher than that of the cognitive variability explained by lacunes in cases with and without Alzheimer Disease lesions. Qualitatively, these findings imply that lacunes may represent a common denominator between PSD and vascular dementia. In contrast, and as already proposed in previous studies, elderly subjects with diffuse formation of microinfarcts in neocortical association areas may be more prone to cognitive decline.

The role of lacunes in the pathogenesis of late-onset mood disorders is still controversial. A possible deleterious effect of MRI hyperintensities on affective regulation was suggested within the theoretical framework of the "vascular depression hypothesis." Our results with respect to lacunes give additional support to the idea of, at least partly, a vascular origin of late-onset depression. However, they also point to the fact that, unlike vascular depression in which mood disorder is associated with MRI-defined fronto-subcortical lesions in the white matter, both central and periventricular demyelination are not related to increased risk for PSD. There are 2 possible explanations for this difference. Two recent studies comparing MRI to postmortem data demonstrated a poor correlation between the presence of white matter hyperintensities and demyelination. In fact, white matter lesions depicted on magnetic resonance images correspond to variable combinations of myelin and axonal loss, as well as scattered microinfarcts, astrogliosis, and dilatation of periventricular spaces. Alternatively, PSD and vascular depression may have distinct pathogeneses. Supporting this point of view, it has been recently shown that the presence of white matter hyperintensities does not increase the risk for PSD in elderly patients with cardiovascular risk factors. However, the absence of relationship between white matter demyelination and PSD should be interpreted with caution because it is based on a semiquantitative assessment of its severity. Recently, new MRI methods have successfully provided quantitative estimates of white matter hyperintensities in patients with multiple sclerosis. Their use in PSD may provide valuable in vivo data to compare with our autopsy findings.

The definition of a neuroanatomical background for PSD reported here does not necessarily exclude the role of psychobiological factors such as physical disability, ineffective coping skills, and lack of social resources in the pathogenesis of this disorder. This is consistent with a proposed classi-


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