Clinical diagnosis of Binswanger’s disease

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Abstract
To aid in the prospective study of Binswanger’s disease, a poorly understood form of vascular dementia, a standardized criteria for its antemortem diagnosis was proposed. These criteria include dementia, bilateral radiological abnormalities on computed tomography (CT) or magnetic resonance imaging (MRI), and at least two of the following three clinical findings: A) a vascular risk factor or evidence of systemic vascular disease; B) evidence of focal cerebrovascular disease; and C) evidence of “subcortical” cerebral dysfunction. These criteria were validated in two ways. First, by retrospectively applying them to a series of 30 demented patients with various pathological diagnoses. Second, by prospectively applying them to a series of 184 patients with clinically typical Alzheimer’s disease. The sensitivity and specificity of the criteria appear adequate for use in clinical research.

Vascular disease is consistently reported as the second leading cause of dementia. Nonetheless, neither its prevalence nor defining clinical, radiological or histopathological features are settled. Much of the controversy stems from the heterogeneity of the vascular dementias. Therefore, recent reviews of vascular dementia stress the need to distinguish between the various vascular dementias and to develop specific clinical, radiological and pathological criteria for each type.

Binswanger’s disease (BD), a form of vascular dementia, was for years considered a relatively rare disorder diagnosed only at necropsy. The sensitivity of magnetic resonance imaging (MRI) to subcortical white matter pathology, however, has rekindled interest in the disorder and raised the possibility of its antemortem diagnosis. Unfortunately, the typical radiological lesions of BD are routinely seen in both elderly demented and non-demented patients. Furthermore, not all of the lesions visualised by MRI have a vascular basis. In fact, about 30% of patients with clinically typical Alzheimer’s disease (AD) have similar lesions.

For physicians evaluating demented patients, the controversy surrounding the radiological abnormalities poses the clinical dilemma of how to diagnose demented patients who have white matter lesions (WMLs) on computed tomography (CT) or MRI. Clearly, many of these patients do not have BD. Resolution of this dilemma requires standardised criteria for the clinical diagnosis of Binswanger’s disease. The purpose of this paper is to propose such criteria.

Although there is undoubtedly a prodromal phase of BD when dementia is not evident, Binswanger considered this illness a dementing disorder and a recent review by Babikian and Ropper concluded that the illness is “characterized clinically by disorders of memory, mood, and cognition”. Therefore, we propose that the diagnosis be reserved for patients who are demented. The identical restriction is placed on the diagnosis of AD. For research purposes, the presence of dementia should be confirmed by neuropsychological testing.

Radiological criteria for BD are complicated by the fact that several types of lesions are identifiable on MRI. Periventricular caps and rims are nearly ubiquitous findings on MRI. Pathologically, they represent areas of subependymal gliosis, and probably do not have a vascular aetiology. Subcortical WMLs may be either small infarcts, focal areas of demyelination, or dilated perivascular spaces. It is difficult to distinguish between these lesions. However, a recent MRI-pathological study found that the majority of MRI lesions corresponding to dilated perivascular spaces were round or linear, isointense relative to cerebrospinal fluid, and less than 2 x 2 mm. Therefore, the radiological criteria for the diagnosis of BD requires bilateral leukoaraisos on CT, or bilateral, multiple or diffuse, subcortical high signal T2 weighted

Table 1 Criteria for the clinical diagnosis of possible Binswanger’s Disease

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<th>BD Diagnosis Criteria</th>
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<tr>
<td>Presence of a vascular risk factor or evidence of systemic vascular disease (e.g., hypertension, diabetes, history of myocardial infarction, cardiac arrhythmia, or congestive heart failure).</td>
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<tr>
<td>Evidence of focal cerebrovascular disease (e.g., history of stroke, or demonstration of a focal pyramidal or sensory sign).</td>
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<tr>
<td>Evidence of “subcortical” cerebral dysfunction (e.g., a Parkinsonian, magnetic, or “sensorial” gait, Parkinsonism or gait dysmetria, or a history of incontinence secondary to a spastic bladder).</td>
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1. Dementia must be established by clinical examination and confirmed by neuropsychological tests.
2. One finding from two of the following three groups must be present:
   A) the presence of a vascular risk factor or evidence of systemic vascular disease (e.g., hypertension, diabetes, history of myocardial infarction, cardiac arrhythmia, or congestive heart failure).
   B) evidence of focal cerebrovascular disease (e.g., history of stroke, or demonstration of a focal pyramidal or sensory sign).
   C) evidence of “subcortical” cerebral dysfunction (e.g., a Parkinsonian, magnetic, or “sensorial” gait, Parkinsonism or gait dysmetria, or a history of incontinence secondary to a spastic bladder).
3. The radiological criteria requires bilateral leukoaraisos on computed tomography (CT), or bilateral and, multiple or diffuse, subcortical high signal T2 weighted lesions greater than 2 x 2 mm on magnetic resonance (MR) scan.

The proposed criteria lose their validity in the presence of:

1. Multiple or bilateral cortical lesions on CT or MR; or
2. Severe dementia (e.g., MMSE < 10)
lesions greater than 2 x 2 mm on MRI. To separate BD from other types of vascular dementia, the radiological diagnosis of BD also requires the absence of either large or multiple cortical lesions which may contribute to the patient’s dementia.

The proposed clinical and historical features of BD which should accompany dementia and the appropriate MRI or CT examination are based on a review of pathologically verified cases of BD in the English and French language literature. The criteria are outlined in table 1. Three classes of findings define BD. These include: A) a vascular risk factor or evidence of systemic vascular disease; B) evidence of focal cerebrovascular disease; and C) evidence of “subcortical” cerebral dysfunction. We excluded reports of mixed AD/BD, mixed vascular dementia, and non-vascular demyelinating syndromes, as well as cases with very atypical histories, unilateral involvement, lack of clinical data, or lack of clinical evidence of dementia. Of the 62 remaining pathologically verified cases of BD,8,18-30 41 (66%) met all three clinical criteria presented in table 1, and 59 (95%) had at least two of three clinical findings. We therefore propose that two of the three clinical findings outlined above are necessary for the diagnosis of BD.

In this paper we report the results of two evaluations of the validity of these diagnostic criteria. In the first study, the sensitivity of the criteria was assessed by retrospectively applying them to a series of 30 pathologically diagnosed cases of dementia of varying aetiology. In the second study, the specificity of the criteria was evaluated by applying them prospectively to a series of 184 patients with clinically typical AD.

Method
Part I Pathological series
One neurologist (DAB), blind to the pathological diagnosis, reviewed the medical records of 45 patients who had a clinical diagnosis of dementia and a brain necropsy performed at Rush Presbyterian-St Luke’s Medical Center (RPSLMC) between 1975–88. Patients without clinical evidence of dementia, a complete neurological examination, and a CT or MRI scan were excluded, leaving 30 cases. The clinical, radiological and pathological data were recorded on a standardized form. Only variables explicitly mentioned in the chart were scored as present. The diagnostic criteria outlined in table 1 were then applied to the clinical and radiological data on the 30 cases. The pathological criteria for the diagnosis of BD were those outlined by Olszewski.25 There had to be diffuse areas of demyelination sparing the subcortical U-fibres, arteriosclerosis of the penetrating blood vessels, and small infarcts in the subcortical white or grey matter. Although controversial, additional subcortical gliosis was supportive, but not necessary for the diagnosis. If other abnormalities were present, cases were classified as mixed (for example, mixed BD/AD).

A diagnosis of AD was made when numerous neuritic plaques (NP) were present throughout the hippocampus and neocortex. After 1985, NP were quantified and the diagnosis of AD followed the recommendations of Khachaturian et al.20 A diagnosis of Multi-infarct dementia (MID) required large multiple cortical strokes. No attempt was made to quantify the amount of infarcted tissue. Other diagnoses were made by contemporary standards.

Part II Clinical series
The sample consisted of 795 consecutive patients referred to the Rush Alzheimer’s Disease Center (RADC) between 1985–88 for evaluation of possible dementia. Evaluations included a standard medical history, neurological examination, neuropsychological testing, and standard laboratory procedures. Selection from this series required a diagnosis of typical AD,19 a technically satisfactory MRI scan, and a modified ischaemic score less than three;18 184 patients met these criteria. The MR scans were performed on a Technicare 0.5 Tesla superconducting scanner at the RPSLMC. Examinations included T1 weighted sagittal and axial acquisitions and T2 weighted multislice multiecho sagittal and axial acquisitions. All MRIs were rated for the number and location of abnormalities.13 The proposed diagnostic criteria were then applied to these 184 patients. To assess the incremental validity of the MRI, the cases were classified both with and without the MRI criterion.

Results
Part I Pathological series Table 2 depicts the pathological diagnoses of the retrospectively reviewed cases of dementia. Four patients had a pathological diagnosis of BD and all four met BD criteria. One of two patients with mixed BD and AD met criteria. Two patients had MID, one of whom also had concomitant AD. Both met the clinical criteria for BD, but not the radiological criterion because of multiple cortical lesions on their brain scans. Twelve patients had AD, only one of whom fulfilled the criteria. Of five cases of Creutzfeld-Jakob disease, one met the criteria. None of the remaining cases, including patients with Pick’s disease, thalamic gliosis, Parkinson’s disease with dementia, and two with no pathological diagnosis met the criteria. The agreement between the clinical and pathological diagnoses was significant (Fisher’s Exact Test, p = 0.0008, two-tailed).

Part II Clinical series Of the 184 patients with a diagnosis of AD, 32 (17-4%) met at least two of the three clinical criteria. However, only three of these patients also met the radiological criteria. Therefore, only 1-6% (3/184) of these patients with clinically typical AD met the proposed criteria. In four of these 184 patients, AD was confirmed pathologically.

Gait disorders and incontinence are common findings in severely demented patients. We therefore compared dementia severity in those who did and did not meet clinical criteria. The
form former had an average Mini-Mental State (MMS) examination of 11.5 (5-9); the latter had a mean (SD) MMS of 14.2 (8.3). Although this trend is not statistically significant (t (1,182) = 1.57, p = 0.057), it suggests caution when applying these criteria to severely demented patients.

**Discussion**

Guided by reports of pathologically verified cases, we developed an explicit diagnostic scheme for the antemortem diagnosis of BD based on historical, clinical, and radiological information. Diagnoses based on these criteria were in close agreement with pathological diagnoses in a retrospective series of 30 patients. Application of the criteria to a series of 184 patients with clinically typical AD resulted in few diagnostic misclassifications (1.6%). We propose that these criteria may be useful in clinical dementia research. Indeed, differences in memory and affective disturbances can be demonstrated between patients with AD and those meeting our criteria. We recognise, however, that prospective clinico-pathological studies are needed for both verification and refinement of this scheme.

Until 1978, the diagnosis of BD was made only at necropsy. Caplan and Schoene were the first to attempt an antemortem diagnosis of BD. They reviewed five cases of pathologically confirmed BD (one of whom had concomitant AD) and made clinical diagnoses in six other patients. They emphasised many of the same historical and clinical findings that we advance. Babikian and Ropper also stressed similar data in a 1987 review of BD. However, both papers stopped short of advocating a specific diagnostic scheme.

For the specific clinical criteria, vascular risk factors and focal cerebral dysfunction are widely recognised features of the syndrome. However, other features of the syndrome remain controversial.

Although bothBinswanger and Alzheimer regarded BD as a dementing illness, Olzewski, in his trenchant 1962 review, advocated that the diagnosis be made strictly on pathological grounds. Recent reviews, however, have reverted to the earlier position, thereby reintroducing the clinical requisite that dementia be documented to make the diagnosis. We recognise that this represents a somewhat arbitrary limitation to the syndrome. However, we were guided by the precedent set with Alzheimer's disease and by the belief that a more uniform definition of BD will ultimately lead to a better understanding of the disease.

Our criteria include neurological signs of "subcortical" cerebral dysfunction such as a gait disorder, Parkinsonism or incontinence. Although these findings are common in BD, they are not widely appreciated. However, gait disorders and Parkinsonism resulting from subcortical vascular disease are well described in the neurological literature.
vascular disease can result in pseudobulbar signs, Parkinsonian features and an akinetic-rigid syndrome with dementia. 4 Although the term "arteriosclerotic Parkinsonism" is currently out of vogue, in a recent survey of 33 leading authorities in movement disorders from ten countries, 16 agreed that the designation is acceptable, while only six disagreed and 11 were uncertain. 47

In a recent clinical series, Parkinsonism was a common finding in vascular dementia in general, 48 and BD in particular. 49 These patients had multiple strokes prohibiting precise clinico-anatomical correlations. However, focal subcortical vascular lesions implicate the thalamus and putamen in disorders of stance, gait and incontinence. Thus there is ample evidence to support the criteria of gait disorders, Parkinsonism and incontinence.

It is the role of neuroradiology in the diagnosis of BD which is perhaps the most controversial. Rosenberg et al first reported bilateral white matter hypodensities on CT in a man with dementia, hypertension and spasticity, with pathologically proven BD. 50 Loizou et al followed this report by using similar CT findings to confirm the clinical diagnosis of BD in 15 patients. 51 Their patients were clinically similar to Caplan's and one case of BD was verified at necropsy. In 1985, Kinkel et al compared the sensitivity of MR in 23 patients (eight of whom were asymptomatic) with CT documented "leukoencephalopathy of unknown origin". 52 MRI was unquestionably more sensitive in delineating WMLs, and they concluded that "the lack of neurological findings in this group is not necessarily inconsistent with the diagnosis of subcortical arteriosclerotic encephalopathy [BD]."

A number of other investigators now advocate that WMLs on MRI are sufficient evidence for a diagnosis of BD. 7 Yet, several studies have shown that not all white matter abnormalities occur in BD. 4-12 In fact, such lesions are seen in many individuals without neurological deficits and in about 30% of patients with typical AD. 13 They are highly age-related among healthy elderly individuals and also correlate with the presence of cerebrovascular risk factors, though not necessarily symptomatic cerebrovascular disease. 10 Despite this apparent lack of specificity, it does appear that MRI scanning is exceptionally sensitive to vascular lesions. Furthermore, well-designed clinical studies have consistently demonstrated increased CT and MRI abnormalities in vascular dementia, compared with AD. 51 Of the 62 pathologically verified reports of BD, 18 had a brain scan. Of those, 83-3% (15/18) showed leukoaraiosis on CT and 100% (3/18) showed multiple bilateral white matter abnormalities on MRI. Finally, within our own clinical series, the addition of the MRI criterion to the diagnostic system significantly reduced apparent misdiagnoses of patients with AD from 17-4% to 1-6%. We submit therefore that these radiological findings be considered a necessary, but not sufficient, component of the clinical diagnosis of BD.

Our criteria offer several advantages over Hachinski's ischaemic score (IS). 46-52 First, the IS was not designed for BD though it has been used. 53 In fact, less than half of the 62 pathologically verified cases of BD in the English and French literature met IS criteria for multi-infarct dementia. Second, we emphasise clinical evidence of "subcortical" cerebral dysfunction. Third, we incorporate radiological confirmation of bilateral white matter pathology. Fourth, we eliminate items which are common in other dementias, for example, nocturnal confusion, personality changes and depression. 54 And fifth, items which are difficult to assess and have poor interrater reliability are excluded. 55

Although the diagnostic system presented here holds promise, it is not without its limitations. Most importantly, it cannot distinguish BD from mixed AD/BD. The same criticism is levied against the IS. Unfortunately, until there is a diagnostic marker for AD, this limitation seems inevitable. Mixed AD/vascular dementia probably represents the chance occurrence of two common diseases in the elderly. However, the combination of AD and BD may not always be fortuitous. Brun and England 56 suggest that loss of myelin with "incomplete" white matter infarction and reactive gliosis are common histopathological findings in AD. These lesions are difficult to distinguish from BD on MRI scan and may result from hypo perfusion. 47 In addition, there is some evidence implicating AD in the development of a neurogenic vasculopathy. 57 Finally, the histopathological findings of BD may also be seen in patients with cerebral amyloid angiopathy with and without concomitant AD. 58-59

A second problem is how to classify cases of mixed vascular dementia, that is mixed BD and cortical strokes. In an effort to define a more homogeneous sample of BD patients for research purposes, we chose to exclude patients with strokes other than lacunar and subcortical strokes. Although Tomlinson et al recommend that a diagnosis of MID requires at least 50 ml, and preferably 100 ml, of infarcted brain tissue, 1 this suggestion does not take into account lesion location, which studies demonstrate is important in the pathophysiology of vascular dementia. 60 In fact, in a recent clinicopathological study of MID, only five of 23 patients with a pathological diagnosis of vascular dementia had more than 50 ml of infarcted tissue, and seven had less than 10 ml. 61 The status of BD resembles that of AD before the seminal work of Tomlinson and his colleagues 20 years ago. At that time, AD was an underrecognised cause of mental deterioration with poorly defined clinical features. Since then the introduction of standardised criteria for the clinical diagnosis of AD has greatly increased diagnostic accuracy. 39-40 Standardised criteria for BD are likely to have a similar impact on the study of this illness. Since CT and MRI abnormalities are common in the elderly, clinical criteria must accommodate radiological findings when making the antemortem diagnosis of BD. Such criteria should be specific enough to exclude patients
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with AD from the sample. Our criteria meet these objectives and should therefore prove useful in the prospective study of this puzzling disease.

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