Vascular cognitive impairment in small vessel disease: clinical and neuropsychological features of lacunar state and Binswanger's disease

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Abstract

Background: ischaemic cerebrovascular small vessel disease (SVD) is a prevalent and under-diagnosed condition that triggers vascular cognitive impairment (VCI).

Objective: to describe the neuropsychological and clinical profiles in SVD (Binswanger's disease, BD; lacunar state, LS) from the clinician's perspective at the VCI stage.

Methods: a total of 1257 patients admitted to a tertiary center with a diagnosis of stroke, neuroradiological vascular disease, cognitive impairment/dementia, during a 13-year period were investigated. We prospectively assessed cognition in a subset of 141 patients with VCI (LS \( n = 28 \), BD \( n = 69 \), large vessel disease—LVD—\( n = 44 \)) with MMSE, CAMDEX-H, WAIS-R, EXIT-25 and Trail making test.

Results: executive dysfunction (ECD) \((n = 89, 91.7\% \text{ versus } n = 10, 22.7\%; P < 0.001)\) and gait disturbances \((n = 74, 76.3\% \text{ versus } n = 15, 34.1\%; P < 0.001)\) characterized SVD. Prior strokes \((n = 9, 9.3\% \text{ versus } n = 23, 52.3\%; P < 0.001)\) and embologenous cardiopathy \((n = 39, 40.2\% \text{ versus } n = 28, 63.6\%; P < 0.04)\) featured LVD cases. BD was defined by hypertension \((n = 52, 75.4\% \text{ versus } n = 30, 44.1\%; P < 0.001)\), ECD \((n = 65, 94.2\% \text{ versus } n = 34, 47.2\%; P < 0.001)\) and VCI onset with cognitive impairment but not strokes \((n = 44, 63.8\% \text{ versus } n = 34, 50\%; P < 0.01)\).

Conclusions: ECD and a frontal gait are SVD's clinical landmarks in our sample. LS and BD cases share a similar cognitive profile.

Keywords: dementia, Binswanger, lacunar, behaviour, executive dysfunction, gait, cognitive impairment

Introduction

Cerebrovascular small vessel disease (SVD) accounts for the presence of silent ischaemia in neuroimaging studies in 20% of the elderly [1] and 25% of symptomatic ischaemic strokes [2]. It clinically translates into subcortical ischaemic disease, which is the most common and most homogeneous form of vascular cognitive impairment (VCI) [3].

There are two SVD pathological subtypes, lacunar state (LS) and Binswanger's disease (BD) that share risk factors and present typical radiological correlates [4]. Lacunar infarcts (LI) have been associated with the development of VCI that does not reach the degree of dementia, and eventually to vascular dementia. BD is different because it provides a model combining the contribution of white matter ischaemic disease to cognitive decay and the effect of lacunes. Additionally, VCI is a prevalent clinical entity that...
is frequently associated with Alzheimer’s disease. VCI is also difficult to diagnose since its criteria encompass a very clinically heterogeneous group of disorders. This is a critical issue because in its early stages VCI may be a preventable and treatable condition.

The aim of the present study is to analyse the main features of BD and LS from the clinician’s perspective at the initial VCI stage, prior to dementia. We will describe the risk factors, clinical presentation and neuropsychological profiles of SVD.

Patients and methods

Study population and design

A total of 1,257 inpatients from the community (not previously institutionalised) with an initial diagnosis of stroke, transient ischaemic attack, neuroradiological vascular disease, cognitive impairment or dementia fulfilling the ICD-10 criteria were investigated. A thorough description of this population has been previously published [5]. Briefly, the study was carried out in an 1,100-bed teaching tertiary institution in Spain from 1990 to 2003. Three hundred and thirty-two patients (26.4% of the sample) developed vascular dementia and 314 fulfilled our inclusion criteria [5]. Two hundred and sixty-six patients with VCI (72% of the sample) were assessed prospectively. Of those, 159 patients developed large or SVD (not mixed pictures). Patients with a mixed (cortico-subcortical) component and 18 subjects with strategic strokes were excluded. Therefore, 141 patients were included in the present study: BD \( n = 69 \), LS \( n = 28 \) or large vessel disease (LVD) \( n = 44 \).

Two authors collected data independently, and a neuro-radiologist and two other contributors assessed CT scans. All participants received at least a total of three neuroimaging studies. Disagreements (<5%) were resolved by consensus. The patient and co-dwellers were interviewed personally, and contacted by telephone when required [5]. All patients underwent a standardised dementia protocol [5].

Patients with Alzheimer’s disease, CADASIL, any other type of dementia, other causes of VCI or subjects lacking clinical or neuroradiological cerebrovascular disease data were excluded [5]. We also removed patients with vestibular dysfunction and visual deficits to ensure a proper gait and cognitive evaluations.

All patients received at least two cognitive assessments (1 month after their first admission, 3 months after their first admission; and if required an additional one at the moment of dementia diagnosis) as previously reported [5]. We report the results at the 3-month mark. The authors performing the cognitive testing were blind to the medical history and neuroimaging results. Briefly, VCI was determined by deficits in a single cognitive area assessed in seven domains (orientation, memory, attention, executive function and reasoning, praxis, language and visuospatial). Modified Mini-mental State Examination (MMSE) cut-off point was set at 21 points for dementia and 27 for VCI [5].

Participants underwent Hachinski’s scale, WAIS-R [6], Exit-25 [7], Trail making test [8], Blessed Dementia scale [5] and CAMDEX H questionnaire [9]. Mood was assessed with the geriatric and Hamilton’s depression scale [5]. A neurologist and a trained primary care provider, assessed gait features.

Working definitions

We divided VCI into two groups depending on the onset:

(i) Onset with Cognitive Impairment No Dementia (CIND): Patients with VCI developing prior to any symptomatic cerebrovascular events, started with CIND. These patients could have or not symptomatic ischaemic events after VCI onset.

(ii) Onset with ischaemic events: Those subjects without cognitive impairment and a first symptomatic ischaemic insult [LI or cortical stroke or transient Ischaemic attack (TIA)]. These patients developed VCI after their initial ischaemic insult and then progressed to dementia.

Radiological definitions:

(i) Silent ischaemia: One or more infarcts in CT scan without a history of a corresponding symptomatic stroke or TIA at any point of the follow-up. Patients with silent ischaemia were included in the CIND or the onset with ischaemic events group as per our previous definitions.

(ii) Ischaemic white matter disease (WMD): CT scan hypodensities in the frontal or occipital horns, and in periventricular areas.

VCI period was defined in two different blocks of time from the onset of CIND or overt ischaemia to the moment the diagnosis of dementia was made: \( \leq 24 \) and \( >24 \) months.

Clinical diagnosis of vascular dementia was achieved when a patient who previously presented VCI, developed impairment in two areas of cognition and met the criteria for any of the following subtypes of vascular dementia:

(i) Cortical dementia due to SVD: Including LI and BD. LI had one of the five classical syndromic presentations and typical radiological features [5]. LS was diagnosed in patients with isolated multiple lacunes in CT in the absence of cortical infarctions or WMD. BD was diagnosed when Caplan’s and Bennett’s criteria were met [5].

(ii) Cortical dementia due to LVD: Diagnosed when patients with VCI and a cortical distribution of the ischaemic lesions met eventually met the ADDTC criteria for probable vascular dementia [5].

Statistical analysis

Continuous variables were expressed as mean and standard error of the mean (SEM). \( \chi^2 \)-test, Student’s \( t \)-test,
Small vessel ischaemic cognitive impairment

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<th>Table 1. General sample features</th>
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<td>BD (n = 69)</td>
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<td>Females</td>
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<td>Age (years)</td>
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<td>Mini-mental exam</td>
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<td>Onset CIND versus stroke</td>
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<td>Unrecognised VCI</td>
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<td>VCI &gt; 24 m</td>
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<td>Dilated cardiopathy</td>
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<td>Gait disorder</td>
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<td>Frontal Gait</td>
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Values are expressed as n (%), except age and mini-mental test: mean (SEM).
BD, Binswanger’s disease; LS, Lacunar state; LVD, Large vessel disease; SVD, Small vessel disease; CIND, cognitive impairment, not yet dementia; VCI, Vascular cognitive impairment, not yet dementia.

Kruskal-Wallis H, Mann-Whitney U and ANOVA analysis P ≤ 0.05, ad hoc values provided, confirmed by Bonferroni’s post hoc calculations.

Results

Baseline features of the 141 patients with a diagnosis of VCI describing the differences among BD, LS and LVD plus those of LVD versus SVD are displayed in Table 1.

Table 2 shows the data distribution for the significant executive function tests providing raw and z-scores for BD, LS and LVD. It also compares SVD versus LVD. There were no significant differences for the comprehension, similarities and block design subtests.

Table 3 shows a third logistic regression with the variables that significantly predicted the presence of SVD versus LVD. Patients with SVD did not have previous clinical ischaemic cerebrovascular events or cardiopathy, while the presence of gait abnormalities and executive dysfunction (ECD) made SVD more likely. We defined ECD as a deficient performance in at least two different tests. Discriminant analysis allowed substituting ECD for a z-score composite (EXIT 25 + digit span + digit symbol) in Table 3: SVD = 1.9 * gait abnormalities − 1.3 * cardiopathy at diagnosis − 2.8 * symptomatic ischaemic events prior to diagnosis − 0.2 composite of z-scores for EXIT 25, digit symbol and digit span + 0.2. This equation has a sensitivity of 92.8%, specificity of 77.7%, PPV of 88.2%, NPV of 82.1%, and a positive likelihood ratio of 3.4 and negative predictive value of 0.1. When ECD was substituted by EXIT 25 z-scores and digit symbol z-scores all variables remained significant.

BD patients are prone to being hypertensive (P < 0.001) and developing ECD (P < 0.001) and VCI onset with CIND but not stroke (P < 0.01) when compared with the group without WMD (LS and LVD): 2.8* ECD + 1.3* hypertension + 1.1* VCI onset with CIND (versus stroke) − 3.6 in another logistic regression: Sensitivity 89.9%, specificity 66.7%, PPV of 72.1%, NPV 87.3% and positive likelihood ratio of 5.6. Discriminant analysis allowed substituting ECD by digit symbol and digit span z-scores in a second equation or by a composite z-score of exit 25 and digit span and digit symbol tests. ECD was defined in another logistic regression by 2.2* WMD in
When required, Mann–Whitney’s U or Kruskal–Wallis H and Λ0va analysis with *ab hoc* values provided; (P-value); and confirmed by Bonferroni’s *post hoc* calculations; BD, Binswanger’s disease; LS, Lacunar state; LVD, Large vessel disease; SVD, Small vessel disease.

## Data expressed as raw scores: Mean (SEM); P (percentile in normal standardised values adjusted for age).

For Trail B the percentile values are based on normalised data [27].

Table 2. Executive function assessment calculations; BD, Binswanger’s disease; LS, Lacunar state; LVD, Large vessel disease; SVD, Small vessel disease.

### Table 3. Small vessel disease versus large vessel disease

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<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td>Early ECDs</td>
<td>0.8</td>
<td>(0.7–0.9)</td>
<td>&lt;0.01</td>
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<tr>
<td>Ischaemia during VCI</td>
<td>0.1</td>
<td>(0.02–0.2)</td>
<td>&lt;0.01</td>
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<tr>
<td>Embologenous Cardiopathy</td>
<td>0.3</td>
<td>(0.1–0.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gait Abnormalities</td>
<td>6.8</td>
<td>(2.1–16)</td>
<td>&lt;0.01</td>
</tr>
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*Composite of z-scores for Exit + Digit symbol + Digit span. Please, note that the nature of the cognitive test scores will make the composite more like to be low if ECD is present. Hence, in this case ECD predicts the occurrence of SVD. All variables remained significant when substituting the composite z-scores for any of the following variables: early ECD, or EXIT z-scores, or a composite of z-scores for Digit symbol + Digit span. VCI, vascular cognitive impairment, not yet dementia. Logistic regression analysis (P < 0.05).

CT + 2.1* frontal gait −0.3. Specificity was 85.7%, PPV was 91%. Actually, 94.1% of patients with WMD in periventricular and basal ganglia areas had ECD. There were no significant differences between those with isolated periventricular ischaemia (71%) and individuals with lesions limited to the basal ganglia white matter (86.7%).

### Discussion

VCI secondary to SVD is a very common condition [3, 5] that may present as symptomatic ischaemic insults (lacunes) [3, 5, 10] or as CIND in the context of silent (asymptomatic) lacunes [1] or WMD in radiological studies [4]. Its diagnosis is difficult and usually delayed [5]. Understanding the disruption of white matter cortico-subcortical loops is critical to identify CIND in SVD [11–14]. Bearing this concept in mind, we will discuss risk factors, physical exam findings and natural history insights, according to our data.

Regarding vascular risk factors, we have confirmed prior observations establishing hypertension as the most relevant vascular risk factor for WMD [15, 16]. This happens because the SVD territory is a special hemodynamic substrate given its high capacitance, low compliance and limited vasoconstrictive properties. In BD, the chronic effect of hypertension on the vessel wall adds to the loss in the ability of small vessels to autoregulate blood flow and manifests as silent ischaemia and WMD [17]. Thus, hypertension was more frequent in our BD group, which is relevant because we have compared three groups of patients that have a higher incidence of hypertension than the general population.

We know that embologenous cardiopathy is a relevant risk factor for stroke and VCI. However, this effect was more prominent in the LVD group (typically medium cerebral artery territory cortical strokes secondary to atrial fibrillation). Interestingly, BD and LVD patients shared a higher cardiopathy incidence than LS cases, probably due to the higher hypertension incidence in the BD subgroup.

With respect to physical examination findings, gait abnormalities were more frequent in patients with SVD in our population. LVD patients had cortical lesions and most frequently presented with a hemiparetic gait after medium or anterior cerebral artery stroke. Conversely, we observed a typical frontal gait (marche à petit pas) in BD [16] when there was WMD in CT scan in the tracts connecting subcortical areas to the frontal lobes [18]. These patients had a wide-based, stooped, shuffling gait, with trunk rigidity, preserved arm swing and turns broken down in many steps or turning on one leg [16]. Recognising these patterns is essential because these patients have a higher risk of developing CIND and eventually dementia [19].
Early ECD, though not specific to vascular disease, is a prominent feature of SVD in our sample and in prior studies [11, 20, 21]. WMD and lacunes may disrupt the networks connecting the basal ganglia and dorsolateral prefrontal cortex. These lesions hinder the patient’s ability to conceptualise all aspects of a task and translate it into appropriate and effective behaviour. Generally, patients with BD performed worse than those with LS in executive function testing. This was more evident when comparing the mean percentiles for each group. These results are on the same line of previous work on LS, WMD and BD; and probably reflect on the importance of extensive WMD on the neural networks [12, 13, 20–25].

It is difficult to define a specific cognitive profile given the heterogeneity of the anatomical lesions and sample populations reported in diverse SVD studies [12, 13, 20–25]. ECD might be a marker of SVD with or without Alzheimer’s disease. We detected significantly worse scores in digit span and digit symbol, TRAIL B, TRAIL B-A and EXIT 25. These tests take a limited amount of time to perform with exception to the EXIT 25 (10, 3, 10 and 45 min, respectively) and may be useful as a screening tool in the office [5, 22]. It is noteworthy to highlight that our results and other previous reports showed that MMSE scores do not correlate with ECD.

Finally, concerning the natural history of the disease, LVD patients develop a classical VCI, pattern of post-stroke dementia [5, 26]. They are more prone to present with stroke and recurring ischaemic events prior to dementia diagnosis. Conversely, patients that had VCI onset with CIND were more prone to have silent ischaemia and BD (SVD) and eventually progress through a VCI stage for longer than 2 years prior to dementia development [5]. However, BD’s more insidious course also leads to a delayed diagnosis of VCI and vascular dementia [5]. This natural history should not mislead physicians to consider SVD as a benign condition. The prognosis of LI strokes is benign in the initial follow up period (30 days post-stroke or 1 year after stroke) [27]. However, patients with LI infarcts had a mortality rate of 25% after 5 years of follow-up [28] that increases to 60–75% after 10–15 years since the first lacune happened [29, 30].

Our study has some limitations. First, our results may be reflective of our population and may not be extensive to other groups. For example, we reported the unexpected finding that dyslipidaemia was not present in LS cases versus one-third of BD patients. However, we feel external validity is assured by our inclusion criteria.

Second, VCI of CIND type and early Alzheimer’s disease may be clinically very similar. We cannot exclude that some of our cases could be mixed dementias (Alzheimer plus vascular), because our study as many other trials in the field, lacks pathological confirmation [19–22, 24, 25]. However, we excluded those cases that met the current clinical–radiological criterion for Alzheimer’s disease and those with early amnestic VCI. Yet, there is increasing evidence that many cases will eventually develop a pathological profile consistent with a mixed dementia. This situation should not deter clinicians from seeking an early diagnosis of VCI. In this context, our goal remains to provide practitioners with clinical hints that may lead to a further work up. The same problem applies to SVD cases with respect to CADASIL. We carefully excluded those patients with a family history of dementia and those with early temporal lobe involvement. However, there was no genetic testing available when the study started.

Third, we reported WMD in CT scans according to the ADDTC criteria [5]. While CT is less sensitive than MRI at detecting SVD, it has a higher specificity and positive predictive value. Hence, we only detected severe WMD cases. Besides, we do not provide with a quantitative measure of WMD. Yet, our approach pertains to daily primary care practice, where MRIs and quantitative measures of WMD are not available. We focused on clinical aspects (i.e. gait disturbance/subtle cognitive deficits) that might hint the need for further testing.

In conclusion, SVD patients clinically present in a heterogeneous way because symptoms depend on the site where the ischaemic insults occur. However, there are typical epidemiological and clinical features that may facilitate VCI diagnosis at its early stages prior to the development of dementia. These patients are typically hypertensive and have gait disturbances. They may not present with overt strokes, but CIND. Finally, ECD testing by general physicians in the outpatient clinic will help detect early VCI due to SVD.

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**Keypoints**

- VCI of small vessel origin is very prevalent and either undiagnosed or not identified at an early stage.
- Small vessel VCI may present with lacunar strokes or with insidious cognitive deficits.
- Gait disturbances and ECD may herald VCI.
- Short simple cognitive tests can help screen for VCI diagnosis in the primary care clinic in 30 min.

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**Conflicts of interest**

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