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Identifying preclinical vascular dementia in symptomatic small vessel disease using MRI

Christian Lambert[a,b,*], Eva Zeestraten[b], Owen Williams[b], Philip Benjamin[b], Andrew J. Lawrence[c], Robin G. Morris[d], Andrew D. Mackinnon[e], Thomas R. Barrick[b], Hugh S. Markus[c]

[a] Wellcome Centre for Human Neuroimaging, 12 Queen Square, WC1N 3BG London, UK
[b] Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, SW17 0RE, UK
[c] Stroke Research Group, Clinical Neurosciences, University of Cambridge, CB2 0QQ, UK
[d] Department of Psychology, King's College Institute of Psychiatry, Psychology, and Neuroscience, London, UK
[e] St George's NHS Healthcare Trust, Atkinson Morley Regional Neuroscience Centre, London, UK

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ABSTRACT

Sporadic cerebral small vessel disease is an important cause of vascular dementia, a syndrome of cognitive impairment together with vascular brain damage. At post-mortem pure vascular dementia is rare, with evidence of co-existing Alzheimer's disease pathology in 95% of cases. This work used MRI to characterize structural abnormalities during the preclinical phase of vascular dementia in symptomatic small vessel disease.

121 subjects were recruited into the St George's Cognition and Neuroimaging in Stroke study and followed up longitudinally for five years. Over this period 22 individuals converted to dementia. Using voxel-based morphometry, we found structural abnormalities present at baseline in those with preclinical dementia, with reduced grey matter density in the left striatum and hippocampus, and more white matter hyperintensities in the frontal white-matter. The lacunar data revealed that some of these abnormalities may be due to lesions within the striatum and centrum semiovale.

Using support vector machines, future dementia could be best predicted using hippocampal and striatal Jacobian determinant data, achieving a balanced classification accuracy of 73%. Using cluster ward linkage we identified four anatomical subtypes. Successful predictions were restricted to groups with lower levels of vascular damage. The subgroup that could not be predicted were younger, further from conversion, had the highest levels of vascular damage, with milder cognitive impairment at baseline but more rapid deterioration in processing speed and executive function, consistent with a primary vascular dementia. In contrast, the remaining groups had decreasing levels of vascular damage and increasing memory impairment consistent with progressively more Alzheimer's-like pathology. Voxel-wise rates of hippocampal atrophy supported these distinctions, with the vascular group closely resembling the non-dementing cohort, whereas the Alzheimer's like group demonstrated global hippocampal atrophy.

This work reveals distinct anatomical endophenotypes in preclinical vascular dementia, forming a spectrum between vascular and Alzheimer's like pathology. The latter group can be identified using baseline MRI, with 73% converting within 5 years. It was not possible to predict the vascular dominant dementia subgroup, however 19% of negative predictions with high levels of vascular disease would ultimately develop dementia. It may be that techniques more sensitive to white matter damage, such as diffusion weighted imaging, may prove more useful for this vascular dominant subgroup in the future.

This work provides a way to accurately stratify patients using a baseline MRI scan, and has utility in future clinical trials designed to slow or prevent the onset of dementia in these high-risk cohorts.

1. Introduction

It is generally accepted that future treatments for dementia should aim to start prior to symptom onset, when extensive pathology will already be present and difficult to reverse (Langbaum et al., 2013). Therefore accurately identifying individuals during the preclinical phase of their illness is paramount to developing effective therapies. Vascular cognitive impairment is defined as a syndrome in which at

* Corresponding author at: Wellcome Centre for Human Neuroimaging, 12 Queen Square, WC1N 3BG London, UK.
E-mail address: christian.lambert@ucl.ac.uk (C. Lambert).

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least one cognitive domain is impaired, together with evidence of vascular damage (Thal et al., 2012), and becomes vascular dementia once a second cognitive domain becomes affected (Gold et al., 1997). This clinically heterogeneous entity is the second most common cause of dementia after Alzheimer's disease (Jellinger and Attems, 2010), and can manifest due to a broad range of sporadic and familial conditions where the net result is vascular damage to the brain. The most common cause is cerebral small vessel disease (SVD), a highly prevalent, age-related condition affecting the small vessels of the brain (De Leeuw et al., 2001; Pantoni, 2010) that is associated with characteristic changes on magnetic resonance imaging (MRI) including white matter hyperintensities (WMH), lacunar infarcts, cerebral microbleeds, and brain atrophy (Gouw et al., 2011).

This work examines, in a cohort followed for 5 years, the structural correlates of preclinical vascular dementia using MRI to predict the development of future dementia in a cohort of individuals with sporadic "*symptomatic small vessel disease*", defined as both clinical and radiological evidence of a lacunar syndrome together with confluent WMH (modified Fazekas grade ≥ 2), but without evidence of large cortical infarcts, cerebral amyloid angiopathy or other cause of white matter disease.

1.1. Dementia in cerebral small vessel disease – pathology

The most common pattern of pathology observed in vascular dementia is a subcortical vascular encephalopathy. This is used to describe a severe form of SVD due to arteriolosclerosis and lipohyalinosis (Ferrer, 2010; Thal et al., 2012), appearing as confluent leukoaraiosis on brain imaging with sparing of the cortico-cortical u-fibers (Jellinger and Attems, 2010). It is thought that the white matter damage in leukoaraiosis leads to dementia by way of a progressive disconnection syndrome due to damage of the cortical-subcortical and cortical-cortical connections (Lawrence et al., 2013). In addition single strategic infarcts may also cause or contribute to dementia when structures normally involved in mediating cognitive processes are damaged, for example the thalamus (particularly the paramedian or medio-dorsal thalamic nuclei) and hippocampi (Ferrer, 2010; Benjamin et al., 2014). However it should be noted that pure vascular dementia is rare at post-mortem, performed predominantly in elderly individuals, with histological evidence of co-existing Alzheimer's disease pathology present in 90–95% of cases (Jellinger and Attems, 2010; Thal et al., 2012).

1.2. Dementia in cerebral small vessel disease – clinical

The characteristic cognitive pattern associated the subcortical white-matter disease caused by SVD is that of prominent executive function and processing speed dysfunction, with relative preservation of episodic memory (Lawrence et al., 2013). In contrast, Alzheimer's disease and the mixed dementia subtypes are typified by more marked memory involvement (Reed et al., 2007).

1.3. Dementia in cerebral small vessel disease – MRI correlates

Whilst cognitive impairment in SVD has been shown to associate with a number of different MRI features including lacunar infarcts, WMH, and less consistently microbleeds (Patel and Markus, 2011; Benjamin et al., 2014), the imaging correlates of vascular dementia are less well defined. The most consistent finding is increased deep white matter hyperintensities (Smith et al., 2016; Altamura et al., 2016), associated with measures of reduced integrity of the white matter structural network (Tuladhar et al., 2016), which in combination have been found to be predictive of progression to future dementia. Whilst these previous MRI studies have not distinguished between vascular dementia subtypes, PET imaging using Pittsburgh compound B (PiB) to detect the β-amyloid protein has allowed the spectrum between the pure vascular, mixed and pure Alzheimer's dementias to be better characterized (Lee et al., 2011). These studies have found that individuals with pure vascular dementia are younger with substantially more lacunar infarcts (Lee et al., 2011; Kim et al., 2014) compared to those with evidence of co-existing β-amyloid pathology.

1.4. Hypotheses

Here we test the hypothesis that, within a cohort of individuals with symptomatic small vessel disease, there are particular localized structural abnormalities in those destined to convert to dementia within five years ("*preclinical vascular dementia*") that can be identified from the baseline structural imaging (T1-weighted and FLAIR MRI). Furthermore, simple machine learning techniques (i.e. support vector machines) can be used to predict future dementia from the baseline MRI imaging. We also test the hypothesis that vascular dementia is associated with differences in the voxel-wise rate of cortical atrophy or WMH expansion. Finally, due to the known heterogeneous nature of vascular dementia, we aimed to use the structural imaging to define whether distinct anatomical endophenotypes exist within the preclinical cohort, and if so, were there any differences in the clinical manifestation or disease progression between these groups.

2. Methods

2.1. Subjects

Supplementary Fig. 1 summarizes the baseline and longitudinal data used, conversion to dementia and reasons for dropout. This work primarily focused on stratifying preclinical dementia based on the initial baseline assessment, and therefore included all individuals irrespective of their long-term outcome.

2.2. Subjects - baseline

121 subjects (78 male, mean age male = 67.96 ± 10 years, female = 73.74 ± 8.12 years) with symptomatic SVD were recruited as part of the prospective St George's Cognition and Neuroimaging in Stroke (SCANS) study (Lawrence et al., 2013). Recruitment was from acute stroke units or outpatient stroke clinics in three hospitals covering a contiguous catchment area in South London (St George's, King's College and St Thomas' Hospitals). Inclusion criteria comprised a clinical lacunar syndrome (Bamford et al., 1987) with an anatomically corresponding lacunar infarct in addition confluent WMH on MRI (modified Fazekas grade ≥2) (Fazekas et al., 1987; Hassan et al., 2003) on MRI. Exclusion criteria were: any cause of stroke mechanism other than SVD, other major central nervous system disorders, major psychiatric disorders, any other cause of white matter disease, contraindications to MRI, or non-fluent in English. All subjects provided written consent, and the study was approved by the local ethics committee. The study is registered with UK Clinical Research Network (http://public.ukcrn.org.uk/, study ID:4577). The T1-weigthed MRI for two of these individuals was corrupted by artifact (see Lambert et al., 2015) that resulted in very inaccurate tissue segmentations and therefore were excluded from this work. The remaining 119 individuals were used for all baseline analysis.

2.3. Subjects – longitudinal

Subjects were invited for cognitive testing and clinical assessment annually for five years. During the first three years they also underwent annual MRI scanning. Recruitment began in December 2007 and ended in August 2010. MRI scanning began in January 2008 and was completed in October 2013. If a participant was diagnosed with dementia at any point over the five years, they were allocated to the preclinical vascular dementia (PreVaD) baseline cohort.

In the MRI longitudinal rate analysis, follow-up data up to year