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Review

White matter lesions and depression: A systematic review and meta-analysis

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ABSTRACT

We sought to determine if an association exists between overall, deep, and periventricular white matter hyperintensities and depression. We searched PubMed (Medline) and Scopus (Embase) from April –October 2012 using the MeSH terms: "White matter lesions" OR "white matter disease" OR "Cerebrovascular Disease" OR "Leukoencephalopathies" AND "Depressive Disorder" AND "magnetic resonance imaging," and "Depression" AND "leukoaraiosis." No language limits were implemented. Hand searching was performed of all included studies and relevant review articles. 913 PubMed and 188 Scopus citations were identified. Relevant, human, non-overlapping magnetic resonance imaging studies were eligible for inclusion if they reported generic data. We extracted the most adjusted odds ratios reported generated from comparing depression across severe (determined either volumetrically or visually) and mild/no white matter lesion groups. 19 reports were included. Cross-sectional subgroup analyses showed that deep white matter hyperintensities significantly associated with depression ($N = 2261$, odds ratio 1.02, 95% confidence interval 1.00–1.04, $p = 0.02$), whereas periventricular ($N = 3813$, odds ratio 1.08, 95% confidence interval 0.99–1.17, $p = 0.07$) and overall did not ($N = 5876$, odds ratio 1.12, 95% confidence interval 0.96–1.30, $p = 0.14$). Overall longitudinal analysis revealed a pooled odds ratio of 1.12 ($N = 2015$; 95% confidence interval 0.97–1.29; $p = 0.13$; $Q = 7.19$, $p = 0.07$; $I^2 = 58.3\%$). Longitudinal subgroup analyses revealed that overall white matter hyperintensities ($N = 1882$, odds ratio 1.22, 95% confidence interval, 1.06–1.4, $p < 0.01$) significantly associated with depression but deep did not ($N = 660$, odds ratio 2.02, 95% confidence interval, 0.56–7.22, $p = 0.281$). No significant heterogeneity was present in subgroup analyses. In conclusion, we found a significant, but weak association between white matter hyperintensities and depression.

1. Introduction

White matter hyperintensities (WMH) on T2 and fluid-attenuated inverse recovery (FLAIR) MRI sequences are often reported in patients with late-onset depression (Greenwald et al., 1996; Tupler et al., 2002; Taylor et al., 2005). However, it is unclear to what extent, if any, WMH represent lesions that play a role in the development of depression. Currently, the predominant view is that WMH are representative of underlying small vessel disease (Van Swieten et al., 1991; Moody et al., 1997) that, via hypoperfusion injury to cortical fiber tracts, predisposes for depression (Culang-Reinlieb et al., 2010). However, the findings are inconsistent.

Four reviews (Culang-Reinlieb et al., 2010; Casanova et al., 2011; Gorelick et al., 2011; Hommet et al., 2012) and 2 meta-analyses (Herrmann et al., 2008; Arnone et al., 2012) have been conducted recently that have included at least some data concerning WMH and depression. Of the two recent meta-analyses, one conducted a meta-regression analysis of studies examining the morphometric correlates of depression and reported that WMH volumes were larger in depressed patients (Arnone et al., 2012). These findings were generated from pooling the results of 4 studies (Kumar et al., 2000; Hannestad et al., 2006; Taylor et al., 2007; Dalby et al., 2010) that included WMH data, yielding a total of 448 patients (mean age

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68, standard deviation 7). Only one of the included studies (51 patients) reported adjusted odds ratios (Kumar et al., 2000).

The second meta-analysis (Herrmann et al., 2008), which was conducted in 2008, specifically investigated (in a secondary analysis) the association of WMH across late versus early onset depression. Depending on the onset group (late onset, early onset, late life), analyses were conducted using between 133 and 514 patients per analysis. The authors (Herrmann et al., 2008) found that patients with late onset depression were more likely to have WMH than those with early onset and postulated that cerebrovascular etiologies might explain this discrepancy. They cautiously noted however that no certain cut-point could be introduced to dichotomize age of onset and that reporting bias may have enhanced observed differences between the groups.

Several factors might be of importance when considering the possible relationship between WMH and depression. First, it seems plausible that WMH occurring in certain anatomic locations (e.g. frontal and paralimbic areas) exhibit stronger associations with depression than others (Thomas and O'Brien, 2009). To date, the majority of research has differentiated between WMH occurring in periventricular (PVWMH) and deep (DWMH) cortical locations. Neuropathology evidence suggests however that the etiology of PVWMH and DWMH may differ (Thomas, 2003). Moreover, PVWMH and DWMH may differentially associate with depression.

Secondly, when assessing the relationship between WMH and depression, it is important to take risk factors predisposing for WMH into account. Age and hypertension are among the most frequently cited risk factors for WMH (De Leeuw et al., 2001; Dufouil et al., 2001), but evidence suggests that additional risk factors like diabetes mellitus and the metabolic syndrome are likely to also play a role in WMH development (Bokura et al., 2008).

Finally, risk factors predisposing for depression are worth consideration. Physical disability, cognitive impairment, cardiovascular disease, and previous history of depression have all been shown to associate with depression (Hackett and Anderson, 2005).

To our knowledge, no meta-analyses to date have leveraged risk factor-adjusted data and performed a comprehensive meta-analysis of WMH (differentiating between PVWMH and DWMH) and depression.

The purpose of this meta-analysis was to determine whether an association between WMH and depression exists if data from studies that have reported adjusted findings are pooled. Additionally, along these lines, we sought to determine if PVWMH and DWMH differentially associate with depression.

2. Method

2.1. Searching data sources

This review was conducted in accordance with MOOSE guidelines (Stroup et al., 2000). We identified original epidemiological studies assessing the relationship between WMHs and depression using computerized literature searches of the PubMed (based on MEDLINE) and Scopus (based on EMBASE) databases. Two readers (CL and LW) searched the PubMed and Scopus databases using the medical subject heading (MeSH) terms: "White matter lesions" OR "white matter disease" OR "Cerebrovascular Disease" OR "Leukoencephalopathy" AND "Psychotic Disorders" OR "Depressive Disorder" AND "magnetic resonance imaging," and finally "Depression" AND "leukoaraiosis." Hand searching was performed of all included studies and relevant review articles.

2.2. Study eligibility

The review included any original human studies having to do either directly or indirectly with WMHs and depression. No selection was made based on language of publication. Studies were only eligible if MRI included T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences had been performed on patients to distinguish WMH.

2.3. Inclusion criteria/Data extraction

Original studies were included if they assessed the relationship between depression (for assessment inventories and cut-points, see Table 1) and WMH (see Tables 2 and 3) and reported generic data (odds ratios or relative risk estimates) in humans using T2 or FLAIR MRI.

In instances where findings were reported from studies multiple times using the same participant/patient sample (i.e. overlapping publications), we included only the most detailed results with the largest study sample appropriate to our purpose (i.e. those results that specifically assessed the relationship between depression and OWMH, PVWMH, and/or DWMH either cross-sectionally, longitudinally, or in a case–control manner). No sample size requirements were assigned for inclusion. For a study sample to be eligible for inclusion, the average age of that sample needed to be over 30 years. In instances where varying degrees of adjustments were used to generate odds ratios or relative risks, we included the maximum adjusted estimate and reported degree of adjustment. If multiple odds ratios were generated for varying severities of WMH, we included the odds ratio generated from comparing the "most severe WMH group" with the "no WMH group." In instances where randomized controlled trials reported specific findings and odds ratios based on a randomization arm, only the patients within that randomization arm were included.

2.4. Meta-analysis

We conducted a random effect meta-analysis and calculated odds ratios and prediction intervals for studies assessing overall WMH (OWMH), PVWMH, DWMH, and depression. Random effect modeling is better suited for higher degrees of heterogeneity and prediction intervals help estimate a range for the true treatment effect in an individual, heterogeneous, setting (akin to reference ranges for a given medical laboratory value) (Egger et al., 1997b; Riley et al., 2011). The endpoint chosen for the meta-analysis was depression (as assessed by clinical interview/symptom severity cut-point) and determinants were OWMH, PVWMH, and DWMH.

In this meta-analysis, "longitudinal studies" were defined as studies that evaluated baseline white matter hyperintensities and depression, and then performed follow-up depression assessment. Depression as an outcome variable was defined for longitudinal studies as the onset of new depressive symptoms (incident depression) or progression of depression symptoms between the time of original MRI and follow-up MRI scans. If possible, only odds ratios generated from comparing incident depression with baseline WMH were used (for original generation of odds ratios, please see Table 1). "Cross-sectional" indicated prospective studies that evaluated depression onset and white matter lesion load at 1 time-point. In cases where prospective cohort studies included both longitudinal and cross-sectional data, that study was included in both longitudinal and cross-sectional analyses. Depression as an outcome variable was defined for cross-sectional studies as the presence of depression at the time of MRI.

For subgroup analyses, studies were stratified according to methodological similarity (i.e., WMH assessment: OWMH, DWMH, PVWMH, frontal lobe WMH; method of WMH assessment: volumetric vs. visual; study design: cross-sectional vs. longitudinal; depression scale used and cut-point/profile analysis; and degree of original adjustment) and included into random effects models that