Journal of Affective Disorders 135 (2011) 315–320

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

MRI signal hyperintensities and failure to remit following antidepressant treatment

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ARTICLE INFO

Article history:
Received 6 June 2011
Accepted 29 June 2011
Available online 29 July 2011

Keywords:
MRI
Late-life depression
Vascular depression
Remission
Antidepressant medication

ABSTRACT

Background: MRI signal hyperintensities predict poor remission to antidepressant treatment. Previous studies using volumetrics in outpatient samples have relied on total lesion volume. The purpose of this study was to test whether remission from geriatric depression depends on lesion volume by region of interest (ROI).

Method: Thirty-eight patients received baseline MRIs as part of a larger 12-week, randomized clinical trial comparing sertraline and nortriptyline in the treatment of late-life depression. MRIcro was used to quantify MRI-hyperintensity volume into total hyperintensity, deep white matter hyperintensity (DWMH), and periventricular hyperintensity (PVH) volumes. High versus low total, DWMH, and PVH volumes were defined based on the highest quartile of their respective distributions. Remission from depression was defined as a 24-item Hamilton Rating Scale for Depression score ≤ 7 for two consecutive weeks.

Results: Patients classified as having high DWMH were 7.14 times more likely not to remit following antidepressant treatment compared to patients classified as having low DWMH ($p = 0.02$). Similar odds ratios were obtained for PVH (OR = 4.17, $p = 0.16$) and total volumes (OR = 5.00, $p = 0.05$). Importantly, adjusting for age did not change the magnitude of these effects.

Limitations: A small and predominantly White sample.

Conclusions: This is the first study to test whether remission from geriatric depression depends on lesion volume by ROI in an outpatient sample. The pattern of remission rates and odds ratios was similar when patients were classified as having high DWMH, PVH or total volume suggesting that lesion location may not be critical.

1. Introduction

MRI signal hyperintensities are common in late-life depression (LLD). When compared with age-matched controls, high rates of MRI abnormalities have been consistently observed in patients with LLD (Coffey et al., 1993; Fujikawa et al., 1993; Hickie et al., 1995; Krishnan, 1993; Lesser et al., 1996). MRI

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doi:10.1016/j.jad.2011.06.052

hyperintensities in LLD appear to be overrepresented in frontal and subcortical regions (Firbank et al., 2004; Greenwald et al., 1998; O'Brien et al., 1996; Taylor et al., 2003a), are associated with cognitive deficits (Kramer-Ginsberg et al., 1999; Lesser et al., 1996; Potter et al., 2007), and have been hypothesized to form the basis for vascular depression in late-life (Alexopoulos et al., 1997a, 1997b; Krishnan and McDonald, 1995; Krishnan et al., 1997; Steffens and Krishnan, 1998); that is, depression resulting from structural damage to corticostriatal circuits due to cerebrovascular disease that is characterized by executive dysfunction and poor antidepressant treatment response (Culang-Reinlieb et al., 2010).

Patients with LLD characterized by significant MRI signal hyperintensities have been shown to respond poorly to antidepressant treatment (Alexopoulos et al., 2002, 2008; Hickie et al., 1995; Navarro et al., 2004; Patankar et al., 2007; Simpson et al., 1998; Taylor et al., 2003b). For example, the sum of severity ratings across three brain areas (deep white matter, periventricular, and subcortical nuclei) based on a visual rating scale of MRI signal hyperintensities predicted depression symptom severity after 12 weeks of antidepressant treatment (Sheline et al., 2010). In another recent study, patients who failed to remit following treatment with antidepressant medication had significantly greater MRI signal hyperintensity burden compared to both patients who remitted and elderly comparison subjects using total lesion volume based on a semi-automated lesion quantification method (Gunning-Dixon et al., 2010).

However, not all studies agree (Janssen et al., 2007; Krishnan et al., 1998; Salloway et al., 2002b; Sneed et al., 2007). One study examined the predictive utility of age of onset, executive dysfunction, and MRI hyperintensity burden on antidepressant treatment response in depressed patients aged 75 and over and found that MRI hyperintensity severity did not predict poor response (Sneed et al., 2007). Similarly, a placebo-controlled trial of sertraline in older depressed outpatients found no association between MRI hyperintensities and acute treatment response to antidepressant medication (Salloway et al., 2002a). However, all of these studies have relied on either visual rating scales of lesion severity (Hickie et al., 1995; Navarro et al., 2004; Simpson et al., 1998; Sneed et al., 2007; Taylor et al., 2003a) or semi-automated methods to calculate total lesion volume (Gunning-Dixon et al., 2010; Sheline et al., 2010).

Only one study has attempted to decompose total volume into anatomically separate regions of interest to determine the relationship between volume of lesion location and outcome (Janssen et al., 2007). This 12-week controlled trial of venlafaxine or nortriptyline did not find an association between location and outcome but was conducted in depressed geriatric inpatients only. Therefore, the specificity of lesion location hypothesis has not been tested. This is interesting considering 1) the predictions based on the vascular depression hypothesis, 2) differences in the pathophysiology of deep white matter hyperintensities (DWMH) and periventricular hyperintensities (PVH) (Thomas et al., 2002a, 2002b, 2003), and 3) DWMH are more strongly associated with depressive symptoms in late-life than PVH (Krishnan et al., 2006; Nebes et al., 2001).

The purpose of this study is to examine the relationship between lesion volume location (as well as total volume) and remission from depression following antidepressant treatment. To address this issue, we use data from a 12-week, randomized, double-blind study of depressed older adult outpatients treated with sertraline or nortriptyline. To our knowledge, this is the first attempt to test the specificity of lesion volume location, which is important because lesion volume ratings are a more sensitive indicator of cerebrovascular disease than severity ratings (Gunning-Dixon et al., 2010). We hypothesized based on the vascular depression hypothesis that there would be a significant association between non-remission and high DWMH and total lesion volume but not PVH volume.

2. Methods

2.1. Participants

Thirty-eight patients meeting DSM-IV criteria for MDD of the melancholic or non-melancholic subtype received MRIs of the brain as part of a larger (N = 112) double-blind, randomized, 12-week clinical trial of nortriptyline and sertraline. Patients were recruited by radio and newspaper advertisements and/or through referral from other physicians to our university-based geriatric psychiatry clinic. At the initial visit, a comprehensive psychiatric evaluation, including a Structured Clinical Interview for DSM-IV, 24-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), a Mini-Mental State Examination (MMSE) (Folstein et al., 1975), and a medical history was performed. If the patient met inclusion criteria and signed informed consent, a physical examination, an electrocardiogram, complete blood count, chemistries, electrolytes, and thyroid panel were performed.

Inclusion criteria were 1) age ≥ 45; 2) unipolar depression, single or recurrent, nonpsychotic, by DSM-IV criteria; 3) HRSD ≥ 16 at the initial visit and at the end of 1 week of placebo; and 4) willing and able to give informed consent. Exclusion criteria were 1) history of or current psychotic disorder, or substance dependence within the past year (other than nicotine) by DSM-IV criteria; 2) judged to have a current suicide risk or serious suicide attempt within the past year; 3) patients with coronary artery disease (e.g., myocardial infarction, coronary artery bypass, angioplasty), or with positive history of angina or positive stress test; 4) QRS interval greater than 0.12 s or Qtc interval ≥ 46 ms; 5) treatment with coumadin, heparin, or type 1 antiarrhythmic medications; 6) diagnosis of narrow angle glaucoma; 7) MMSE score ≤ 24; 8) stroke, epilepsy or Parkinson's disease; 9) an acute, severe or unstable medical condition; 10) positive urine toxicology screen for drugs of abuse (e.g., amphetamine, barbiturates, cocaine, marijuana, methadone, methaqualone, opioids, PCP); and 11) treatment in the current episode of depression with either nortriptyline with a plasma level between 50 and 150 ng/ml, desipramine or imipramine at a plasma level of 250 ng/nl or greater for at least 4 weeks, or paroxetine 40 mg, fluoxetine 40 mg or sertraline 200 mg for at least 4 weeks. Patients were asked but not required to participate in an MRI study prior to medication treatment.

2.2. Treatment

Patients who met inclusion/exclusion criteria and signed informed consent were given a one week, single-blind, placebo lead-in. If patients still met inclusion/exclusion criteria at the end of the placebo lead-in, or their HRSD scores did not