Progress in Neuro-sychopharmacology & Biological Psychiatry 32 (2008) 1501–1507

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression

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ARTICLE INFO

Article history:
Received 28 December 2007
Received in revised form 25 April 2008
Accepted 10 May 2008
Available online 20 May 2008

Keywords:
Bipolar disorder
Major affective disorders
Major depressive disorder
Suicide
White matter hyperintensities

ABSTRACT

The aim of this study was to evaluate whether deep white matter hyperintensities (DWMH) and periventricular white matter hyperintensities (PVH) are associated with suicidal behavior in patients with major affective disorders. Subjects were 99 consecutively admitted inpatients (42 men; 57 women; mean age: 46.5 years [SD = 15.2; Min./Max. = 19/79]) with a diagnosis of major affective disorder (bipolar disorder type I, bipolar disorder type-II and unipolar major depressive disorder). 44.4% of the participants had made at least one previous suicide attempt. T2-weighted brain magnetic resonance images were rated for the presence and extension of WMH using the modified Fazekas scale. Patients were interviewed for clinical data on average 5 days after admission. Bivariate analyses, corrected for multiple-testing, and logistic regression analysis were used to test the association between suicide attempts and clinical variables. Attempters and nonattempters differed only in the presence of PVH—the former were more likely to have PVH. The logistic regression indicated that the presence of PVH was robustly associated with suicidal behaviors after controlling for age (OR: 8.08). In conclusion, neuroimaging measures may be markers of risk for suicidal attempts in patients with major affective disorders.

1. Introduction

In the year 2000, approximately one million people died by suicide. For every completed suicide, there are somewhere between 10 and 40 attempted suicides (World Health Organization, 1999, 2002). Other sources estimate that there are ten to 25 non-fatal suicide attempts for every completed suicide, and these numbers rise to 100–200 for adolescents (Maris, 2002). However, no reliable data exist on the real dimension of the burden of suicide attempts worldwide, but, nevertheless, there is general agreement that the risk of repeated non-fatal suicidal acts seems to be growing.

Suicidal behavior as a whole is a complex phenomenon often resulting from the interplay of many factors. Despite efforts to predict and prevent it, inroads toward the reduction of completed and attempted suicide rates remain modest. Both biological and psychological models have been employed to better understand this behavior. Several neuroimaging studies have suggested possible biological markers for suicidal behavior (Ahearn et al., 2001; Oquendo et al., 2003).

White matter hyperintensities (WMH) appear as hyperintense signals on T2-weighted magnetic resonance images (MRI) and represent ependymal loss and differing degrees of myelination in elderly samples (Thomas et al., 2002a,b). Little is known about the

Abbreviations: 1-fet, one-sided Fisher exact test; 95%CI, 95% confidence intervals; BD-I, bipolar disorder type I; BD-II, bipolar disorder type-II; χ^2, Chi-squared test; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; MDD, unipolar major depressive disorder; MRI, magnetic resonance images; OR, Odds ratio; WMH, white matter hyperintensities; PVH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities.

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doi:10.1016/j.pnpbp.2008.05.009

histopathologic correlates of WMH in the young population, and these lesions can be related to a wide variety of clinical conditions and pathophysiological processes (Barkhof and Scheltens, 2002; Pantoni, 2002).

WMH, depending on the localization, are commonly classified as periventricular hyperintensities (PVH) or deep white matter hyperintensities (DWMH). Deep white matter hyperintensities were identified as having mainly a vascular etiology, and periventricular hyperintensities could be due to ependymal loss, differing degrees of myelination and cerebral ischemia (Thomas et al., 2002a,b). WMH are reported to be commonly associated with older age (Silverstone et al., 2003), and cardiovascular risk factors such as hypertension and diabetes (Ovbiagele and Saver, 2006; Steffens and Krishnan, 1998; Videbech, 1997).

Degenerative changes in brain white matter have been studied in conjunction with many psychiatric disorders and associated with suicidal behavior (Ehrlich et al., 2005; Ehrlich et al., 2004; Pompili et al., 2007). Studies have found a higher rate and intensity of WMH in patients with unipolar depression, as well as in those with bipolar disorder, in comparison with individuals who were not ill (Chang et al., 2005; Coffey et al., 1993; Hajek et al., 2005; Hickie et al., 1995; Sassi et al., 2003; Soares and Mann, 1997; Zanetti et al., 2007). Specifically, increased WMH in groups of elderly subjects with depression have been a well-replicated finding (Coffey et al., 1990; Howard et al., 1993; Krishnan et al., 1993; Lesser et al., 1991; Rabins et al., 1991; Zubenko et al., 1990). However, negative findings with younger groups have also been reported (Brown et al., 1992; Guze and Szuba, 1992). Pompili et al. (2007) found that subjects with WMH were 4.7 (95% Confidence Intervals: 1.4, 16.1) times more likely to have had a past suicide attempt than subjects without WMH.

Previous studies hypothesized that patients with WMH may be at higher risk for suicide because of possible disruption of neuroanatomic pathways (Taylor et al., 2001). Mood regulation depends on the complex system composed of the prefrontal cortex, amygdala–hippocampus complex, thalamus, basal ganglia and the extensive connections between these areas (Soares and Mann, 1997). Lesions in one specific part or disruption of interconnections can result in malfunctions in other areas. Mood regulation abnormalities could confer a biological vulnerability which, in combination with environmental stressors, results in suicidal behavior. The etiology of WMH with respect to suicidality and mood disorders could be hypoxic–ischemic insults during birth which are especially common in preterm infants. Perinatal white matter lesions, represent damage of association-commissural and projection fibers and may lead to disturbances in the organization and use of neural systems (Judas et al., 2005; Peterson, 2003). Whitaker et al. (1997) indicated that neonatal cranial ultrasound abnormalities suggestive of white matter injury significantly increase the risk for psychiatric symptoms.

The aim of the present study was to evaluate whether the presence of DWMH and PVH and their extension are associated with suicide attempts in patients with major affective disorders. This study is a development of a previous study evaluating the association between WHM and suicide attempts (Pompili et al., 2007). We hypothesize that those who have hyperintensities, by whatever etiology, may be at higher risk of suicide.

2. Materials and methods

2.1. Subjects

From September 2006 to June 2007, a total of 142 white Italian patients consecutively admitted to the Sant'Andrea Hospital's psychiatric ward in Rome were studied. The inclusion criterion was a DSM-IV-TR diagnosis of major affective disorders (unipolar major depressive disorder, bipolar disorder type I, bipolar disorder type II). Of these, 43 were not included in the final sample; 84% of those patients were excluded because they were diagnosed with schizophrenia, and 16% were excluded because they refused to undergo the MRI scans although they were consistent with the inclusion criterion. However, these patients did not differ significantly from the patients included in the final sample in demographic variables, diagnosis, or history of suicide attempts.

The final sample consisted of 99 participants whose mean age was 46.5 years (SD = 15.2; Min./Max.: 19/79). 40.4% of the participants were diagnosed as bipolar type I (BD-I), 21.2% were diagnosed as bipolar type-II (BD-II) and 38.4% were diagnosed as unipolar major depressive disorder (MDD). 21.2% of the participants reported current substance abuse (13.1% of the patients reported alcohol abuse, 6.1% reported illicit drug abuse, most commonly cannabis, and 2.0% reported a concurrent abuse of alcohol and illicit drugs). A comparison of the demographic and diagnostic variables in the suicide attempters and nonattempters is shown in Table 1. Of the 99 patients included in the sample, 44 inpatients (28 women and 16 men) had attempted suicide in the past 6 months (and not less than 14 days) that resulted in physical injury. (35% of the attempters used a violent method for suicide.). According to revised nomenclature (Silverman et al., 2007a, b) these acts should be labelled as suicide attempts type II, that is, a self-destructive act with some degree of intent to end one's life and some identifiable injuries.

Exclusion criteria were a diagnosis of neurological disorder (e.g., epilepsy, multiple sclerosis, and Alzheimer's Disease), a current diagnosis of schizophrenia or other psychotic disorders, delirium,

Table 1
Bivariate analyses for suicidal groups

Variables	Bivariate analysis				Multivariate analysis	
	Non attempters	Attempters	Test	Sig. ($p<$)	OR (95%CI)	Sig. ($p<$)
	(N=55)	(N=44)				
Women—N (%)	29 (50.9)	28 (49.1)		.19[a]		
Men—N (%)	26 (61.9)	16 (38.1)				
Age—M (SD)	47.27 (14.54)	45.57 (16.10)	.55 (df: 97)	.58[b]	.97 (.94\1.00)	.08
Diagnosis—N (%)			2.19 (df: 2)	.34		
Bipolar disorder type I	19 (47.5)	21 (52.5)				
Bipolar disorder type II	14 (66.7)	7 (33.3)				
Major depressive disorder	22 (57.9)	16 (42.1)				
Antidepressants—N (%)	15 (55.6)	12 (44.4)		.59[a]		
Mood stabilizers—N (%)	26 (48.1)	28 (51.9)		.08[a]		
Antypsychotics—N (%)	30 (55.6)	24 (44.4)		.58[a]		
Drug or alcohol abuse—N (%)	11 (52.4)	10 (47.6)		.47[a]		
DWMH—N (%)	16 (45.7)	20 (55.6)		.07[a]		
PVH—N (%)	7 (25.9)	20 (74.1)		**.001*****[a]	8.08 (2.67/ 24.51)	.001
Hypertension—N (%)	8 (47.1)	9 (52.9)		.24[a]		
Total cholesterol—M (SD)	177.26 (33.80)	195.11 (34.07)	−2.17 (df: 69)	**.05**[b]		
Triglycerides—M (SD)	131.31 (89.27)	118.15 (45.87)	.80 (df: 67)	.42[b]		
Glycaemia—M (SD)	89.16 (19.51)	87.78 (20.77)	.30 (df: 60)	.77[b]		

OR: Odds Risk; 95%CI: 95% Confidence Intervals; DWMH: Deep White Matter Hyperintensities; PVH: Periventricular White Matter Hyperintensities.
Benjamini and Hochberg's correction: * test significant for $p<.05$; ** test significant for $p<.01$; *** test significant for $p<.001$.
[a] one-side Fisher exact test.
[b] t-test.