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ORIGINAL PAPER

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White matter hyperintensities and their associations with suicidality in patients with major affective disorders

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Abstract *Introduction* A large body of evidence suggests that predisposition to suicide, an important public health problem, is mediated to a certain extent by neurobiological factors. The objective of this cross-sectional study was to compare the prevalence of white matter hyperintensities (WMH) in patients with major affective disorders with and without histories of suicide attempts. *Methods* T2-weighted magnetic resonance images (MRI) of 65 psychiatric inpatients with major depressive disorder or bipolar disorder were rated for the presence of WMH. Diagnoses, presence or absence of suicide risk and substance abuse were determined by the Mini International Neuropsychiatric Interview (MINI). Medical charts were reviewed to ascertain history of suicide attempt and basic clinical variables. Fisher's Exact Tests and logistic regression modeling were used to test the association between WMH and suicidality. Suicidal patients and controls were not matched for demographic variables and exposure to some risk factors. *Results* Bivariate analysis showed that the prevalence of WMH was significantly higher in subjects with past suicide attempts (Fisher's Exact Test, $p = 0.01$) and other clinical indicators of elevated suicide risk. Logistic regression analyses controlling for age, sex, and several clinical risk factors supported this finding (odds ratio = 4.7; 95% confidence interval: 1.4, 16.1). *Conclusions* The increased prevalence of WMH in adults with major affective disorders and a history of suicide attempt, compared to similar patients without such a history, is consistent with previous findings in depressed children, youth and young adults. However, the association between WMH and suicidality holds true for both, depressed and bipolar patients. Our results suggest that WMH in patients with major affective disorders might be useful biological markers of suicidality.

Key words mood disorders · suicide · white matter hyperintensities

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Introduction

Major affective disorders are commonly associated with a high degree of suicidality. Epidemiological studies showed that 29% of individuals with a diagnosis of Bipolar Disorder (BD) and 15% of those with Major Depressive Disorder (MDD) attempt suicide at least once in their lifetime [8]. About 10–15% of the

patients with BD and 2–12% of the patients with MDD end their lives by committing suicide [6, 33]. Clinical risk factors for completed suicides in major affective disorders include male gender, history of previous suicide attempts and hopelessness. Risk factors for suicide attempts comprise family history of suicide, history of previous suicide attempts, severe depressive episodes, substance abuse, comorbid anxiety or eating disorders, early physical or sexual abuse and single marital status [3, 16].

In the recent decades researchers sought to identify the biological basis of suicidality. Twin studies show that monozygotic twins have a greater concordance rates of suicidal behavior than dizygotic twins even after adjusting for presence of psychiatric disorders. Adoption studies also suggest that there may be genetic factors in suicide. The variability in suicidal behaviour explained by genetics was estimated to be 43% [7, 24]. Although many association studies reported inconclusive results, two gene polymorphisms, one in the gene coding for the tryptophan hydroxylase 1 (TPH1 A218C) and the other in the serotonin transporter gene (5-HTTLPR), were found in meta-analyses to be associated with suicidal behaviour [5]. In line with two serotonin system candidate genes, suicide attempters and victims have a variety of abnormalities in the serotoninergic system such as low cerebrospinal fluid 5-HIAA, fewer serotonin transporter sites in the prefrontal cortex and upregulated postsynaptic 5-HT1A and 5-HT2A receptors [22].

In depressed patients three recent studies have shown associations between White Matter Hyperintenisties (WMH) and a history of suicide attempts [1, 13, 14]. These studies cover the populations of children and adolescents, young adults and elderly women. WMH appear as hyperintense signals on T2-weighted magnetic resonance images (MRI). They are commonly classified into periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH). WMH represent ependymal loss and differing degrees of myelination [36, 37]. In comparison to healthy control subjects, WMH have been shown to be more prevalent in patients suffering from major depressive disorder (MDD) or bipolar disorder (BD). Furthermore, WMH are commonly associated with older age and cardiovascular risk factors such as hypertension and diabetes [29, 35, 38].

The objective of this study was to investigate the relationship of WMH with suicidality in psychiatrically hospitalized adult patients with major affective disorders.

Methods

The sample population consisted of subjects consecutively admitted to the psychiatric inpatient unit of a major university hospital who had clinical MRI brain scans between April 2005 and September 2006. Referral to brain imaging was part of the clinical evaluation. For this analysis, were included only individuals with a DSM-IV discharge diagnosis of MDD or BD but without an additional Axis I diagnosis of schizophrenia or psychosis NOS. Our final sample consisted of 65 caucasian subjects, 29 (44.6%) with a history of at least one suicide attempt. Controls (i.e., people without any history of suicidal behaviour) were selected not restricting variability of nuisance variables and matching suicidal people for exposure to risk factors, since this could have resulted in a biased association between variables. Sociodemographic and clinical characteristics are listed in Table 1.

Measures

Brain MRI was performed using a Sonata, Siemens, Eriangen Scanner (1.5 T). FLAIR (ax: TR 10000; TE 125; thickness 5 mm; matrix 144×256) proton density and T2-weighted images were obtained (DP and T2 ax: TR 2870; TE 13/107; thickness 5 mm; matrix 147×256) in the axial and the coronal planes. Axial and sagital T1-weighted images were also obtained (T1 ax: TR 647; TE 17; thickness 5 mm; matrix 128*192 T1 sag: TR 552; TE 17; thickness 5 mm; matrix 231×192). The presence of WMH were assessed by a neuroradiologist blind to all clinical information using the modified Fazekas four-point rating scale, which describes MRI hyperintensities on an ascending scale of severity and frequency [15]. A second neuroradialogist, blind to all clinical information and previous ratings, reviewed all MRI films. The κ value for interrater reliability was 0.96.

Following approval from the hospital's Institutional Review Board, patients gave written informed consent and were assessed using the Mini International Neuropsychiatric Interview, Italian

Table 1 Socio-demographic and clinical variables by suicidality and WMH

	No h/o suicide attempt (n = 36)	h/o suicide attempt (n = 29)	Test/Sig.	No WMH (n = 38)	WMH (n = 27)	Test/Sig.
Female—N (%)	17 (47.2)	24 (82.8)	0.003*	20 (52.6)	21 (77.8)	0.03
Age—Mean (SD)	44.61 (13.95)	42.17 (13.51)	0.71[b]/0.48	39.66 (12.73)	48.96 (13.38)	2.84[b]/0.01*
MDD	18 (50.0)	8 (27.6)	0.06	17 (44.7)	9 (33.3)	0.25
Age of onset—Mean (SD)	35.59 (9.86)	39.68 (11.07)	1.56[b]/0.13	35.43 (9.48)	40.20 (11.46)	1.83[b]/0.07
Previous major depressive episodes—N (%)	14 (38.9)	20 (69.0)	0.02*	19 (50.0)	15 (55.6)	0.43
Gotland Depression Scale—N (%)						
Moderate depression	14 (38.9)	17 (58.6)	4.59[a]/0.10	15 (39.5)	16 (59.3)	5.53[a]/0.06
High depression	7 (19.4)	7 (24.1)		7 (18.4)	7 (25.9)	
Total symptoms (GSI)—Mean (SD)	95.42 (53.44)	137.59 (62.87)	2.92[b]/0.01*	142.52 (54.95)	94.13 (57.83)	3.39[b]/0.001*
Substance use—N (%)						
Alcohol	5 (13.9)	6 (20.7)	0.68[a]/0.71	9 (23.7)	2 (7.4)	4.13[a]/0.13
Illicit Drugs	3 (8.3)	3 (10.3)		2 (5.3)	4 (14.8)	

Test = Fisher Exact test; [a]chi suare; [b]t-test
*Significant *p*-values after correction for multiple testing with Hochberg's Sequential Method

Version 5.0 [20, 31]. The Mini International Neuropsychiatric Interview (MINI) is a short structured interview with high validity and reliability [2] developed to explore 17 disorders according to DSM-III-R. Although MINI should not substitute a psychiatric investigation, validation studies confirm the validity of this instrument as a reliable tool in psychiatry [31]. MINI diagnoses were confirmed by clinical DSM-IV-TR diagnoses. Clinical diagnoses were assigned by a staff psychiatrist and the attending physician who were blind to the results of MINI and MRI.

Informations about suicidal ideation, the presence and lethality of suicide history were determined by clinical interviews and previous medical charts by trained physicians blind to MRI results. In addition, current suicide risk and substance abuse were assessed using MINI.

Severity of depression was assessed through The Gotland Male Depression Scale [26, 27] which consists of 13 items. Each item is rated on a four-point Likert scale. The standardization of the total score is as follows: 0–12 = no depression; 13–26 = probable depression and antidepressants should be considered; 27–39 = definite depression and antidepressants should be prescribed.

Symptom severity was determined using the global severity index (GSI) of the symptom checklist SCL-90-R [9]. The SCL-90 is a 90-item multidimensional self-report inventory designed to screen for a broad range of psychological problems and symptoms of psychopathology. A variety of studies have demonstrated the reliability, validity, and utility of the instrument [10, 11].

Blood pressure and total cholesterol were retrieved from official medical records. Hypertension was defined as the presence of more than one systolic blood pressure reading ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or current use of antihypertensive medication [17].

Statistical analysis

Analyses were carried out using SPSS 11.5 for Windows. If not otherwise indicated statistical tests are two-tailed with alpha = 0.05.

Results

Association between WMH and suicide history

MRIs of 27 (41.5%) subjects showed WMH. There was no significant difference in the frequency of previous suicide or WMH between subjects with MDD and BPD. The prevalence of WMH in subjects with histories of suicide attempts was significantly higher than in nonattempters. Only 10 (27.8%) of 36 subjects without a history of suicide attempt had WMH, but 17 (58.6%) of 29 subjects with such a history had WMH (One sided Fisher's Exact Test (1s-FET): $p = 0.01$). Twenty-four subjects (48%) with an elevated suicide risk as assessed by M.I.N.I. had WMH but only 3 (20%) without such risk (1s-FET: $p = 0.05$). Lifetime suicidal ideation was also positively associated with the presence of WMH on MRI. However, suicidal ideation in the absence of a history of suicide attempt was not significantly associated with WMH (44.4% vs. 40.4%; 1s-FET: $p = 0.5$). Subanalyses of the relationship between suicidality and WMH depending on diagnosis revealed the same results for bipolar patients (n = 39) but was not meaningful for patients with MDD due to the small sample size (n = 26). Finally, neither hypertension (1s-FET: $p = 0.64$) nor total cholesterol (177.21 mg/dl (SD = 43.56) vs. 188.07 mg/dl (SD = 28.29); t = 1.16; $p = 0.25$) were associated with a positive history of suicide attempts.

Logistic regression models were performed to predict a positive or negative history of suicide attempt(s) as the dependent variable (Table 2), after controlling for demographic and clinical covariates. The models showed that WMH were a significant predictor of past suicide attempt. The demographic control variables age and gender but neither the dichotomous clinical control variables diagnosis and substance abuse (Models 2–3) nor the variables indicating high cholesterol and hypertension had a significant impact on the probability of past suicidality (M6, M7).

According to the model in which only significant predictors were included (M final), subjects with WMH were 4.7 (95% CI: 1.4, 16.1) times more likely to have had a past suicide attempt than subjects without WMH. Female subjects were 5.7 (95% CI: 1.6, 20.2) times as likely as males to have had a past suicide attempt and older subjects were significantly less likely to have had a past suicide attempt (0.95; 95% CI: 0.93, 0.98). Analysis of interaction (not shown) failed to reveal any differences.

Table 2 Nested taxonomy of fitted logistic regression models in which patients history of suicide attempt is predicted by white matter hyperintensities and controlling for several other variables

	Predictor	M1	M2	M3	M4	M5	M6	M7	M final
Question variable	WMH	1.70 ns	5.20**	4.67*	3.94*	3.99*	4.59*	4.28*	4.67*
Control variables	Age		0.98**	0.95***	0.96**	0.96**	0.96**	0.94*	0.95***
Demographics	Gender (female)			5.73**	6.19**	6.42**	6.05**	5.4**	5.73**
Control variables	Diagnosis (MDD)				0.42 ns	0.47 ns	0.45 ns	0.46 ns	
Symptoms	Substance abuse					1.80 ns	1.83 ns	1.41 ns	
	Hypertension						0.60 ns	0.63 ns	
	Cholesterol							1.01 ns	
Model summary	χ^2	1.84	9.68	18.19	20.08	20.86	21.16	22.11	18.18
	Change in χ^2	1.84 ns	7.84**	8.50**	1.90 ns	0.79 ns	0.30 ns	0.95 ns	3.94 ns
	Cox & Snell R^2	0.028	0.138	0.244	0.266	0.275	0.278	0.288	0.244

Values are given as odds ratios
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, ns $p > 0.05$

Association between WMH and other factors

In addition to examining the association between MRI hyperintensities and suicidality, we further investigated the effects of control variables in predicting WMH presence. Bivariate statistics (Table 1) showed significant positive correlations between age and WMH as well as symptom severity (determined by SCL 90 total symptom score) and WMH, even after adjusting *p*-values for multiple testing. These associations were confirmed using logistic regression models predicting the absence or presence of WMH and controlling for all other variables (not shown). WMH were also related to hypertension (29.6% vs. 2.6%; 1s-FET: $p = 0.003$) and total cholesterol (196.13 mg/dl (SD = 30.37) vs. 169.89 mg/dl (SD = 39.82); t = 2.88; $p = 0.01$), but not to smoking (96.3% of the patients with WMH smoked more than 10 cigarettes a day vs. 92.1% of the patients without WMH; 1s-FET: $p = 0.45$).

Discussion

We found increased incidence of WMH in patients with major affective disorder and a history of suicide attempt. These findings support and extend the results of previous studies showing an association between WMH and suicidality in patients with MDD [1, 13, 14]. Furthermore, WMH in patients with major affective disorders did not distinguish between non-suicidal individuals and suicidal ideators who had never attempted suicide, a finding that is also consistent with earlier work [13, 14].

The relationship between suicidality and WMH has not been investigated previously in adult patients with BD. Our study suggests that WMH are not only a marker for past suicide attempts in patients with MDD but also in patients with BD. Models controlling for additional risk factors such as comorbid substance abuse did not change the relationship. This contradicts the findings of Ehrlich et al. in children and adolescents [14]. In this study, WMH were significantly associated with a history of suicide attempt only among a subgroup of children and adolescents with MDD. The general prevalence of WMH in the present study (41.5%) was only slightly higher than in the studies by Ehrlich et al. (28.8% and 34.3%). However, differences might be attributed to the distinct age group, the different conceptualization of pediatric BD [40] and the utilization of different criteria for WMH.

Logistic regression analyses showed that besides WMH, female gender was another strong predictor of suicidality in patients with major affective disorder. This is supported by epidemiological data from the general population whereas in patients with MDD and BD some but not all studies found a clear association between female gender and the prevalence of previous suicide attempts [3, 16].

Age was positively correlated with the frequency of WMH. This can be explained by the well-replicated association of cardiovascular risk factors with deep white matter hyperintensities which was confirmed in the present study [29, 35]. However, the prevalence of past suicide attempts was inversely associated with age even in the presence of WMH. This is in line with previous findings and might support the hypothesis by Ehrlich et al. that WMH associated with suicidality are different from those associated with cardiovascular risk factors [12]. For example, the etiology of WMH significant to suicidality 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 [18, 30]. Neonatal cranial ultrasound abnormalities suggestive of white matter injury significantly increase the risk for psychiatric symptoms [39], maybe triggering malfunctions in other areas of the emotional regulatory circuit [34] and conferring a biological vulnerability.

Bivariate analyses showed a positive relationship between WMH and symptom severity. Complementing our findings, other researchers have reported similar results. Higher rates of WMH were associated with multiple psychiatric admissions, higher rates of relapse and poor long-term outcome [28, 32, 41]. Furthermore, lower intelligence test scores, impaired psychomotor speed, information processing and executive ability are also associated with increased severity of white matter lesion ratings [19, 21].

Limitations

The findings of this study should be considered in light of the following limitations. First, like previous studies the individuals received inpatient treatment and were referred for clinical brain imaging, which may constitute a selection bias limiting the generalizibility of our findings to the more general population of persons with affective disorders. However, the evaluation of suicide risk is of particular importance in this severely ill patient group. Therefore a reliable biological marker of suicidality, even if applicable only to this patient population, would be a benefit. Secondly, the generalizability of our findings is limited by the usual difficulties of a retrospective assessment of suicide attempts and the review of clinical chart records. Furthermore, suicide attempts could not be classified retrospectively regarding to their potential lethality. Thirdly, our patients had in some cases complex treatment regimens, including antidepressants administered alone, in combination or as add-on therapy. It could be argued that these patients suididality was induced by antidepressant treatment. However strong and clear scientific evidence supporting this notion is still lacking [4, 25].

Fourthly, patients with WMH were significantly older than patients without WMH. WMH are known to be associated with cardiovascular risk factors which become more prevalent with older age [12]. Older subjects and especially older subjects with WMH were significantly less likely to have had a history of suicide attempt. Fifthly, due to the lack of data we were not able to differentiate between subtypes of WMH. Previous studies found a positive association between periventricular hyperintensities and suicidality whereas deep white matter hyperintensities were more closely related to cardiovascular risk factors [13]. Finally, WMH have been found to be more prevalent in a variety of psychiatric and neurologic disorders [29]. Future studies in adult patients should address the specificity of WMH as a marker for previous suicide attempts.

Conclusion

Our study suggests that adults with major affective disorders and WMH are more likely to have a history of suicide attempt compared to similarly ill subjects without WMH. This adds support to previous findings pointing to a neurobiological substrate of suicidality. A biologic correlate of suicidality, whether or not causally related, needs to be evaluated as a potentially predictor of suicide attempts because clinical predictors have proven to have reasonable sensitivity but insufficient specificity. Combining clinical and biologic predictors that are independent, may provide an improved predictive model [23].

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