Biochemical Correlates of MRI White Matter Hyperintensities

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The aims of the study are to investigate the relationship between the presence of white matter hyperintensities (WMH) at magnetic resonance imaging (MRI) and blood biochemical anomalies in Romanian adult psychiatric patients. The authors performed a transversal research onto 2 study groups: a group of 40 psychiatric patients with a suicidal attempt history and a group of 45 psychiatric patients without declarative suicidal ideation (control group). At MRI, a higher rate of Fazekas type 1 and 2 WMH was encountered in patients with suicidal attempt compared to control group. Patients with a history of suicidal attempt also registered lower levels of cholesterol and platelet serotonin compared to control group ($p < 0.001$). Other blood parameters (triglycerides, total proteins, blood cells) registered no statistically significant differences. Relative risk analysis showed that the presence of deep and periventricular WMH associated with low level of cholesterol and platelet serotonin increase the risk of suicidal attempt. The presence of morphological brain alterations and biochemical blood anomalies can predict a potential suicidal attempt in psychiatric patients.

Keywords: magnetic resonance imaging, white matter hyperintensities, platelet serotonin, cholesterol, triglycerides, biochemical anomalies

Researchers worldwide tried to identify a neurobiological and biochemical basis of suicidality, and recent studies showed an association between the presence of white matter hyperintensities (WMH), biochemical anomalies, suicidal attempts and suicidal ideation. White matter hyperintensities are classically divided into periventricular (PeWMH) and deep white matter hyperintensities (DWMH) and indicate myelin pallor, mild gliosis and tissue rarefaction.

From a biochemical point of view, there is evidence for the relevance of a serotonin ($C_{10}H_{12}N_2O$) and dopamine ($C_8H_{11}NO_2$) model of aggression as a major risk factor for suicide and their involvement in depressed mood [1], and possibly the individual's ability to cope with imminent suicidality (fig. 1). Platelet serotonin concentration has been proposed as a peripheral marker of the central serotonergic synaptosomes, thus related to disturbances in the central serotonergic system. Cholesterol is one of the main components of the neuronal membrane and its level has been associated with the functioning of the serotonergic system [2].

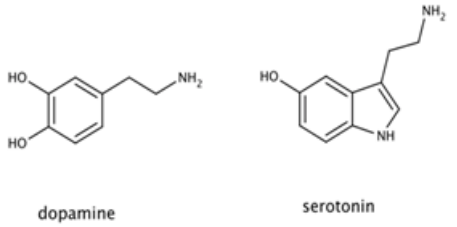

Fig. 1. Chemical structure of dopamine and serotonin

Several clinical features in depression such as anxiety, panic disorders, sleep disturbances, poor concentration, drug addiction seem to be linked to suicide, being highly associated with early death within one year of initial assessment. Suicidal attempts are defined as intentional, self-inflicted, and life-threatening acts that do not result in death. Suicidal ideation is broadly defined as a range of thoughts an individual may have related to the act of committing suicide [3]. Worldwide there is a rate of one million deaths/year by suicide and 15% are considered consequences of primary affective disorder [4, 5].

The aims of the study are to investigate the relationship between the presence of white matter hyperintensities (WMH), blood biochemical anomalies and suicidal behaviour in Romanian psychiatric adult patients.

Experimental part

Materials and methods

The study is a transversal research performed between april 2010-october 2012 at the University Psychiatric Hospital *Socola* from Iasi, Romania.

The sample population consisted of two study groups defined as it follows:

- group 1 –40 psychiatric patients (21 males, 19 females), aged between 18-51 years, with a history of suicidal attempt who underwent cerebral MRI after the suicidal attempt;

- group 2 –45 psychiatric patients (24 males, 21 females), aged between 18-55 years, without a declarative suicidal ideation who underwent cerebral MRI after the psychiatric examination.

Inclusion and exclusion criteria are detailed in table 1.

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Inclusion criteria	Exclusion criteria
-age between 18 and 50 years; -informed consent for inclusion in the study; -provided MRI examination images; -blood samples; -DSM IV diagnosis of major affective disorder (unipolar major depressive disorder, bipolar disorders type 1 and 2) [6]; -previous suicidal attempt for inclusion in group 1.	-other neurological or psychiatrical disorders; - history of head trauma; -different degrees of mental retardation; -congenital disorders; -MRI contraindications.

Table 1
INCLUSION AND EXCLUSION CRITERIA

Variable	Group 1	Group 2	Significance
Sex (M)	52.5	53.33	n.a.
Age	42.4	39.5	0.01
Addictive behavior (%)	5	4.44	0.003
Comorbidities (cancer, cardiovascular diseases, diabetes) (%)	7.5	6.67	0.002

Table 2
SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY GROUPS

	Group 1	Group 2
Type I bipolar disorder	22 (55%)	20 (44.44%)
Type II bipolar disorder	11 (27.5%)	23 (51.11%)
Major depressive disorder	15 (37.5%)	26 (57.78%)

Table 3
PSYCHIATRIC DIAGNOSIS IN STUDIES GROUPS

	DWMH	PeWMH
Group 1	18 (45%)	16 (40%)
Group 2	15 (33.33%)	13 (28.89%)
Type I bipolar disorder	15 (35.72%)	14 (33.33%)
Type II bipolar disorder	9 (26.47%)	7 (20.59%)
Major depressive disorder	9 (21.95%)	8 (19.51%)

Table 4
INCIDENCE OF WHITE MATTER HYPERINTENSITIES IN THE STUDIED GROUPS AND ACCORDING TO PATHOLOGY

	Group 1	Group 2
DWMH 0	22 (55%)	30 (66.67%)
DWMH 1	10 (25%)	9 (20%)
DWMH 2	7 (17.5%)	5 (11.11%)
DWMH 3	1 (2.5%)	1 (2.22%)
PeWMH 0	24 (60%)	32 (71.11%)
PeWMH 1	9 (22.5%)	8 (17.78%)
PeWMH 2	6 (15%)	5 (11.11%)
PeWMH 3	1 (2.5%)	0

Table 5
DISTRIBUTION OF WHITE MATTER HYPERINTENSITIES ACCORDING TO FAZEKAS SCALE

Clinical diagnosis was assigned by a psychiatrist blind to the results of the MRI examination or blood tests.

MRI examinations were performed in various medical imaging departments from public hospitals and private centers located in different towns from the region of Moldavia. All examinations contained axial and sagittal FLAIR sequences, axial and coronal T2 sequences, axial T1 sequences pre and post-Gadolinium injection and were provided in DICOM format by the patient and re-analyzed by the same neuroradiologist with no knowledge of the written result provided by the originator medical imaging department.

The presence of WMH was evaluated according to the Fazekas scale and graded 0 to 3 (0 – absence of WMH, 1 - multiple punctate WMH, 2 - beginning confluency of WMH, 3 - large confluent WMH) for both periventricular and deep white matter hiperintensities [7].

Blood samples were collected from all patients and all evaluations included complete lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), total proteins and fractions, complete blood count (CBC), and platelet seronin level (spectrofluorimetric method).

Chi-squared test, Student t-test, and logistic regression were performed in order to estimate the association between suicidal attempts, suicidal ideation, white matter hyperintensities and blood paramaters.

Results and discussions

Sociodemographic and clinical characteristics of the study groups are listed in table 2.

Most patients in group 1 were diagnosed with type I bipolar disorder (55%) compared to group 2 patients who had predominantly a major depressive disorder (57.78%) (table 3).

The prevalence of both DWMH and PeWMH was significantly higher in group 1, compared to group 2 (Chi-squared $p = 0.02$ and respectively 0.007) (table 4).

Analysis of percentage of patients with WMH depending on the diagnosis revealed a significantly higher incidence of DWMH and PeWMH at patients with type I bipolar disorder (chi-squared $p = 0.01$) and no difference between patients diagnosed with type II bipolar disorder and major depressive disorder.

One patient included in group 1 and one patient included in group 2 had type 3 DWMH and PeWMH. There was no significant difference between the accounted frequencies of type 1 and type 2 DWMH and PeWMH between the groups (table 5).

DWMH were mostly located in frontal and parietal lobes, and PeWMH were more frequently observed in corona radiate and trigonal areas with no significant differences between the groups (table 6).

	Group 1	Group 2
Location of DWMH		
Frontal	9	8
Parietal	5	4
Temporal	2	2
Occipital	2	1
Location of PeWMH		
Corona radiata	6	5
Trigonal area	8	7
Other	2	1

Table 6
LOCATION OF WHITE MATTER HYPERINTENSITIES

	Group 1		Group 2		p
	Females	Males	Females	Males	
Total cholesterol (mg/dL)	153±41.7	167±53.2	182±27.5	185±30.2	<0.001
Erythrocytes (x10^6/µL)	4.17±0.92	4.27±0.73	4.78±0.65	4.63±0.50	<0.001
Total proteins (g/dL)	6.61±0.85	7.02±0.61	6.87±0.76	6.75±0.77	0.311
Platelet serotonin (nmol/platelet)	4.5±0.7	4.5±0.8	5.1±0.5	4.9±0.4	<0.001

Table 7
BLOOD SAMPLES RESULTS IN THE STUDY GROUPS

Logistic regression was performed in order to estimate the association of suicidal behavior with WMH. Both PeWMH and DWMH significantly associated with suicidal attempts and suicidal ideation after controlling for age, comorbidities and addictive behavior ($p = 0.002$ for PeWMH and $p = 0.001$ for DWMH).

Concerning blood test resuts, both male and female patients with suicidal attempts registered significantly lower concentrations of cholesterol and platelet serotonin compared to the control group (table 7).

Multivariate analysis proved that cholesterol <165, platelet serotonin <4.5, and the presence of WMH increase 1.81 times the risk of suicide among psychiatric patients (95% CI 0.97-3.37, $p=0.02$).

Several studies performed in the past decade [8,9] stated that WMH are more frequently encountered in patients with bipolar disorders compared to control subjects and Pompili [10] reported that WMH are strongly associated with suicidal attempts. The authors found few comparisons in the analyzed literature concerning the presence of WMH and biochemical anomalies between patients with suicidal attempt and patients with bipolar disorders and no suicidal attempt or ideation. Results of the current study demonstrate that patients with attempted suicide presented a lower cholesterol level. Deisenhammer et al. [16] reported that there is no relationship between serum cholesterol and course of depression, but they did not include a suicide group in their research. Other researchers like Law et al. [17] and Boston et al. [18]stated that low cholesterol is more a result of reduced appetite and body weight in depressed individuals and could not demonstrate the causality relation between cholesterol level and attempted suicide. Kunugi et al. [19] found that low levels of cholesterol in patients with suicidal attempt are unassociated with physiological status (malnutrition).

Impulsivity and aggressive behaviour are characteristics of patients with suicide attempts associated with low tryptophan levels and diminished serotonin synthesis [20, 21]. Alvarez suggested that reduced platelet serotonin level is the consequence of a decreased uptake mechanism secondary to receptor up-regulation. Also, low cholesterol levels could result in diminished central serotonergic transmission.

Results of the current study show that patients with attempted suicide registered a higher incidence of WMH (60% cumulated frequency) compared to control group.

The authors encountered a higher rate of Fazekas type 1 and 2 WMH in patients who had suicidal ideation or suicidal attempt compared to control group (fig. 2).

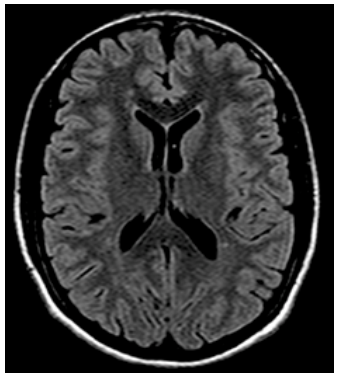

Fig. 2. Type 2 bipolar disorder and grade 1 Fazekas DWMH and PeWMH on a 30 years old female patient

There was no significant difference regarding the location of WMH between study groups, but given the small number of patients, the current results are not consistent.

In another study performed in 2008, Pompili et al. [11] concluded that PeWMH are more likely associated with a history of suicidal attempt but logistic regression performed in our study after controlling for age, comorbidities and addictive behavior showed that both PeWMH and DWMH are significantly associated with suicidal attempts and suicidal behavior.

The authors did not include in the current study individuals older than 55 years in order to diminish the effect of vascular factors after taking into account the hypothesis of *vascular depression* as it was proposed by Alexopoulos et al. [12] who suggested that cerebrovascular disease generated WMH can trigger a secondary depression by affecting white matter pathways involved in mood regulation.

Extensive studies have described the relation between this type of lesions and the suicidal behavior but the mechanism by which patients with WMH may be at a higher risk for suicide has not been elucidated [13]. Taylor et al. [14] have suggested that WMH possibly disrupt anatomic pathways involved in mood regulation such as superior longitudinal fasciculus and fronto-occipital fasciculus, critical in cognitive control. These disruptions involve key areas responsible for mood regulation, which include frontal cortex, amygdala-hippocampus complex, thalamus, basal ganglia. Mood regulation abnormalities could confer biological alterations, which, combined with environmental stressors, trigger a suicidal behavior [15].

Anatomically, these critical regions are interconnected by associative fibers that form the three subdivisions of the superior longitudinal fasciculus: components I, II, and III. In frontal lobe, superior longitudinal fasciculus I fibers project to the supplementary motor area and dorsal Brodmann's areas 6 and 9 and convey information from these areas back to the parietal lobe cortices and probably into the precuneus. Superior longitudinal fasciculus II connections end in Brodmann's areas 6, 8, 9/46, and 44, and superior longitudinal fasciculus III fibers end in ventral Brodmann's areas 6 and 44 [22].

Another critical region is located in the right extreme capsule of the basal ganglia, lesions of this region determining an interruption of the dorsolateral prefrontal circuit, responsible for connections between the basal ganglia and dorsolateral prefrontal cortex gray matter. This circuit projects from Brodmann's area 9/46 to the dorsolateral caudate, then to the lateral mediodorsal globus pallidus and rostrolateral substantia nigra. The basal ganglia afferentates forwards the ventral anterior and mediodorsal thalamus and backwards, the dorsolateral prefrontal cortex [22, 23].

The amygdala connections interrupted by lesions of the uncinate fasciculus have important implications in disorders of emotion processing. WMH in the inferior longitudinal fasciculus adjacent to the parahippocampal gyrus are associated with interruption of connections between V4 in the occipital cortex and the medial temporal structures, amygdala, hippocampus, and parahippocampus. The amygdala is known to have neuromodulatory effects on the extrastriate visual cortex. Thus, in suicidal behavior it may be that the affective valence signals are not normally transmitted [24, 25].

The mechanism for this interaction is unclear and worthy of further investigation.

The obtained results argue for the regional specificities in patients with affective disorders, if the lesions occur in critical cortical regions for executive and emotional processing. In order to optimize the clinical and biochemical diagnosis we consider important to anatomically localize the lesions involved in cognitive impairment.

As stated by several studies, patients that commit a suicidal act present morphological changes in the prefrontal dorso-lateral and in the orbitofrontal cortical areas [26, 27].

Neuropsychologically, the prefrontal cortex is involved in attention deficits and cognitive dysfunctions while orbito-frontal cortex is involved in depressed mood, hopelessness, inefficient thinking, preoccupation with death, delusions of guilt or worthlessness, loss of self-esteem.

Orbito-frontal cortex anomalies reflect a dysfunction of the serotoninergic system highly associated with vulnerability to suicide act, slightly increased by the association with basal affective disorders [21, 28, 29].

Conclusions

Actually, suicide is a complex, multi-phase behavior, and researches are trying to identify an explanatory neurobiological model of suicidal behavior in order to understand the phenomena, to identify truly high-risk groups and to facilitate development of appropriate treatments. Suicidal behavior is very changeable from individual to individual and in our opinion it is an end-point of a process in which subject's consciousness is balanced between inner disorders and environmental factors, a concept that underlies a vulnerability made up by neurochemical and physiological traits. The presence of morphological brain alterations and biochemical blood anomalies can predict a potential suicidal attempt in psychiatric patients.

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