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White matter hyperintensities and cognitive function in patients with late onset mania

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Abstract

Bipolar disorder is characterized by affective episodes in the mania-depression spectrum. Ninety per cent of the cases have an onset before age 50. In the patients with late onset mania, white matter hyperintensities (WMH) may be seen in the MRI FLAIR sequence, although these are of uncertain significance. A case-control study was done, including patients with late onset mania attended at the National Institute of Neurology and Neurosurgery, as well as healthy controls which were paired by age, sex, and academic level. Sagital FLAIR CUBE volumetric images were obtained, and later on assessed by an expert neuroradiologist, blinded to the diagnostic category. Neuropsychological measures were obtained. The patients with late onset mania showed statistically significant deficiencies ($p < 0.05$) in motor programming tasks, and inhibitory control tasks, according to the Frontal Assessment Battery, as well as a significant increase in the number of WMH in the right third frontal gyrus, the left first temporal gyrus, and the left second temporal gyrus. The total number of WMH and the Frontal Assessment Battery total score showed a significant inverse correlation. (Gac Med Mex. 2016;152:531-8)

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Background

The concept of mania

Mania is a medical concept formulated since ancient times, as it appears in the *Corpus Hippocraticum,* developed in Greece and dated between the years 450-350 B.C.[1]. Since the 19th century, mania is conceived as a psychiatric syndrome characterized by serious disturbances of the mental state and behavior, which usually appear in the course of manic-depressive psychosis or bipolar disorder, as it is currently known. According to Campbell's Psychiatric Dictionary[2], mania "is characterized by an euphoric or elation, although unstable, mood; increased psychomotor activity, restlessness and agitation; and an increase in the number of ideas and in the velocity of thought and speech, which in the serious forms leads to flight of ideas, usually with delusions of grandeur." In mental disorders current classifications, generated by the American Psychiatric Association[3] and the World Health

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Organization[4], mania is considered to be a clinical phase of bipolar disorder I, under the "manic episode" nomenclature, although it is also admitted that mania can be due to neurological or systemic disorders or to the effect of drugs[3,4].

Age of mania onset

It is well known that most patients with manic states will experience their first episode since adolescence and before the fifth decade of life; it appears that there are two main incidence peaks, one of them between 15 and 19 years of age, and the second, longer, between 20 and 30 years of age[5]. Median age of onset is 18 years, according to an epidemiological study of the US National Institutes of Health[6]. Most patients with mania will be diagnosed as having a bipolar disorder, and 90% of patients with this diagnosis will have overt clinical manifestations before the age of 50[7].

Late-onset mania

In the past few decades, a subgroup of patients with a late-occurring first mania episode, frequently associated with neurological disorders, has been identified[8]. In a sample of 277 subjects, the group of patients without a family history of psychiatric conditions contained a significantly larger number of subjects with a first manic episode after reaching 50 years of age ($p = 0.007$), which suggests a different etiology in this subgroup, with less familial contribution[9]. Probably, this subgroup is heterogeneous from the etiologic perspective[8]. The neurological entities that have been proposed as possible etiologic substrates include neurodegenerative diseases, in particular the behavioral variant of frontotemporal dementia[10] and stroke[8,11]. The pathophysiology of late-onset manic states is a subject under investigation. Frequently, these subjects display white matter hyperintense images in magnetic resonance imaging (MRI) studies when the T2 and FLAIR sequences are observed. It is not clear whether these images correspond to changes expected with age or to small-vessel vascular lesions, or even to other processes (inflammatory or degenerative). There are few neuroimaging studies carried out in patients with late-onset mania. One study in 52 patients with affective disorders and 14 controls showed that patients with late-onset affective disorders exhibit more white matter hyperintense lesions than patients with early-onset affective disorders, as well as in comparison with control subjects. Most significant lesion locations were the frontal lobes and the left parieto-occipital region[12]. One study conducted in Brazil compared 10 patients with late-onset bipolar disorder, 49 patients with early-onset bipolar disorder and 24 control subjects; late-onset patients showed a larger number of lesions in the deep white matter of the parietal lobe and basal ganglia in comparison with the other groups[11], which supports the hypothesis that manic syndrome advent is favored by cortical-subcortical circuits structural and functional disconnection[13]. Disconnection of these circuits predicts neuropsychological disturbances, although there are few neuropsychological studies in adults with late-onset mania. In general, processing speed, verbal memory and executive functions deficits have been found[14,15], which correlates with global functioning, especially in instrumental activities of daily living[15].

Materials and methods

Design

We conducted a case-control observational study at the National Neuropsychiatry and Neurosurgery Institute (INNN – *Instituto Nacional de Neuropsiquiatría y Neurocirugía)* of Mexico, once institutional approval from the Clinical Research Committee was obtained, and in strict adherence to the Declaration of Helsinki. In all cases, an informed consent letter was read and signed, specifying that the study does not imply additional risks or additional costs with regard to the standard of care and warranting confidentiality.

Population and sample

The target population comprises patients with late-onset bipolar disorder. We obtained the sample at the INNN (January 2011-July 2013), by means of consecutive cases non-probabilistic sampling.

Selection criteria

– Inclusion criteria: We included patients with late onset mania, i.e., subjects presenting with a first episode of mania (from 50 years of age on), and that were attended to at the Neuropsychiatry Unit of the INNN. Patients were included if they met the International Classification of Diseases[4], 10th version (ICD-10), criteria for mania without psychotic symptoms (coded as F30.1), as well as mania with psychotic symptoms (coded as F30.2). According to the American Psychiatric Association

DSM-IV criteria[3], all patients were classified as having type I bipolar disorder, current manic episode.
- Exclusion criteria: History of a neurological diagnosis was an exclusion criterion both in cases and controls, which were paired by age, gender and level of education.

Variables and measurement instruments

Diagnostic evaluations

All patients and controls were assessed by a diagnostic clinical team comprised by two psychiatrists, one clinical neurologist and one neuropsychology specialist in order to rule out other neurological or psychiatric conditions (e.g., dementia, delirium or schizophrenia spectrum psychotic disorders). During the recruitment stage, the DSM-IV[16] and the ICD-10[4] criteria for mania were used. During the data analysis phase, it was verified that all patients in the late-onset mania group met the DSM-IV criteria for manic episode and type I bipolar disorder[3].

Clinimetric evaluations

The Young mania scale was used to evaluate the severity and symptom profile of the manic state[17,18]. There is a version in Spanish language available, which was validated in 1997 and has a cutoff value of 28 points, a sensitivity of 96% and specificity of 98%.

Neuropsychological evaluations

To obtain an overview of cognitive functioning, we used the Neurobehavioral Cognitive Status Examination test[19]; to obtain executive functioning measurements, we used the Frontal Assessment Battery test[20], which assesses conceptualization (abstraction), mental flexibility, motor programming, sensitivity to interference, inhibitory control and environmental autonomy tasks. In addition, we used the Trail Making Test[21], which evaluates processes of sustained attention, divided attention, sequencing and processing speed.

Neuroimaging variables

- Image acquisition: The magnetic resonance protocol was carried out in a General Electric 3T scanner. A T1-weighted image was acquired in order to obtain a high-resolution anatomic reference (3D-SPGR, TE = 13 ms, TR = 5.6 ms, matrix size = 224 x 224 mm, slice thickness = 1.2 mm^3). In addition, T2-weighed images were obtained (spin echo, TE = 130 ms, TR = 6,734 ms, echo train = 21, matrix size = 512 x 512 mm, FOV phase = 0.75, FOV = 24 cm, slice thickness = 3 mm, spacing = 0.5 mm). Finally, volumetric images were obtained with sagittal FLAIR CUBE sequences, TR = 6.200 ms, echo train = 160, matrix size = 224 x 224 mm, FOV phase = 1, FOV = 22 cm, slice thickness = 2 mm, images = 128.
- FLAIR images processing: FLAIR images reconstruction was processed in all three anatomic planes using the FLAIR CUBE volumetric images. An expert neuroradiologist systematically visualized each slice at each plane of each patient or control, by means of single blinding, in such a way that the expert was unaware of the nosological category of the subject in question (patient with late-onset mania vs. control subject). The expert proceeded with the description and systematic localization of each hyperintense lesion, which was recorded in the protocol database using the SPSS software, for further statistical analysis.

Statistical analysis

We carried out the data description in terms of central tendency and dispersion measures for numerical variables, as well as percentages for nominal variables. Normality tests were performed in the case of numerical variables. For the comparison of nominal variables between groups, we used Pearson's chi-square test or Fisher's exact test. For the comparison of numerical variables we used Student's t-test. For the correlation between numerical variables we employed Pearson's correlation coefficients.

Results

Recruitment and sample size

The recruitment was carried out within the January 2011-July 2013 period, with a total of 22 patients with a first episode of late-onset mania and 22 control subjects paired by age, gender and level of education being included. Of the 22 subjects included in the study, 20 were at manic phase and 2 patients were at manic state remission (euthymic). Both euthymic patients were receiving treatment with a mood stabilizer (lithium) at standard doses.

Table 1. Socio-demographic data comparative analysis between patients with late-onset mania (n = 22) and healthy controls (n = 22)

Socio-demographic variable	Patients with late-onset mania (n = 22)	Control subjects (n = 22)	p
Age in years, mean (SD)	59.63 (8.89)	57.09 (7.38)	0.307
Female gender, n (%)	11 (50%)	10 (45.5%)	0.763
Level of education in years, mean (SD)	10.42 (5.58)	9.18 (6.06)	0.503

Socio-demographic data comparative analysis

Table 1 shows that there were no significant differences with regard to age, gender and years of education.

Neurocognitive comparison between cases and controls

When patients and controls performance was compared (Table 2), the following was observed: in the Frontal Assessment Battery instrument, a statistically significant difference was found in the motor programming (2.41 ± 0.79 vs. 2.95 ± 0.22, p = 0.006) and inhibitory control areas (2.05 ± 1.04 vs. 2.75 ± 0.55, p = 0.1). Resolution times of part A and part B of the Trail Making Test were not significantly different. In addition, when COGNISTAT total scores were analyzed, no figures below the mean for the general population were observed, and no statistically significant differences were found between control and patient scores in any of its sections.

FLAIR sequence hyperintense lesions analysis

Between-group comparison

Table 3 shows the comparison of hyperintense lesions frequency (in the FLAIR sequence) between patients and subjects of the control group. Although 37 regions of interest where lesions were found within any of both groups were analyzed, the table includes only the 3 regions where significant differences were observed, namely: the 3rd right frontal gyrus, the 1st left temporal gyrus and the 2nd left temporal gyrus. In all three cases, lesions were more common in the group of patients with late-onset mania (p < 0.05). In addition, the left insular region showed an important statistical trend. Finally, the "total lesion load" variable was included in the table, with regard to which an interesting statistical trend was also observed (21.5 ± 25 vs. 13.5 ± 15.9, p = 0.191, Student's t-test).

Pharmacological treatment effect

Eight patients were treatment-naive. Eleven patients received mood stabilizers (lithium or valproate) or antipsychotics (olanzapine or quetiapine) since their hospitalization; in these cases, the MRI was performed no later than one week after the treatment was started. No statistically significant differences were found in the number of white matter hyperintense lesions between patients who received treatment and those who were naive to antipsychotic treatment. Three patients were on remission and had received treatment for prolonged periods, although their number of hyperintense lesions was not higher than the maniac patients' group average.

Correlation analysis

Table 4 shows the analysis of the correlation between FLAIR sequence hyperintense lesions and neuropsychological performance. There are significant correlations when total lesion load and 3rd right frontal gyrus are considered:

- Total lesion load: With regard to total lesion load, inversely proportional correlations between the COGNISTAT scores (orientation, repetition, verbal memory, calculation, abstraction) and total number of lesions stand out. There is a directly proportional correlation between information processing speed in the Trail Making Test (part B) and total lesion number. Apart from that, there are inversely proportional correlations between Frontal Assessment Battery-assessed global executive

Table 2. Comparison of neuropsychological variables between patients with late-onset mania (n = 22) and control subjects (n = 22)

Variable	Patients with late-onset mania	Control subjects	p
Frontal assessment battery			
Total score	13.95 ± 3.592	15.60 ± 2.393	0.092
FAB 1. Conceptualization	2.05 ± 0.999	1.75 ± 0.910	0.324
FAB 2. Mental flexibility	2.73 ± 0.703	2.70 ± 0.571	0.892
FAB 3. Motor programming	2.41 ± 0.796	2.95 ± 0.224	0.006
FAB 4. Sensitivity to interference	2.59 ± 0.666	2.70 ± 0.571	0.574
FAB 5. Inhibitory control	2.05 ± 1.046	2.75 ± 0.550	0.010
FAB 6. Environmental autonomy	2.27 ± 0.767	2.60 ± 0.821	0.189
Trail making test			
Execution time (part A)	84.5 ± 51.91	74.7 ± 36.87	0.487
Errors (part A)	1.14 ± 2.66	0.80 ± 1.93	0.723
Execution time (part B)	201.55 ± 99.80	165.35 ± 98.88	0.245
Errors (part B)	5.68 ± 3.60	5.80 ± 3.96	0.934
COGNISTAT			
Orientation	10.82 ± 1.68	11.30 ± 1.45	0.329
Attention	5.36 ± 2.01	5.00 ± 2.24	0.583
Language-comprehension	5.50 ± 0.74	5.85 ± 0.48	0.081
Language-repetition	10.09 ± 2.11	10.00 ± 2.27	0.894
Language-naming	6.86 ± 0.64	6.85 ± 0.22	0.570
Constructional abilities	3.77 ± 1.60	3.85 ± 1.75	0.882
Memory	6.23 ± 4.36	8.10 ± 3.16	0.122
Calculation	2.91 ± 1.23	3.55 ± 0.82	0.057
Reasoning-judgment	4.09 ± 1.71	3.90 ± 1.83	0.729
Reasoning-similarities	3.50 ± 1.22	3.20 ± 1.50	0.105
Total score	59.14 ± 12.95	62.90 ± 11.00	0.319

Table 3. Comparison of FLAIR sequence hyperintense lesions between patients with late-onset mania (n = 22) and control subjects (n = 22)

Hyperintense lesions location	Patients with late-onset mania (n = 22)	Healthy controls (n = 22)	p
Total lesion load, mean (SD)	21.5 (25)	13.5 (15.9)	0.191
3rd right frontal gyrus, n (%)	15 (68.8)	8 (36.4)	0.035
1st left temporal gyrus, n (%)	5 (22.7)	0 (0)	0.018
2nd left temporal gyrus, n (%)	7 (31.8)	0 (0)	0.004
Left insula, n (%)	8 (36.4)	3 (13.6)	0.082

Table 4. Analysis of correlations between FLAIR sequence hyperintense lesions and neuropsychological performance considering total lesion load and 3rd right frontal gyrus lesions

Neuropsychological variable	Total lesion load		On 3rd right frontal gyrus	
	R	P	R	P
COGNISTAT orientation	**–0.554**	**< 0.001**	**–0.528**	**0.001**
COGNISTAT repetition	**–0.572**	**< 0.001**	**–0.558**	**0.001**
COGNISTAT verbal m.	**–0.418**	**0.006**	**–0.369**	**0.016**
COGNISTAT calculation	**–0.474**	**0.002**	**–0.380**	**0.013**
COGNISTAT abstraction (similarities)	**–0.428**	**0.005**	**–0.307**	**0.048**
COGNISTAT total	**–0.528**	**< 0.001**	**–0.471**	**0.010**
TMT B	**0.469**	**0.002**	**0.394**	**0.010**
FAB total score	**–0.384**	**0.012**	**–0.506**	**0.001**
FAB mental flexibility	–0.207	0.188	**–0.568**	**0.001**
FAB motor programming	–0.282	0.070	**–0.684**	**0.001**
FAB sensitivity to interference	–0.170	0.282	**–0.347**	**0.024**
FAB inhibitory control	**–0.404**	**0.008**	–0.383	0.079

performance and total lesion number; a significant negative correlation with regard to inhibitory control stands out. No statistically significant correlations were found with regard to Young's rating scale global score.

– 3rd right frontal gyrus lesions: Inversely proportional correlations are observed between the number of 3rd right frontal gyrus lesions and COGNISTAT scores (orientation, repetition, verbal memory, calculation, abstraction). There is a directly proportional correlation with regard to information processing speed in the Trail Making Test (part B). In addition, there are inversely proportional correlations with regard to executive performance as evaluated with the Frontal Assessment Battery, with an emphasis on mental flexibility, motor programming and sensitivity to interference. No statistically significant correlations were found with regard to Young's rating scale global score.

Discussion

– Patients with late-onset mania exhibit neuropsychological deficiencies in the performance of executive functions: The patients with a first late-onset manic episode included in this study had normal scores in general cognitive tests, as measured by COGNISTAT, which rules out the diagnosis of dementia. However, Frontal Assessment Battery-measured executive functions show disturbances in two areas: inhibitory control and motor programming. Inhibitory control is an executive function that has been reported to be frequently altered in chronic patients with bipolar disorder and in their unaffected relatives, and a cognitive endophenotype of the disease has even been considered[22]. This function is regulated by the frontal ventrolateral network, which in turn has extensive connections with the limbic system and is thought to be involved with emotion and impulse control[23]. The other altered function in these patients was motor programming. This is a complex function that involves several executive processes such as planning and sequencing, which mostly depend on the activity of the dorsolateral prefrontal network (Brodmann areas 9, 10 and 46) that is interconnected with structures of the paralimbic belt, which are in charge of visceral regulation and visceroceptive perception. Together, both these neural networks have been proposed as key zones in emotional processing.

Our study is consistent in the broader context of early-onset bipolar disorder. There is extensive documentation on attention, working memory and verbal fluidity failures, as well as in other executive processes[24-27]. Specifically, inhibitory control failures are well documented in patients with bipolar disorder and their relatives and, for this reason, this alteration has been proposed to represent a cognitive endophenotype of the disorder[22], associated with ventrolateral prefrontal cortex dysfunction[28]. Few neurocognitive studies have been carried out in adults with late-onset mania. In spite of methodological differences and scarce number of studies in this subgroup, cognitive disturbances are consistent with findings in young subjects, including processing speed, verbal memory and executive functions' deficiencies[14,15], which is correlated with global functioning, especially in instrumental activities of daily living[15].

- Patients with late-onset mania show a statistically significant increase in the frequency of FLAIR-sequence hyperintense lesions: The results of the present study show a statistically significant increase in the frequency of FLAIR-sequence hyperintense lesions at 3 cerebral regions: 3rd right frontal gyrus, 1st left temporal gyrus and 2nd left temporal gyrus. In addition, total lesion load was higher in patients (21 ± 25) in comparison with the control group (13 ± 15), although this result only showed a statistical trend ($p = 0.191$). These results support previous observations in patients with late-onset affective bipolar disorder, according to which there is an increase in white matter hyperintense lesions[11], particularly in the frontal lobes[12]. Moreover, these results are consistent with observations in patients with early-onset bipolar disorder, which suggest a pathophysiological continuum between both entities: one meta-analysis[29] that included 27 studies showed that adult patients diagnosed with (early-onset) bipolar disorder are more likely to show deep white matter hyperintense lesions (OR: 3.2; 95% CI: 2.2-4.5). This is particularly related to frontal lobes white matter[30], in tracts that connect cortical and subcortical structures responsible for emotional regulation. It is possible (in the context of bipolar disorder) that these lesions are related to an increased risk for experiencing a poor clinical outcome[31,32], for example, higher risk for suicidal behavior[33], although these lesions might be reduced with the use of lithium[34].
- White matter abnormalities in patients with late-onset mania. Etiologic perspective: Stroke is the only clinical entity that should be taken into account[8]. Patients with small vessel disease and those with vascular risk factors have an increased frequency of white matter hyperintense images[35]. The most accepted hypothesis to explain the pathophysiology of these images proposes that small caliber vessels, affected by atherosclerosis, induce lesions in the deep white matter by chronic hypoperfusion and blood-brain barrier rupture, which produces an invasion of plasma to the white matter[36]. This increase in the proportion of fluid can be detected as a hyperintense image in the T2 and FLAIR sequences. Other mechanisms of white matter lesion cannot be ruled out with data obtained in this study, including inflammatory and autoimmune processes.
- Limitations of the study and future outlook: the main limitation corresponds to the cross-sectional design of the study, which reduces the interpretation margin for causality attribution. Early events in the patients' biography, which might contribute to the genesis of mental disorder, cannot be assessed in a reliable and valid manner due to memory biases. A follow-up would allow for the clinical course of this syndrome and its prognostic variables to be known, as well as initial data with regard to treatment response. On the other hand, with the current design it is not possible assessing whether antipsychotic and mood-stabilizing treatments increase or reduce the likelihood for developing white matter hyperintense images in the FLAIR sequence, although patients who used such drugs in this study showed no significant differences with regard to patients who did not use them; the fact that the reduced sample size precludes a rigorous analysis of this variable should be taken into account. The neuroimaging techniques used in this study allow for structural connectivity to be assessed, but do not provide information on other structural measures as, for example, those referring to grey matter volume, and neither do they provide information on functional connectivity and brain metabolism. Complementarily, the neuroimaging studies here presented should be complemented with studies on structural connectivity, which would enable for white matter integrity loss in specific tracts to be quantified according to specific anatomic maps[37], and with positron emission tomography scans, in order to determine brain metabolism abnormal patterns.

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