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Migraine life-time prevalence in mental disorders: concurrent comparisons with first-degree relatives and the general population.

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Key words: primary headache, comorbidity, psychiatric patients

Abstract. The authors quantified the prevalence of migraine in subjects with mental disorders, first-degree relatives and the adult general population (GP) in Mérida, Venezuela. After validation, a modified, short version of the Lipton's diagnostic scale was administered to consecutively admitted in- and out-patients (n = 1059), their first-degree relatives (n = 445) and a probabilistic sample of the GP (n = 516). In the GP, the frequency of migraine (percentage and 95% confidence interval) was 14.9 (11.8-17.9). The migraine frequencies were (percentage and odd ratio probability against the GP: bipolar disorder (15.7%, p = 0.5), schizophrenia (8.3%, p = 0.08), depression and dysthimia (24.4%, p = 0.2), anxiety disorders (10.0%, p = 0.02), personality disorders (11.4%, p = 0.15), all other disorders (15.5%, p = 0.4), relatives of bipolar patients (4.4%, p < 0.001), relatives of schizophrenia patients (3.5%, p = 0.003), and relatives of patients with all other mental disorders (12.8%, p = 0.4). Migraine was more common in women (p < 0.001), and the bipolar patients presented the highest female to male ratio (8:1). A high variability was observed in migraine prevalence among the diagnostic categories, but it was particularly high in subjects with affective disorders, mainly in women, who thus deserve special attention from clinicians.

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Prevalencia de migraña en trastornos mentales: comparación concurrente con familiares de primer grado y con la población general.

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Palabras clave: cefalea primaria, comorbilidad, pacientes psiquiátricos.

Resumen. Los autores cuantificaron la prevalencia de migraña en sujetos con trastornos mentales, sus familiares de primer grado y la población general (PG) en Mérida, Venezuela. Se utilizó una versión abreviada de la escala diagnostica de Lipton. Luego de un estudio de validez, tal escala se administró a pacientes ambulatorios u hospitalizados atendidos en forma consecutiva (n = 1.059), a sus familiares de primer grado (n = 445) y a una muestra probabilística de la PG (n = 516). La frecuencia de migraña en la PG (porcentaje e intervalo de confianza de 95%) fue de 14,9 (11,8-17,9). La frecuencia para los diversos trastornos (porcentaje y probabilidad asociada a la razón de momios (odds ratio) con respecto a la PG) fue: trastorno bipolar (15,7%, p = 0,5), esquizofrenia (8,3%, p = 0,08), depresión y distimia (24,4%, p = 0,2), trastornos de ansiedad (10,0%, p = 0,02), trastornos de personalidad (11,4%, p = 0,15), todos los otros trastornos (15,5%, p = 0,4). En los familiares, la frecuencia fue: trastorno bipolar (4,4%, p < 0,001), esquizofrenia (3,5%, p = 0,003), otros trastornos (12,8%, p = 0,4). El diagnóstico de migraña fue más frecuente en mujeres (p < 0,001), y los sujetos con trastorno bipolar presentaron el mayor índice mujer:hombre (8:1). Se observó una alta variabilidad en la prevalencia de migraña en las diversas categorías diagnósticas. Tal frecuencia fue particularmente elevada en sujetos con trastornos afectivos, principalmente en mujeres, las cuales ameritan una atención especial por parte de los médicos tratantes.

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INTRODUCTION

Migraine, a class of primary headache (1), is a severe neurological disorder which affects between 12 and 28% of people at some point in their lives (2-8). The one-year prevalence of migraine in the general population (GP) ranges from 6% to 15% in adult men and from 14% to 35% in adult women (2-8). At all ages, migraine without aura is more common than migraine with aura, with a ratio between 1.5:1 and 2:1 (6, 7).

An association between general psychopathology and migraine was observed as early as in 1873 by E. Liveing (cited by Low *et al.*, ref. 9). Subsequent studies confirmed a complex relationship between migraine and mental disorders in community (9-17) and clinical samples (18-40). Specifically, an elevated frequency of migraine has been reported in psychiatric conditions as dissimilar as eating (18), personality (19-21) and anxiety disorders (21-25), substance abuse (26) and most notably, mood disorders (27-37).

Recent studies have emphasized the association between migraine and bipolar disorders (BPD) (9, 16, 17, 30-37). This is-

sue is of considerable clinical interest because converging evidence suggests that patients with this comorbidity have a more severe impairment in mental health and social performance than those without it (9, 13,16, 36, 37). In addition, the diagnosis of migraine is often overlooked by patients and doctors (32-34).

In this study, we first validated a short scale for the diagnosis of migraine. We then applied this instrument to a heterogeneous sample of consecutive psychiatric patients attending in- and out-patient facilities, their available first-degree adult relatives and a probabilistic sample from the Venezuelan GP from Mérida city as a key comparison group. Our aim was to describe the migraine prevalence in psychiatric patients according to their specific clinical diagnosis and to have a concurrent comparison with the GP. Besides, by assessing first-degree relatives, we aimed to gain some insight into the family aggregation, particularly in schizophrenia and BPD. There are not published studies on this topic in Venezuela.

METHODS

This study was conducted between January 2007 and December 2010 at the following Venezuelan institutions: Los Andes University Hospital and private clinics (Mérida state), CATESFAM (Center for Attention of Schizophrenic patients and their relatives, Zulia and Táchira states), and Caracas Psychiatric Hospital (Distrito Capital). In sites outside Mérida city, only subjects with schizophrenia, schizoaffective and bipolar disorders were evaluated. The ethics committee of each institution approved the study, and a written informed consent for voluntary participation was signed by each subject.

Subjects

Consecutively admitted adult patients, with age equal or higher than 18 years, attending out-patient (all clinics) or in-patient (only Mérida and Caracas) facilities and their available first-degree adult relatives (parents, siblings and off-springs), were asked to voluntarily fill a short inventory of headache symptoms (see Scale Validation below). In the case of illiterate subjects, the scale was filled by the interviewer. Psychiatric diagnosis was verified by using the Structured Clinical Interview for the DSM-IV (41).

The GP was assessed in Mérida through a probabilistic sample (n = 516) stratified by gender and age according to the last Venezuelan population census. For this purpose, thirteen public places (stores and parks) representing the main city neighborhoods were selected. Thirteen trained and properly identified interviewers selected every third adult passer-by, and requested voluntary participation for answering the scale. Each interviewer completed a previously determined quota of interviewees and no single subject rejected to enter the study.

Scale validation

The instrument was a self-administered screener for life-time migraine symptoms and family history (42) which is compatible with the International Classification of Headache Disorders (1) (Table 1). The scale had 11 items, and each one counted as (1) when positive and (0) when negative. A specific subject could thus have a maximum score of 10 and a minimum of 0 since items 6.1 and 6.2 excluded each other. The interviewers were trained to guarantee a uniform methodology, particularly in the illiterate subjects.

Lipton *et al*. (42) showed that a three-item subset of their scale for migraine detection in primary care, composed by disability, nausea, and sensitivity to light, provided optimum performance with a sensitivity of 0.81, a specificity of 0.75 and a posi-

TABLE I
SCALE FOR THE ASSESSMENT OF MIGRAINE SYMPTOMS

	Yes	No
1. Have you ever suffered from headache?	❑	❑
2. Did that headache ever limit your activities for 1 day or more?	❑	❑
3. During the headache, did you ever had nausea and/or vomits?	❑	❑
4. During this headache, did light and or noise ever increase the pain, making it unbearable?	❑	❑
5. During this headache, did you also have?:		
5.1. Irritability	❑	❑
5.2. Insomnia	❑	❑
5.3. Sadness	❑	❑
6. Do you have relatives who have a headache like the one you have? Please write down who? **(Please mark "yes" in 6.1 or 6.2 but not both)**		
6.1. Both parents	❑	❑
6.2. One parent	❑	❑
6.3. Any other	❑	❑
7. Did you ever visited a doctor because of this headache?	❑	❑

tive predictive value of 0.93. These three items were incorporated in our instrument (Table I, items 2-4) and were also used in the main analysis.

In the validation study, the 11-item scale was administered to 88 patients from the Department of Neurology of Los Andes University Hospital who were diagnosed by an expert neurologist as positives (n = 34) or negative (n = 54) for migraine, according to the International Classification of Headache Disorders (1).

The following figures were obtained for the 11-item scale and for the 3-item subset as defined by Lipton *et al*. (42): Content Validity as assessed by 5 expert neurologists and the Cronbach's Alfa Coefficient of Internal Consistence (43, 44). In addition, by using the clinical judgment as the gold standard criteria for migraine diagnosis, we calculated the Kappa Coefficient, Sensitivity, Specificity, Positive and negative Predictive Value, Reliability and the ROC curve (Receiver Operation Characteristics) for cut-off point calculation (44).

Statistical analysis

The SPSS. version 17.0 Inc. (Chicago, Illinois, USA) was used for the analysis. Data normality was estimated with the one-sample Kolmogorov- Smirnov test and Levene's test for the equality of variances. Since age was not normally distributed, it was analyzed with the Kruskal-Wallis chi-square test. Gender distribution was analyzed with the two- tailed chi-square test with continuity correction followed by the Ryan test as post hoc. Binary logistic regression was conducted to assess the migraine frequency distribution with age and gender as independent variables. Odd ratios between each diagnostic group and the GP were obtained. Results were considered significant when $p < 0.05$.

RESULTS

Scale validation

Results are summarized in Table II. For calculation of the positive and negative predictive values, we used a migraine prevalence value of 20% (2). The content validity figure was "acceptable" for the 11-item (0.73) and for the 3-item (0.89) scales. The Kappa coefficient showed "good agreement" with the clinical diagnosis for both scales (0.69 and 0.73, respectively). The positive and negative predictive values were above 90% for both scales, and in the case of the 3-item scale, the positive predictive value was 100%.

For the classification of patients as positive or negative according to the ROC curve results, cut-off points of 5 and 3 were selected when using the 11-item and 3-item scale, respectively. We used the 3-item scale for the migraine frequency analysis.

Prevalence of migraine

No subject refused the interview. The whole sample comprised 2020 subjects distributed as follows: GP (n = 516), schizophrenia (n = 132), BPD (type I n = 84, type II n= 32, non-specified n = 41, schizo-affective n = 34), depressive disorders (major depression [n = 69] and dysthymia [n = 14]), anxiety disorders (n = 130), personality disorders (n = 105), all other disorders (n = 418), schizophrenia relatives (n = 85), BPD relatives (n = 181), and all other disorder relatives (n = 179). Table III presents the age and gender distribution of the sample.

TABLE II
VALIDATION OF THE SCALE FOR THE DIAGNOSIS OF MIGRAINE

Construct	Instrument	Value	Error	P
Validity of Content	11-item	0.73	0.0039	-
	3-item	0.89	0.0037	-
Cronbach's alfa	11-item	0.71	-	-
	3-item	0.68	-	-
Kappa coefficient	11-item	0.69%	0.073	< 0.001
	3-item	0.72%	0.073	< 0.001
Sensitivity	11-item	73.5%	-	-
	3-item	67.6%	-	-
Specificity	11-item	98.1%	-	-
	3-item	100%	-	-
Positive	11-item	90.6%	-	-
Predictive Value	3-item	100%	-	-
Negative	11-item	93.5%	-	-
Predictive Value	3-item	92.5%	-	-
Reliability	11-item	88.6%	-	-
	3-item	87.5%	-	-
ROC curve	11-item	0.93	0.028	< 0.001
	3-item	0.94	0.028	< 0.001
Cut-off point	11-item	5	-	-
	3-item	3	-	-

ROC = receiver operation characteristics Values for the ROC curve represent the area under the curve.

TABLE III
GENDER AND AGE DISTRIBUTION

Group	Age (a)	Gender Distribution (b)	Age (c)
General population (n = 516)	38.9 ± 15.1	F (n = 219, 42.4%) M (n = 297, 57.6%)	39.6 ± 15.1 38.5 ± 15.1
Bipolar Disorder (n = 191)	43.2 ± 14.4*	F (n = 121, 63.4%) M (n = 70, 36.6%)	44.2 ± 14.0* 41.3 ± 15.1
Schizophrenia (n = 132)	41.7 ± 11.8*	F (n = 39, 29.5%) M (n = 93, 70.5%)	45.2 ± 11.6* 40.3 ± 11.7
Depression & Dysthymia (n = 82)	45.7 ± 17.9*	F (n = 62, 75.6%) M (n = 20, 24.4%)	47.3 ± 17.1* 40.9 ± 19.9
Anxiety Disorders (n = 130)	44.2 ± 16.3*	F (n = 94, 72.3%) M (n = 36, 27.7%)	45.8 ± 16.8* 39.9 ± 13.9
Personality Disorders (n = 105)	35.1 ± 13.7*	F (n = 64, 61.0%) M (n = 41, 39.0%)	37.3 ± 14.4 31.7 ± 11.8*
All others (n = 419)	39.3 ±15.5	F (n = 269, 64.2%) M (n = 150, 35.8%)	40.9 ± 16.3 36.3 ± 13.4
Bipolar Disorder Relatives (n = 181)	44.4 ± 17.8*	F (n = 114, 63.0%) M (n = 67, 37.0%)	45.9 ± 18.1* 41.3 ± 15.1
Schizophrenia Relatives (n = 85)	51.9 ±17.2*	F (n = 64, 75.3%) M (n = 21, 24.7%)	53.1 ± 17.2* 45.3 ± 16.3
All other Disorder Relatives (n = 179)	42.6 ± 15.1*	F (n = 129, 72.1%) M (n = 50, 27.9%)	42.9 ± 14.6* 38.8 ± 17.1

F = feminine; M =masculine; age figures represent mean ± standard deviation.
(a) Kruskal-Wallis chi-square (9) = 80.7, $p < 0.001$; * = significantly different from the general population ($p < 0.05$). (b) χ^2 (9) = 1527, $p < 0.001$. (c) Masculine: Kruskal-Wallis chi-square (9) =22.9, $p = 0.006$; * = significantly different from the general population ($p < 0.05$). Feminine: χ^2 (9) = 55.9, $p < 0.001$; * = significantly different from the general population ($p < 0.05$).

Fifty eight percent of the subjects were women. This trend was observed in all the groups except in the GP and in subjects with schizophrenia (Table III).

In the logistic regression analysis all the independent variables (diagnosis, gender and age) were significantly associated with migraine. Migraine was diagnosed in 13.0% of the whole sample, and it was more frequent in women than in men: 16.7% vs. 7.8%, odds ratio (OR) (95 %CI) = 2.6 (1.9-3.6), $p < 0.001$.

The migraine frequency (percentage and 95% Cl) in the GP was 14.9% (11.8-17.9) (Table IV). Subjects with BPD, depression/dysthymia, or the other disorder group showed a higher but not statistically significant frequency of migraine than the GP. All the other groups displayed lower migraine frequencies than the GP, but the figures only reached statistical significance in the anxiety disorder, schizophrenia and BPD relative groups (Table IV).

Table V displays the frequency of migraine according to the subtype of BPD and in the schizoaffective group. No figure reached statistical significance when compared to the GP ($p > 0.05$).

The frequency of migraine increased with age. When compared to subjects under 20 y of age, the figures (OR and 95% CI) were: 20-40 y group, OR = 2.1 (1.2-3.8),

TABLE IV
FREQUENCY OF MIGRAINE ACCORDING TO THE 3-ITEM SCALE

Group	Frequency % (95% CI)		Odds ratio (95% CI) vs. the general population
	Gender	Total	Total
General population (n = 516)	F 19.6 (14.4-24.9) M 11.4 (8.8-15.0)	14.9 (11.8-17.9)	-
Bipolar Disorder (n = 191)	F 23.1 (15.6-30.6) M 2.9 (0.0-6.8)	15.7 (10.6-20.8)	0.9 (0.5-1.4) p = 0.5
Schizophrenia (n = 132)	F 10.3 (0.8-19.8) M 7.5 (4.1-12.9)	8.3 (3.9-12.7)	0.54 (0.23-1.1) p = 0.08
Depression & Dysthymia (n = 82)	F 25.8 (15.0-36.6) M 20.0 (2.5-37.5)	24.4 (15.2-33.7)	1.4 (0.8-2.6) p = 0.2
Anxiety Disorders (n = 130)	F 12.8 (6.0-19.6) M 2.8 (0.0-8.2)	10.0 (4.8-15.2)	0.5 (0.25-0.9) p = 0.02
Personality Disorders (n = 105)	F 15.6 (4.7-24.5) M 4.9 (0.0-11.5)	11.4 (5.3-17.5)	0.6 (0.3-1.2) p = 0.15
All others (n = 419)	F 20.1 (15.2-24.9) M 7.3 (3.1-11.5)	15.5 (12.0-19.0)	0.8 (0.6-1.2) p = 0.4
Bipolar Disorder Relatives (n = 181)	F 6.1 (1.7-10.5) M 1.5 (0.0-4.4)	4.4 (1.5-7.3)	0.22 (0.1-0.5) p< 0.001
Schizophrenia Relatives (n = 85)	F 4.7 (0.0-11.8) M 0.0	3.5 (0.0-7.4)	0.17 (0.1-0.6) p =0.003
All other Disorder Relatives (n = 179)	F 14.7 (8.6-20.8) M 8.0 (0.5-15.5)	12.8 (7.9-17.7)	0.8 (0.6-1.2) p = 0.4

TABLE V
FREQUENCY OF MIGRAINE ACCORDING TO THE SUB-TYPES OF BIPOLAR DISORDER AND IN THE SCHIZOAFFECTIVE GROUP

Group	Frequency % (95% CI)		Odds ratio (95% CI) vs. the general population
	Gender	Total	Total
General population (n = 516)	F 19.6 (14.4-24.9) M 11.4 (8.8-15.0)	14.9 (11.8-17.9)	-
Bipolar I (n = 84)	F 28.3 (21.7-34.9) M 2.6 (0.0-5.2)	16.7 (12.6-20.8)	0.9 (0.5-1.9) p = 0.9
Bipolar II (n = 32)	F 5.0 (0.1-9.9) M 8.3 (0.3-16.3)	6.3 (2.0-10.6)	0.3 (0.1-1.4) p = 0.1
Bipolar non-specified (n = 41)	F 22.6 (15.1-30.1) M 0.0 (0.0)	17.1 (13.7-27.5)	0.8 (0.3-1.9) p = 0.7
Schizoaffective (n = 34)	F 29.2 (19.9-38.5) M 0.0 (0.0)	20.6 (11.2-22.9)	1.4 (0.8-2.5) p = 0.2

Binary logistic regression: Wald (12) = 35.8, p < 0.001.

p = 0.01; 41-60 y group, OR = 1.8, (0.9-3.3), p = 0.056 and > 60 y group: OR = 1.2 (0.6-2.3), p = 0.7.

Female to male ratio

As mentioned above, the prevalence of migraine in the whole sample was significantly higher in women than in men. Fig. 1 shows that this gender-related difference was recorded in all categories. Interestingly, the highest female to male ratio was observed in the BPD patients with a value of 7.9:1.0.

DISCUSSION

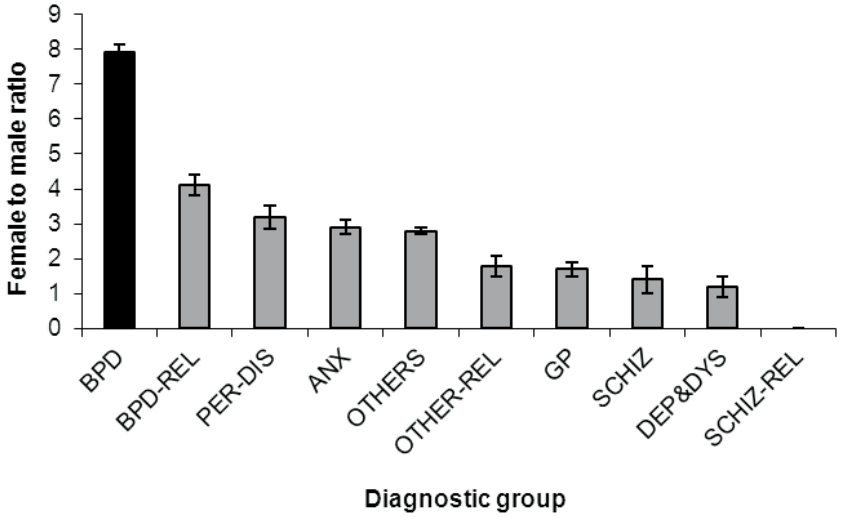
Due to the high level of illiteracy in the Venezuelan psychiatric population, in this pilot study we used a simple scale for the life-time diagnosis of migraine instead of a more complex one, such as that derived from the International Classification of Headache Disorders. Besides, we intended to evaluate subjects with severe mental disorders such as schizophrenia, where perceptual and other aura-related symptoms may be difficult to differentiate from the primarily psychiatric symptoms.

The whole scale (11-item scale) and the Lipton's subscale (3-item scale) showed a fairly similar validity and reliability, as assessed in the validation study with neurological patients. However, the frequency of migraine was almost two-fold with the 11-item instrument (23.9%) when compared to the 3-item scale (13.0%). Even though this study does not allow additional comparisons between both scales, we speculate that the 3-item scale provides a more reliable approach to migraine diagnosis.

Additional distinctive features of this study were the concurrent assessment of subjects from the GP who made up the main reference group and the direct assessment of first degree relatives.

Migraine in the general population

In agreement with previous studies in the GP, migraine was more frequent in women than in men (45) and declined in the elderly (2). The lifetime prevalence of migraine reported here (total= 14.9%;



GP = general population. SCHIZ = subjects with schizophrenia. BPD = subjects with bipolar disorder. SCHIZ-REL = first-degree relatives of schizophrenia patients. BPD-REL = first-degree relatives of bipolar patients. OTHER-REL = first-degree relatives of patients with other disorders. DEP&DYS = subjects with depression or dysthymia. ANX = subjects with anxiety disorders. PER-DIS = subjects with personality disorders. OTHERS = subjects with other disorders

Fig. 1. Female to male ratio in subjects with migraine. The values represent the ratio and the 95% confidence interval.

women: 19.6%; men = 11.4%) is within the range reported by authors in other countries (12-28%) (2-8), but it is higher than that reported in Venezuela using a face to face interview based on the International Headache Society Criteria (12.2% for women and 4.7% for men) (4).

Bipolar disorder, major depression and dysthymia

Subjects with depressive disorders had the highest prevalence of migraine in the whole sample and in women.

The whole BPD group and BPD females displayed the second highest (though non-significant) frequency of migraine. By contrast, migraine frequency in bipolar men was among the lowest. Interestingly, as shown in Fig. 1, the highest women to men ratio in migraine frequency was observed in the BPD group. The higher frequency of migraine in BPD females than in BPD males has been reported by some authors (9, 11, 16, 38); but not by others (30, 32). Hence, while these results did not reach strict statistical significance, they confirm that migraine is a clinically relevant co-morbidity in subjects with affective disorders, particularly in women.

Comparisons between the BPD and the depression/dysthymia groups are of special interest. As stated above, the prevalence of migraine was the highest in the depression/dysthymia group. Few studies have concurrently compared the frequency of migraine between BPD and depressive unipolar subjects. Fasmer (33), for example, found a rather similar frequency in BPD (44%) vs. unipolar (46%) patients, but his sample was not powered enough to conduct gender analysis. However, that study allowed subjects with cyclothymic or hyperthymic affective temperament to be labeled as BPDII, whereas we here used a narrower definition. Thus, it remains unclear whether the frequency of migraine would have been higher in our BPD group had we considered temperament analysis. Another factor that may underestimate the actual frequency in BPD subjects is the late onset of manic or hypomanic episodes (9), or the difficulty in recalling or identifying the latter as abnormal in subjects labeled as unipolar depressives. This issue remains to be properly addressed. It is important to underscore that the ratio female:male in the depression/dysthymia group was close to 1, and contrasts to the high value in the BD group.

Regarding the impact of migraine on general health, McIntyre *et al*. (16) showed that bipolar women with migraine had more comorbid medical disorders and were more likely to require help with personal or instrumental activities of daily living when compared to bipolar women without migraine. These authors also showed that, compared with BPD males without migraine, those with both disorders were more likely to use primary and mental health services, live in a low income household and receive welfare and social assistance. McIntyre *et al*. (16) also reported that these subjects present an earlier age of onset of BPD and have a higher lifetime prevalence of comorbid anxiety. Along the same lines, Ortiz *et al*., (37) showed that BPD patients with co morbid migraine had significantly higher rates of suicidal behavior, social phobia, panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder. It is worthwhile mentioning that an elevated frequency of migraine has also been observed in children and adolescents with BPD (39).

Altogether, these results confirm that BPD patients with migraine are a clinical subpopulation with a considerable health burden that requires particular attention from the mental health system.

An unexpected finding was the significantly low prevalence of migraine in BPD relatives. We did not find any published

study on the family prevalence of migraine in BPD subjects. However, Low *et al.* (9), reported a higher frequency of positive family history for migraine and psychiatric disorder in BPD patients with migraine than in those without it. Disalver *et al*. (46) also reported that a family history of BPD increases the risk for migraine in patients with major depression or BPD. We cannot assess here the bias magnitude and the frequency of lifetime diagnosis in our sample of relatives. Besides, when assessing the frequency of migraine, we did not conduct separate analysis for BPD probands with or without migraine. At any rate, this finding indirectly points out that migraine could be related to the BPD phenotype expression rather than to the shared genetic endowment.

As for the neurobiology of migraine and BPD, some studies suggest a role for a polymorphism in the serotonin transporter (47), a migraine linkage locus on chromosome 4 and a susceptibility locus on chromosome 20, which harbors a gene for the migraine/BPD phenotype (48).

Migraine and schizophrenia

A distinctive feature of this study is the assessment of patients with schizophrenia and their first-degree relatives. Their migraine prevalence was the lowest among all the patients (8.3%): it reached marginal statistical significance compared to that recorded in the GP ($p = 0.08$). We did not find any published study on migraine prevalence in patients with schizophrenia. It must be acknowledged though, that for this clinical population, migraine symptoms and the aura phenomenon can be difficult to distinguish from the perceptual abnormalities often found in the disorder itself. Hence, the reliability of migraine symptoms' assessment in schizophrenia remains an open question.

It is important to point out that the frequency of migraine among schizophrenia relatives was the lowest among all the groups (3.5%, $p = 0.003$ compared to the GP). Since this group sample was not powered enough and since we did not obtain a probabilistic sample, this result suggesting a protective effect of the schizophrenia genotype on migraine, should be investigated further.

Migraine, anxiety and personality disorders

To expand the clinical perspective, this pilot study also considered three heterogeneous groups: anxiety, personality and all other disorders. The former group included patients with generalized anxiety, panic and obsessive-compulsive disorder. The second group encompassed most types of personality disorders, and the all other disorder group was mainly formed by patients in psychotherapy because of problems in interpersonal relationships. In consequence, the sample size in these three groups was not large enough to allow the analysis of specific disorders.

Previous studies assessing the prevalence of migraine in anxiety disorders have mainly focused on panic disorders and phobias (17, 21-25). Recent studies reported the following figures for specific anxiety disorders: generalized anxiety disorder (3.0-14.6%), social phobia (3.0-6.7%), specific phobia (5.6-15.1%), panic disorder (4.6-5.6%), post-traumatic stress disorder (4.5%), and obsessive-compulsive disorder (2.2%) (17-49). In this study, the migraine frequency in the anxiety group (10.0%) was significantly lower than that observed in the GP ($p = 0.02$).

Migraine, particularly without aura, has been associated with high levels of neuroticism (19, 50). It has also been shown that personality traits influence the migraine course in the long term (51). For example, in women above 60 years, the risk for active migraine was strongly associated

with a history of stress susceptibility and high levels of somatic trait anxiety (21). Regarding specific personality disorders, migraine has been particularly associated with borderline personality (52).

We present here the prevalence of migraine in a heterogeneous group of subjects with personality disorders as defined in the DSM-IV criteria without attempting a detailed subtype analysis. In our patients, 13.3% of the whole sample was classified as positive for migraine, and the frequency was clearly higher in women (15.6% vs. 4.8%). The global figure was lower (though no statistically significant) than that observed in the GP.

Finally, the all other disorder group comprised patients in psychotherapeutic counseling (mainly marital disputes) and organic mental disorders. Their migraine frequency and that of their relatives was remarkably similar to that recorded in the GP.

General discussion and limitations

We did not find any diagnostic group with a significantly higher prevalence of migraine compared to values concurrently obtained from the GP. As has been reported by other researchers, subjects with depressive disorders had the highest frequency of migraine, and the highest female to male ratio was observed in the BPD group. Interestingly, the schizophrenia ($p = 0.08$) and the anxiety disorder ($p = 0.02$) groups and the first-degree relatives of schizophrenia ($p = 0.003$) and of BPD patients ($p < 0.001$) displayed rather lower levels than those observed in the GP.

The comparison of our results with previous studies is hampered by methodological differences and limitations of our study, the most important ones being that we concurrently evaluated the GP and used a very short diagnostic instrument that did not discriminate between the different types of migraine and the presence of aura (53). Besides, we did not evaluate the disability degree, the frequency of specific mental disorders in patients with or without migraine (54), and the impact of comorbidity and illiteracy. Hence, the rather similar or lower frequency of migraine in several groups compared to the GP must be considered as preliminary results. Our findings did not provide any additional clue on the well-known impact of the migraine comorbidity on the clinical course of specific mental disorders. Besides, we could not control for overweight, tobacco and alcohol consumption. The GP was assessed with a probabilistic sample only in Mérida, whereas patients and relatives were selected with a non-probabilistic method that did not allow control for place of habitation. However, with the use of a simple diagnostic instrument, we have been able to confirm the importance of assessing migraine in psychiatric practice, hereby providing a testable hypotheses for future studies.

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REFERENCES

1. **Headache Classification Subcommittee of the International Headache Society.** The International Classification of Headache Disorders. Cephalalgia 2004; 24 (suppl. 1).

2. **Lavados PM, Tenhamm E.** Epidemiology of migraine headache in Santiago, Chile: a prevalence study. Cephalalgia 1997; 17: 770-777.
3. **Wang SJ.** Epidemiology of migraine and other types of headache in Asia. Curr Neurol. Neurosci. Rep 2003; 3:104-108.
4. **Morillo LE, Alarcon F, Aranaga N, Autlet S, Chapman E, Conerno L, Estevez E, Garcia-Pedroza F, Garrido J, Macias-Islas M, Mantillo P, Nuñez L, Plascencia N, Rodriguez C, Takeuchi L, Latin American Migraine Study Group.** Prevalence of migraine in Latin America. Headache 2005; 45:106-117.
5. **Stovner LJ, Zwart J-A, Hagen K, Terwindt GM, Pascual J.** Epidemiology of headache in Europe. Eur J Neurol 2006;13: 333-345.
6. **Lipton RB, Stewart WF.** Migraine in the United States: a review of epidemiology and health care use. Neurology 1993; 43 (Suppl 3): S6-S10.
7. **Rasmussen BK, Olesen J.** Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 1992;12: 221-228.
8. **Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB.** The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia 2003; 23: 519-527.
9. **Low NC, Galbaud du Fort G, Cervantes P.** Prevalence, clinical correlates, and treatment of migraine in bipolar disorders. Headache 2003; 43: 940-949.
10. **Merikangas KR, Risch NJ, Merikangas JR, Weissman MM, Kidd KK.** Migraine and depression: association and familial transmission. J Psychiatr Res 1988; 22:119-129.
11. **Merikangas KR, Angst J, Isler H.** Migraine and psychopathology: results of the Zurich cohort study of young adults. Arch Gen Psychiatry 1990; 47: 849-853.
12. **Breslau N, Davis GC, Andreski P.** Migraine, psychiatric disorders, and suicide attempts: an epidemiologic study of young adults. Psychiatry Res 1991; 37: 11-23.
13. **Moldin SO, Scheftner WA, Rice JP, Nelson E, Knesevich MA, Akiskal H.** Association between major depressive disorder and physical illness. Psychol Med 1993; 23: 755-761.
14. **Swartz KL, Pratt LA, Armenian HK, Lee LC, Eaton WW.** Mental disorders and the incidence of migraine headaches in a community sample: results from the Baltimore epidemiologic catchment area follow-up study. Arch Gen Psychiatry 2000; 57: 945-950.
15. **Hirschfeld RM, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA.** Screening for bipolar disorder in the community. J Clin Psychiatry 2003; 64: 53-59.
16. **McIntyre RS Konarski JZ Wilkins K, Bouffard B, Socynska JK, Kennedy SH.** The prevalence and impact of migraine headache in bipolar disorder: results from the Canadian Community Health Survey. Headache 2006; 46: 973-982.
17. **Ratcliffe GE, Enns MW, Jacobi F, Belik SL, Sareen, J.** The relationship between migraine and mental disorders in a population-based sample. Gen Hosp Psychiatry 2009; 31: 14-19.
18. **Brewerton TD, George MS.** Is migraine related to the eating disorders? Int J Eat Dis 1993; 14: 75-79.
19. **Breslau N, Andreski P.** Migraine, personality, and psychiatric comorbidity. Headache 1995; 35: 382-386.
20. **McElroy SL, Soutulio CA, Beckman DA, Taylor P Jr, Keck PE Jr.** DSM-IV intermittent explosive disorder: a report of 27 cases. J Clin Psychiatry 1998; 59: 203-210.
21. **Mattsson P, Ekselius L.** Migraine, major depression, panic disorder, and personality traits in women aged 40-74 years: as population-based study. Cephalalgia 2002; 22: 543-551.
22. **Breslau N, Davis GC.** Migraine, major depression and panic disorder: a prospective epidemiologic study of young adults. Cephalalgia 1992; 12: 85-90.
23. **Marazziti D, Toni C, Pedri, Bonuccelli U, Pavese N, Nuti A, Maratorio A, Cassano GB, Akiskal HS.** Headache, panic disorder and depression: comorbidity or a spectrum? Neuropsychobiol 1995: 31: 125-129.
24. **Ossipova VV, Kolosova AO, Vein AM.** Migraine associated with panic attacks. Cephalalgia 1999; 19: 728-731.

25. **Juang KD, Wang SJ, Fuh JL, Lu SR, Su TP.** Comorbidity of depressive and anxiety disorders in chronic daily headache and its subtypes. Headache 2000; 40: 818-823.
26. **Radat F, Sakh D, Lutz G, el Amrani N, Ferreri M, Bousser MG.** Psychiatric comorbidity is related to headache induced by chronic substance use in migraineurs. Headache 1999; 39: 477-480.
27. **Breslau N, Davis GC, Schultz LR, Peterson EL.** Joint 1994 Wolff Award Presentation: migraine and major depression: a longitudinal study. Headache 1994; 34: 387-393.
28. **Breslau N, Schultz LR, Stewart WF, Lipton RB, Lucia VC, Welch KM.** Headache and major depression: is the association specific to migraine? Neurology 2000; 54: 308-313.
29. **Kececi H, Dener S, Analan E.** Comorbidity of migraine and major depression in the Turkish population. Cephalalgia. 2003; 23: 271-275.
30. **Mahmood T, Romans S, Silverstone T.** Prevalence of migraine in bipolar disorder. J Affect Dis 1999; 52: 239-241.
31. **Mahmood T, Silverstone T.** Twin concordance for bipolar disorder and migraines. Am J Psychiatry 2000; 157: 2057.
32. **Fasmer OB.** The prevalence of migraine in patients with bipolar and unipolar affective disorders. Cephalalgia 2001; 21: 894-899.
33. **Fasmer OB, Oedegaard KJ.** Clinical characteristics of patients with major affective disorders and comorbid migraine. World J Biol Psychiatry 2001; 2: 149-155.
34. **Fasmer OB, Oedegaard KJ.** Laterality of pain in migraine with comorbid unipolar depressive and bipolar II disorders. Bipolar Disord 2002; 4: 290-295.
35. **Oedegaard KJ, Fasmer OB.** Is migraine in unipolar depressed patients a bipolar spectrum trait? J Affect Disord 2005; 84: 233-242.
36. **McIntyre RS, Soczynska JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A.** Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. Curr Opin Psychiatry 2007; 20: 406-416.
37. **Ortiz A, Cervantes P, Zlotnik G, Van de Velde C, Stanley C, Garmham J, Turecki G, O'Donovan C, Alda M.** Cross-prevalence of migraine and bipolar disorder. Bipolar Disord 2010; 12: 397-403.
38. **Blehar MC, De Paulo JR, Gershon ES, Reich T, Simpson SG, Nurnberger JL Jr.** Women with bipolar disorder: findings from the NIMH genetics initiative simple. Psychopharmacol Bull 1998; 34: 239-243.
39. **Jerrell JM, McIntyre RS, Tripathi A.** A cohort study of the prevalence and impact of comorbid medical conditions in pediatric bipolar disorder. J Clin Psychiatry 2010; 71: 1518-1525.
40. **Dilsaver SC, Benazzi F, Oedegaard KJ, Fasmer OB, Akiskal KK, Akiskal HS.** Migraine headache in affectively ill Latino adults of Mexican American origin is associated with bipolarity. Prim Care Companion J Clin Psychiatry 2009; 11: 302-306.
41. **First, MB, Spitzer, RL, Gibbon, M, Williams, JBW.** Structured clinical interview for DMS-IV axis I disorders: clinician version (SCID-CV). American Psychiatric Press, Washington, DC; 1997.
42. **Lipton RB, Dodick D, Sadovsky R, Kolodner K, Endicott J,Hettiarachchi J, Harrison W.** A self-administered screener for migraine in primary care: The ID migraine validation study. Neurology 2003; 61: 375-382.
43. **Hernández-Nieto R.** Instrumentos de Recolección de Datos en Ciencias Sociales y Ciencias Biomédicas. Universidad de los Andes, Consejo de Estudios de Postgrado, Mérida, Venezuela; 2011, p 178-184.
44. **Dawson B, Trapo RG**. Basic & Clinical Biostatistics, Third Edition. The McGraw-Hill Companies, Inc, Canada, 2001.
45. **Silberstein S.** Migraine. Lancet 2004; 363: 381-391.
46. **Dilsaver SC, Benazzi F, Oedegaard KJ, Fasmer OB, Akiskal HS.** Is a family history of bipolar disorder a risk factor for migraine among affectively ill patients? Psychopathology 2009; 42:119-123.
47. **Marino E, Fanny B, Lorenzi C, Pirovano A, Franchini L, Colombo C, Bramanti P, Smeraldi E.** Genetic bases of comorbidity between mood disorders and migraine: possible role of serotonin transporter gene. Neurol Sci 2010; 31: 387-391.

48. **Oedegaard, K J, Greenwood, T A, Lunde, A, Fasmer OB, Akiskal HS, Kelsoe JR.** A genome-wide linkage study of bipolar disorder and co-morbid migraine: replication of migraine linkage on chromosome 4q24, and suggestion of an overlapping susceptibility region for both disorders on chromosome 20p11. J Affect Disord 2010; 122: 14-26.
49. **Cardona-Castrillon GP, Isaza R, Zapata-Soto AP, Franco JG, Gonzalez-Berrio C, Tamayo-Diaz CP.** The comorbidity of major depressive disorder, dysthymic disorder and anxiety disorders with migraine. Rev Neurol 2007; 45: 272-275.
50. **Cao M, Zhang S, Wang K, Wang Y, Wang W.** Personality traits in migraine and tension-type headaches: a five-factor model study. Psychopathology 2002; 35: 254-258.
51. **Mongini F, Keller R, Deregibus A, Raviola F, Mongini T, Sancarlo M.** Personality traits, depression and migraine in women: a longitudinal study. Cephalalgia 2003; 23: 186-192.
52. **Rothrock J, Lopez I, Zweilfer R, Andress-Rothrock D, Drinkard R, Walters N.** Borderline personality disorder and migraine. Headache 2007; 47: 22-26.
53. **Katsarava Z, Manack A, Yoon MS, Obermann M, Becker H, Dommes P, Turkel C, Lipton RB, Diener HC.** Chronic migraine: classification and comparisons. Cephalalgia. 2011; 31: 520-529.
54. **Jette N, Patten S, Williams J, Becker W, Wiebe S.** Comorbidity of migraine and psychiatric disorders -a national population-based study. Headache 2008; 48: 501-516.