Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

To what extent are patients with migraine able to predict attacks?

This article was published in the following Dove Press journal:
Journal of Pain Research

Ana B Gago-Veiga[1]
Josué Pagán[2,3]
Kevin Henares[2,4]
Patricia Heredia[1]
Nuria González-García[5]
María-Irene De Orbe[4]
Jose L Ayala[3,4]
Mónica Sobrado[1]
Jose Vivancos[1]

[1]Headache Unit, Department of Neurology, Instituto de Investigación Sanitaria Hospital, Universitario de la Princesa, Madrid, Spain; [2]Department of Electronic Engineering, Universidad Politécnica de Madrid, Madrid, Spain; [3]Center for Computational Simulation, Universidad Politécnica de Madrid, Madrid, Spain; [4]Department of Computer and Automation Architecture, Universidad Complutense de Madrid, Madrid, Spain; [5]Headache Unit, Hospital Clínico Universitario San Carlos, Madrid, Spain

Purpose: Premonitory symptoms (PSs) of migraine are those that precede pain in a migraine attack. Previous studies suggest that treatment during this phase may prevent the onset of pain; however, this approach requires that patients be able to recognize their PSs. Our objectives were to evaluate patients' actual ability to predict migraine attacks based on their PSs and analyze whether good predictors meet any characteristic profile.

Patients and methods: This prospective, observational study included patients with migraine with and without aura. Patients' baseline characteristics were recorded. During a 2-month follow-up period, patients used a mobile application to record what they believed to be PSs and later to record the onset of pain, if this occurred. When a migraine attack ended, patients had to complete a form on the characteristics of the episode (including the presence of PSs not identified prior to the attack).

Results: Fifty patients were initially selected. A final total of 34 patients were analyzed, recording 229 attacks. Of whom, 158 (69%) were accompanied by PSs and were recorded prior to the pain onset in 63 (27.5%) cases. A total of 67.6% of the patients were able to predict at least one attack, but only 35.3% were good predictors (>50% of attacks). There were only 11 cases in which a patient erroneously reported their PSs (positive predictive value: 85.1%). Good predictors were not differentiated by any specific clinical characteristic. However, a range of symptoms were particularly predictive; these included photophobia, drowsiness, yawning, increased thirst, and blurred vision.

Conclusion: A large majority of patients with migraine experienced a PS and were able to predict at least one attack. Besides, only a small percentage of patients were considered as good predictors; however, they could not be characterized by any specific profile. Nonetheless, when patients with migraine believed that they were experiencing PSs, they were frequently correct.

Keywords: migraine, premonitory symptoms, prediction, real-time, electronic diary, machine learning

Introduction

When we talk about migraine attacks, we are generally referring to headache, which is usually the most disabling part of the attack. However, migraine attacks encompass a far wider range of symptoms. Prior to the pain, patients may experience the so-called premonitory symptoms (PSs), which were first described in 1980 by Blau[1] and are defined as those symptoms that precede and alert patients of a migraine attack between hours and 2 days in advance. According to the International Classification of Headache Disorders, third edition (ICHD-3),[2] they precede aura in migraine with aura

Correspondence: Ana B Gago-Veiga
Headache Unit, Department of Neurology, Instituto de Investigación Sanitaria Hospital Universitario de la Princesa, Calle Diego de León 62, Madrid, CP 28006, Spain
Tel +34 91 520 2416
Fax +34 91 520 2416
Email dra.anagago@gmail.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/JPR.S175602

and pain in migraine without aura. Examples of PSs include euphoria, fatigue, depression, increased appetite, or cravings for a particular type of food.

Studying these symptoms is valuable as they are the first that patients report during an attack and can indicate which anatomical regions and neurochemical mechanisms are affected at onset (mainly, the hypothalamus, limbic system, and dopaminergic mechanisms).[3,4] Another important factor, suggested in several papers, is the administration of the treatment during this phase with the aim of anticipating and preventing the pain onset. Waelkens[5] used domperidone as a treatment in response to the onset of PSs, while Luciani et al[6] used naratriptan. These studies reached similar conclusions, both using samples of ~20 patients. Pain was entirely prevented in approximately two-thirds of the patients; in the remaining one-third, pain occurred but was less intense. However, it should be noted that these studies included only patients who had previously been determined to be good predictors based on their PSs.

A large majority of studies about PSs in the literature followed a retrospective approach;[7–13] it is not possible with this design to assess patients' ability to predict attacks,[14] which is fundamental if we intend to administer treatment during this phase. The few prospective studies that do exist[15–19] are mainly descriptive, with the exception of the articles by Giffin et al[15] and Houtveen and Sorbi,[19] which used electronic diaries to evaluate patients' ability to predict migraine attacks. The advantage of using these diaries is that data can be collected in real time, increasing prediction reliability. In these studies, patients completed a daily questionnaire with questions about "non-headache" symptoms. In the study of Giffin et al,[15] there was also the possibility for patients to record symptoms spontaneously; however, the patients included in this study were selected due to their ability to predict migraine attacks.

As opposed to the methodology of Giffin et al and Houtveen and Sorbi,[15,19] our research does not ask the patients about their symptoms (reactively), but it allows them to spontaneously register their symptoms as soon as they appear (proactively), providing a set of potential symptoms to select from. Our aim is hence to exploit the capability of the patients to recognize their own symptoms in order to drive a potential early intake of the drugs.

Therefore, this study, besides using the benefits of electronic diaries through a mobile application, is the first to assess only the symptoms recognized spontaneously by patients not selected based on their ability to predict an attack and to proactively request the patients to register their PSs. The study aimed to address the following questions: What percentage of patients are able to predict migraine attacks? Do they predict all attacks? Do good predictors have a specific profile? Is any combination of PSs particularly predictive?

Patients and methods

Study population

We performed a prospective, observational study of patients with migraine meeting the following inclusion criteria: age between 15 and 69 years; diagnosis of migraine with or without aura made by a neurologist specialized in headaches, according to the criteria established in ICHD-3;[2] having an average of between one and eight attacks per month in the 3 months prior to the inclusion in the study (in order to record a minimum of two attacks and prevent overlap between the postdrome symptoms of one attack and the PSs of the following one – for that reason, no patient had chronic migraine); being able to complete 2 months of follow-up for the study; having at least 1 year of history of migraine (patients using preventive treatments for migraine at the time of inclusion in the study were allowed to participate); having user-level proficiency with smartphone-type electronic devices; having normal neurological examination results; and having given informed consent to be included in the study. Whether or not patients had previously reported PSs was not considered as an inclusion criterion. The study excluded patients meeting the following criteria: experiencing non-migraine headaches that could not be distinguished from migraine attacks by them, incorrect recording of the details requested in reference to their attacks, cognitive impairment or any other disorder that may prevent them from correctly complying with study conditions, and active infections or acute diseases during monitoring.

Patients were recruited from two specialized headache units (Hospital Universitario de la Princesa and Hospital Clínico San Carlos, both located in the region of Madrid, Spain) from February 1, 2017 until April 30, 2017.

Methodology of the study

Sessions were held with groups of two to three patients to explain the purpose and methodology of the study and to request their participation and informed consent. Patients were asked to install an application (BrainGuard App) on their mobile devices; the application was developed by the research team for devices running Android operating systems (Figure 1). The application, which was installed from the research team's servers, enables patients to anonymously send data to the team's secure cloud servers.

Patients used this application to complete a self-administered questionnaire. In the initial consultation, the patient

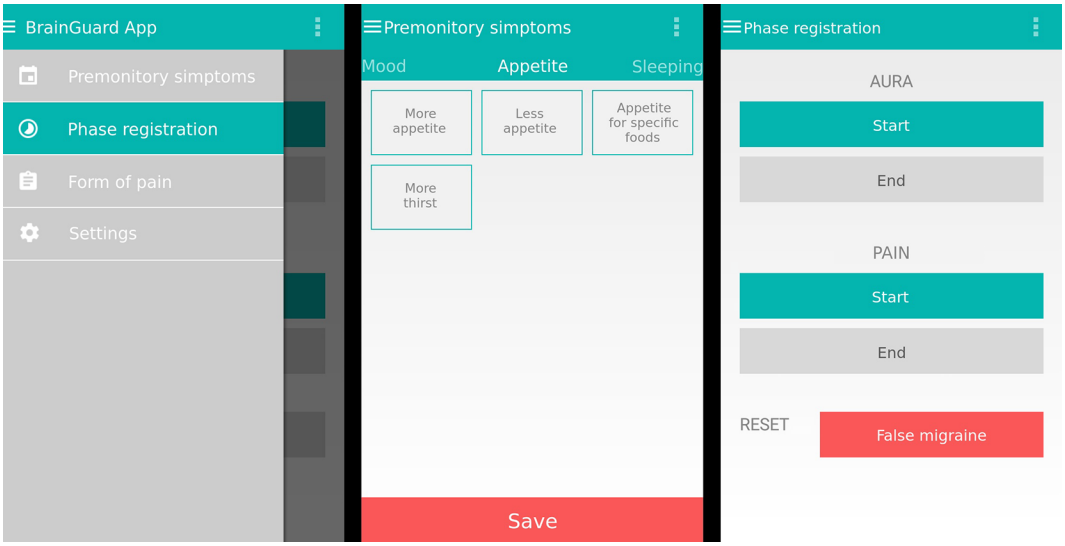

Figure 1 Android smartphone electronic diary screenshots.
Note: The image shows the main menu and sample recordings of a PS and the start/end of aura and/or pain.
Abbreviation: PS, premonitory symptom.

and the neurology consultant completed the first section together. This section concerned patients' baseline data: sex, age, confirmation of diagnosis of migraine with/without aura, age at onset, overall qualities of pain (imploding/exploding/retro-ocular/mixed), pain frequency, presence of a catamenial component, family history (yes/no), level of study (primary education/secondary education/higher education), sleep disorders (sleep-onset insomnia/early awakening/drowsiness), and current preventive treatments for migraine. Four other scales were also administered at this baseline visit: the 6-item Headache Impact Test (HIT-6),[20] the Goldberg scales for anxiety and depression,[21] and the Cognitive Reserve Index questionnaire.[22,23] The latter assesses education, training courses completed, work, languages spoken, reading habits, musical education, and frequency of participation in intellectually challenging activities (eg, crosswords, chess). Higher scores indicate greater cognitive reserve.

Following completion of the baseline questionnaire, the neurologist explained the steps to be taken outside the hospital. The procedure was simulated several times during the consultation to ensure patients' complete understanding; patients were provided the training needed to distinguish PSs from migraine trigger factors. For this purpose, the patients were instructed to detect an external factor the occurrence of which determines the appearance of the migraine (trigger), from those internal statuses that, even removed, would not condition the beginning of the crisis (PSs).[14]

When patients suspected that they were experiencing a PS, they had to select the symptom from a checklist. The symptoms listed were mood alterations (euphoria, hyperactivity, sadness, apathy, irritability, anxiety), cognitive alterations (difficulty writing, speaking, or concentrating), digestive/urinary alterations (nausea and/or vomiting, flatulence, constipation, fluid retention/bloated sensation, frequent urination), altered appetite (increase, reduction, appetite for specific foods, increased thirst), sensory alterations (photo-/phono-/osmophobia, allodynia), changes in perceived body temperature (hot/cold), sleep disorders (insomnia/drowsiness), tinnitus, fatigue, dizziness, yawning, skin/vascular alterations, neck stiffness, blurred vision, and other (blank field). Day and time of symptom occurrence were also recorded. Later, patients recorded the start and end of pain/aura, when these occurred. When the attack ended, patients recording pain were asked to complete a form on the characteristics of the attack: location, quality, accompanying symptoms (photo-/phono-/osmophobia, nausea/vomiting), trigger factors, pain intensity, and postdrome symptoms. If the patient did not record the onset of pain within a period of 72 hours, the event was considered a false positive. This period was established at 72 hours, in line with the limit set by the majority of researchers conducting prospective studies on PSs.[15,19]

Patients could also indicate whether they had experienced PSs but did not recognize them prior to pain onset (non-predictive premonitory symptoms [npPSs]); our analysis differentiated between whether PSs were reported before and after pain onset. Each patient was followed up for 2 months following their baseline visit.

To verify patient's compliance, the application implements an alarm, which sounded every 3 days to remind patients of their participation in the study. Patients were also followed up with weekly telephone calls from the neurologist and technicians to verify the status of incomplete forms and study adherence and to resolve doubts regarding the identification of symptoms or issues with the application, etc.

At the end of the study period, patients completed a survey in which they were asked to indicate whether they already recognized PSs prior to their inclusion in the study and their self-perceived predictive ability ("I am not able to predict my migraines", "I am good at predicting my migraines", "I can only sometimes predict my migraines").

As this study aims to evaluate the predictive capability of the patients, they were not instructed to take any medication during the premonitory phase.

Statistical analyses

Statistical analyses were performed using the MATLAB tool (2017-b version). Categorical data were analyzed using a two-tailed chi-squared test. The Yates correction and the Fisher's exact test were also applied where necessary. Results with a *P*-value of <0.05 were considered as statistically significant.

Machine learning techniques were used to analyze the classification and selection of variables using the Weka tool (version 3.8.1). A random forest algorithm was used to classify predictive events (migraine attacks), using the application's default parameters. Variables were selected using the Information Gain attribute evaluator with the Ranker search method. Logistic regression analysis was used to determine the relationship between a dichotomous outcome (predictive PSs/no predictive PSs) and a set of independent variables, distributed in three separate blocks: block 1 comprised age, education, years of disease progression, and cognitive reserve; block 2 comprised sex, diagnosis, pain quality, and HIT-6 score; and block 3 comprised depression, anxiety, preventive treatment, and clinical history. This initial segmentation of independent variables into groups aimed to validate/invalidate a set of good predictive variables vs those that do not predict the events clearly. The classification was performed by clinical criteria and, in any case, did not condition the results of the study. Variables were selected using the enter method and stepwise selection. We also developed a polytomous model (outcomes: no predictive PSs/<50% predictive PSs/>50% predictive PSs). Logistic regression analysis was performed using the IBM SPSS software (version 23). The likelihood calculation was performed by this logistic regression function and normalized by the *P*-value.

There were no missing data on any patient analyzed. The contrast variable was always predictable.

The statistical study, using the metrics p-valor, f-valor, and chi-square, has been designed to expose the correlations between the predictive capability of the patients and the collected sociodemographical variables, in order to expose any predictive profile of the patients.

The study was approved by Hospital de la Princesa's Ethics Committee (register number: PI-879). All patients signed informed consent forms prior to inclusion in the study. Patient data were anonymized for data analysis.

Results

Description of our sample

We included all the patients who met the inclusion criteria during the recruiting period, resulting in 50 patients, 16 of whom were subsequently excluded: nine experienced no migraine attacks during the study and seven did not correctly comply with study conditions (they did not complete the form when attacks ended or consistently recorded symptoms incorrectly, for example by recording the start/end of pain at the same time; this compromised the reliability of their data). During the follow-up of the study, we assured that the patients did register every event, so there are not missing data in the form. The final analysis, therefore, included a total of 34 patients and 229 migraine attacks (the mean number of attacks analyzed per patient was 6.7 over the 2-month study period). Participants' mean age was 41.2±11.2 years; 30 of 34 (88.2%) patients were women.

A total of 29 (85.3%) patients experienced PSs during at least one episode. The mean number of PSs recorded was 4.3±3.3 per event. The mean number of PSs recorded per event was 3.4±2.0 for symptoms recorded prior to pain onset (predictive premonitory symptom [a priori; pPS]) and 5.1±4.9 for symptoms recorded after onset (npPSs).

Figure 2 shows the time at which the different PSs manifested. The mean time of manifestation was 10 hours 38 minutes prior to pain onset (this evaluation took into account pPSs in order to determine the exact moment that symptoms manifested). The symptoms identified closest to the pain onset (<8 hours; symptoms recorded on at least three occasions) were nausea and vomiting, apathy, difficulty concentrating, blurred vision, and neck stiffness. The symptoms occurring earliest before the pain onset (>12 hours) were osmophobia, allodynia, anxiety, perceived changes in body temperature, yawning, and tinnitus.

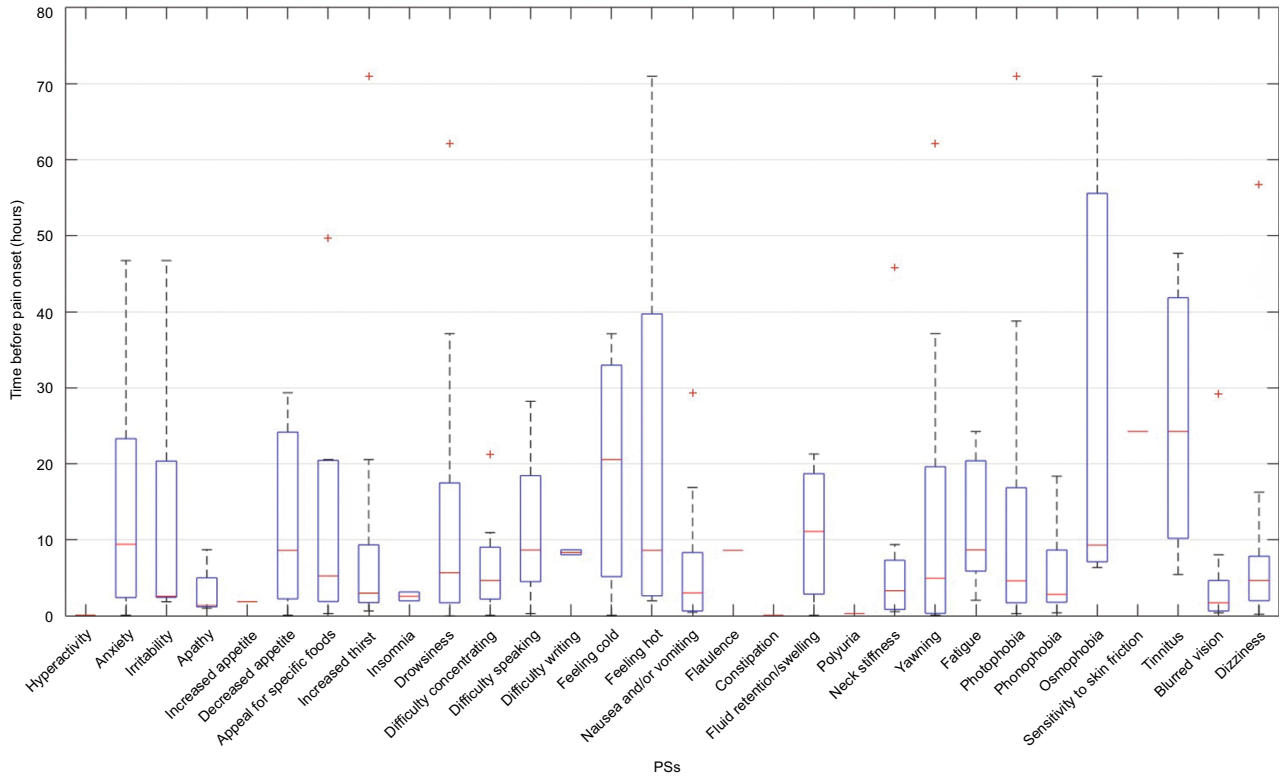

Figure 2 Times at which PSs occurred with relation to pain onset.
Abbreviation: PS, premonitory symptom.

Relationship between patients and their PSs: a priori (predictive capability) and a posteriori

Figure 3 displays the distribution of patients and migraine attacks (events) according to whether attacks were accompanied by PSs and whether these symptoms were recorded before or after pain onset. A single patient may therefore experience all three types of events (without PSs, with pPSs, or with npPSs), only two types, or purely experience one type of event (PSs never experienced, PSs always recognized before pain onset, and PSs always experienced but never recognized prior to pain onset).

A total of 23 patients (colored red on the Venn diagram) were able to predict an attack at least once, implying that patients have a 67.6% likelihood of predicting attacks on occasion, and of these patients who were able to predict attacks on some occasion, 12 (35.3%) were good predictors (able to predict >50% of attacks). However, only four (11.8%) patients were always able to predict attacks when they were accompanied by PSs (two of them only had one migraine attack and they predicted it, and the other two had five migraines, predicting one of them 4 (80%) (in the other migraines, he did not have PS) and the other one predicted 3 (60%) (in the other two migraines he did not have PSs).

A large majority of patients either experienced some event in which they were unable to recognize PSs (25 patients, 73.5%) or never experienced PSs (5, 14.7%). Overall, 11 (32.3%) patients never predicted any attack (PSs were absent or only recognized after pain onset). The largest group (12 patients) comprised those patients who experienced all three types of event (with no PSs, with pPSs, or with npPSs).

A total of 229 migraine attacks were recorded. Of these, 158 (69%) were accompanied by PSs. PSs were recorded prior to pain onset in 63 (27.5%) cases and after pain onset in 95 (41.5%) cases. In all, 71 (31%) events did not involve PSs.

Selectivity of PSs

Selectivity can be assessed by analyzing the difference in the likelihood of PSs accompanying an event and the likelihood of these being predictive (Table 1). The more events with PSs a patient experiences, the lower their probability of predicting an event (lower selectivity). In other words, the percentage of patients predicting events decreases as the proportion of events featuring PSs increases: patients experiencing PSs in 25% of events predicted 51.7% of attacks, whereas patients experiencing PSs in 90% of events predicted only 16.7% of attacks. This led us to consider that the heterogeneity of PSs may play a role. We analyzed whether a higher mean number

of PSs per event were recorded by the latter patient group. The higher the proportion of events featuring PSs the higher the mean number of PSs that were recorded. However, this was not the case in the group of patients with pPSs: the few patients who predicted attacks were more selective, recording lower mean numbers of PSs (3; 1.5 fewer than the mean number recorded in the group as a whole).

Study of false positives

In addition to the migraine attacks recorded, there were 11 cases in which patients recorded a symptom which they believed to be a PS but which ultimately was not; these episodes were considered as false positives. Considering the total of 63 attacks featuring pPSs (true positives) and the 11 false positives, the positive predictive value of recording a symptom, as a potential PS, was 85.1% in our study. Statistical analysis revealed that the number of false positives is similarly distributed between the two groups of patients: those who were able to predict attacks and those who were not.

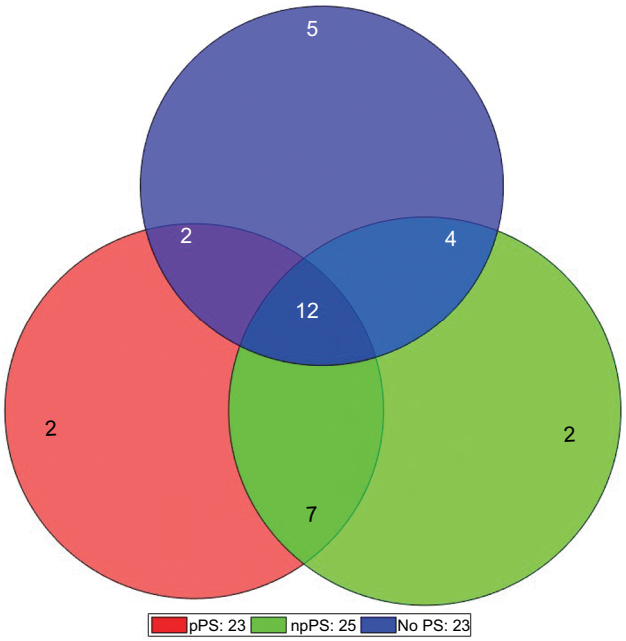

Figure 3 Venn diagram showing the distribution of participants according to the type(s) of event experienced.
Notes: Red: patients who experienced an event with PSs recognized prior to pain onset (n=23). Blue: patients who experienced an event with no PSs (n=23). Green: patients who experienced an event with PSs recognized after pain onset (n=25).
Abbreviations: PS, premonitory symptom; pPS, predictive premonitory symptom; npPS, non-predictive premonitory symptom.

Relationship between patients' baseline characteristics and likelihood of being a good predictor

An analysis of whether any baseline characteristic increased patients' likelihood of being able to predict some attack or of being a good predictor (able to predict >50% of attacks) revealed no statistically significant differences (Table 2), including sex, age, years from onset of headache, and cognitive reserve and associated preventive treatment. Furthermore, neither a classic logistic regression analysis (either with dichotomous or polytomous outcomes) nor an advanced analysis with machine learning techniques revealed any statistically significant difference.

Relationship between the characteristics of the migraine crisis and likelihood of prediction

The event characteristics that most contributed to classification of patients as good predictors were presence of trigger factors (episodes with pPSs featured trigger factors in 52 cases and no trigger factors in 11 vs 41 cases with trigger factors and 29 without in episodes without PSs; P=0.004) and aura (episodes with pPSs featured aura in 16 cases and no aura in 47 vs 16 cases with aura and 150 without in episodes with npPSs or no PSs; P=0.004). We also analyzed the time between the manifestation of PSs and onset of aura in events featuring aura (mean time of 10 hours 24 minutes) in order to verify that these symptoms did not appear only after the

Table 1 Percentage of patients experiencing events with PSs and the percentage of PSs that were predictive

According to number of events	Likelihood of experiencing PSs (%)	Likelihood of experiencing pPSs (%)	Patients with PSs who were able to predict attacks (%)[a]	Mean number of PSs per event with PSs[b]	Mean number of PSs per event with pPSs[b]
In at least 1 event	85.3	67.6	79.3	3.4	3.5
In 1 of 4 events	85.3	44.1	51.7	3.4	3.5
In 1 of 2 events	76.5	35.3	46.1	3.6	3.8
In 3 of 4 events	61.8	17.2	27.9	4.0	3.7
In 9 of 10 events	35.3	5.9	16.7	4.5	3.0

Notes: [a]The fourth column shows the proportion of patients able to predict attacks within each PS group. [b]The final two columns show the mean number of PSs per event for all events with PSs and for events with pPSs.
Abbreviations: PS, premonitory symptom; pPS, predictive premonitory symptom.

Table 2 Relationship between patients' baseline characteristics and likelihood of being a good predictor

Variable	Total	n=34	Prediction rate						*P*
			Zero	n=11	<50%	n=11	>50%[a]	n=12	
	n	%	n	%	n	%	n	%	
Sex (women)	30	88.2%	9	81.8%	10	90.9%	11	91.7%	0.72
University studies	25	73.5%	8	72.7%	8	72.7%	9	75.0%	0.99
Aura (yes)	19	55.9%	4	36.4%	7	63.6%	8	66.7%	0.28
Quality									
Imploding	13	38.2%	3	27.3%	5	45.5%	5	41.7%	
Exploding	6	17.6%	2	18.2%	1	9.1%	3	25.0%	0.53
Mixed	9	26.5%	3	27.3%	2	18.2%	4	33.3%	
Retro-ocular	6	17.6%	3	27.3%	3	27.3%	0	0.0%	
Medical history (yes)	25	73.5%	8	72.7%	8	72.7%	9	75.0%	0.99
Anxiety (yes)	23	67.6%	7	63.6%	7	63.6%	9	75.0%	0.79
Depression (yes)	10	29.4%	4	36.4%	4	36.4%	2	16.7%	0.48
Chronic stress (yes)	19	55.9%	6	54.5%	7	63.6%	6	50.0%	0.80
Preventive treatment (yes)	24	70.6%	9	81.8%	7	63.6%	8	66.7%	0.60
Age (years), mean (SD)	38.3	(14.6)	35.9	(20.3)	42.6	(11.6)	36.5	(10.5)	0.49
Years of disease progression, mean (SD)	24.3	(14.8)	23.3	(17.1)	27.3	(13.3)	22.4	(14.6)	0.71
Cognitive reserve, mean (SD)	15.9	(3.6)	16.5	(3.3)	16.2	(2.7)	15.0	(4.5)	0.56
Age at onset, mean (SD)	15.0	(7.7)	15.5	(6.8)	15.3	(6.5)	14.2	(9.8)	0.91
HIT-6 score, mean (SD)	60.4	(9.6)	61.4	(7.4)	60.7	(7.1)	59.1	(13.4)	0.96
Catamenial migraine	13	38.2%	5	45.5%	5	45.5%	3	25%	0.50
Sleep disorders									0.49
None	15	44.1%	7	63.6%	3	27.3%	5	42.7%	
SOI	5	14.7%	1	9.1%	1	9.1%	3	25%	
SOI/drowsiness	1	2.9%	0	0.0%	1	9.1%	0	0.0%	
SOI/EA	1	2.9%	0	0.0%	1	9.1%	0	0.0%	
EA	7	20.6%	1	9.1%	3	27.3%	3	25%	
EA/drowsiness	2	5.9%	0	0.0%	1	9.1%	1	8.3%	
Drowsiness	3	8.8%	2	18.2%	1	9.1%	0	0.0%	

Notes: [a]Patients able to predict >50% of migraine attacks were considered good predictors.
Abbreviations: HIT-6, Headache Impact Test-6; SOI, sleep-onset insomnia; EA, early awakening.

onset of aura, which would make prediction simpler. The most prevalent PSs in predictive episodes of migraine with aura were photophobia and blurred vision (reported in nine and five of 16 episodes, respectively). However, we found no relationship between patients' ability to predict an attack and the presence of simultaneous symptoms; the location, quality, intensity, or duration of pain; or the presence of postdromal symptoms.

Prevalence, predictability, predictive positive value (PPV), and relevance of each PS

Columns in Table 3 show the "Likelihood of presenting the PSs", "Likelihood of predictability of the PSs", "PPV of the PSs", and a compound metric that evaluates "the relevance" of the prediction as the multiplication of the three previous factors.

It is important to notice that the symptoms registered in Table 3 are presented by the patients as related to their migraine symptoms, being differentiated from their baseline status.

Photophobia and drowsiness were the most relevant PSs in our study; other significant symptoms were yawning, increased thirst, blurred vision, and nausea. Sadness was prevalent but was not predictive in our sample (it was recorded 23 times but always after pain onset).

We performed an advanced study using machine learning techniques to evaluate the ability to know a priori whether an event will be predictive when a patient records his or her PSs. Using the random forest algorithm, boosted with AdaBoost[24] and a 10-iteration cross-validation, we were able to correctly classify 79.0% of events. The resulting quality parameters were very promising: *F*-value: 78.6%, receiver operating characteristic: 89.3%, precision: 78.4%, and recall: 79.0%. The PSs allowing the highest level of accuracy in event classification (as predictive or not predictive) were photophobia, fatigue, sadness, drowsiness, neck stiffness, yawning, phonophobia, and difficulty concentrating.

Table 3 Prevalence, predictiveness, PPV, and relevance of PSs

PSs	Total times recorded	Likelihood of presenting	Likelihood of predictiveness	PPV	Relevance (likelihood of presenting × predictiveness × PPV)
Photophobia	68	42.8	32.3	78.6	10.9
Drowsiness	54	31.9	40.7	75.9	9.8
Yawning	45	26.6	33.3	100	8.8
Increased thirst	32	18.9	43.7	100	8.3
Blurred vision	23	13.6	56.5	86.6	6.7
Neck stiffness	42	24.8	26.2	91.7	6.0
Nausea/vomiting	27	16.0	44.4	80	5.7
Difficulty concentrating	42	24.8	28.6	75	5.3
Phonophobia	45	26.6	25	78.6	5.2
Dizziness	32	18.9	34.4	78.6	5.1
Fatigue	48	28.4	18.7	81.8	4.4
Appetite for specific foods	17	10.1	47	88.9	4.2
Sensation of increased temperature	20	11.8	35	100	4.1
Irritability	26	15.4	23.1	100	3.6
Anxiety	25	14.8	28	77.8	3.2
Difficulty speaking	14	8.3	28.6	80	1.9
Fluid retention	9	5.3	33.3	100	1.8
Osmophobia	10	5.9	30	100	1.8
Tinnitus	16	9.5	18.7	100	1.8
Sensation of decreased temperature	14	8.3	21.4	100	1.8
Apathy	28	16.6	14.3	66.7	1.6
Decreased appetite	6	4.1	42.8	75	1.3
Insomnia	14	8.3	14.3	100	1.2
Difficulty writing	5	2.9	40	100	1.2
Flatulence	11	6.5	9	50	0.6
Frequent urination	4	2.4	25	0	0.6
Allodynia	4	2.4	25	100	0.6
Hyperactivity	5	2.9	20	50	0.3
Increased appetite	10	5.9	10	33.3	0.2
Sadness	23	13.6	0	0	0
Euphoria	2	1.2	0	0	0
Skin and vascular alterations	2	1.2	0	0	0

Note: The second column shows the total number of times each PS was recorded; the third column shows the likelihood of each PS appearing (before and after pain onset); the fourth column shows the likelihood of prediction, given the PSs appearing; the fifth column shows the PPV (true positive/true positive+false positive), and the sixth column shows the relevance (accounting for the number of times each PS was recorded, its predictiveness, and its PPV).
Abbreviations: PPV, predictive positive value; PS, premonitory symptom.

Survey results

In the survey completed by patients at the end of the trial, 16 patients (16 out of 34, 47.1%) reported that although they had already experienced PSs in the past, they were unable to relate them with their attacks until the training received in the baseline visit.

Patients reported self-perceived predictive ability as follows: "I am not able to predict my migraines" (seven out of 34 respondents, 20.6%), "I am good at predicting my migraines" (ten out of 34, 29.4%), "I can only sometimes predict my migraines" (15 out of 34, 44.1%), and "I don't know"/no response (two out of 34, 5.9%). However, comparison against the data obtained revealed that of those patients who considered themselves as good predictors, seven out of ten (70%) were not and that 10 out of 22 (45%) patients who were good predictors believed themselves not to be.

Discussion

This study is the first to assess the ability to predict a migraine attack based only on spontaneous recordings made by patients when they experience what they believe to be a PS. This is of great importance for treating migraine during the premonitory phase:[5,6] experiencing PSs is not the same as being able to recognize them as the onset of a migraine attack prior to the onset of pain.

Based on our findings, we can conclude that there is a high likelihood (67.6%) of patients being able to predict at least

one migraine attack, but only one-third of our patients were good predictors (able to predict more than half of attacks). Furthermore, only 27.5% of migraine crisis presents PSs a priori. However, it should be noted that patients who believed that they were experiencing a PS were very frequently correct (PPV was 85.1%).

No baseline variables were correlated with patients' likelihood of being good predictors or of being able to predict any attack. It is the case, however, that patients were more likely to recognize PSs if they considered the event to have been precipitated by a trigger factor, probably because they knew they would experience PSs. As one limitation of our study, we did not register the time of the trigger, so we cannot correlate them in time with the PSs.

Previous studies in the literature report conflicting results with regard to the prevalence of PSs in patients with migraine. Depending on the study, the reported prevalence ranges from 9%[25] or 33%–39%[8,9,11] to 77%–92%.[7,10,13,16,26] This variability may be due to methodological differences between the different studies, for example whether the approach was prospective or retrospective (where a recall bias may exist, given that patients may not recall all PSs they experienced and the difficulty of associating PSs independently to each attack). Another influence may be the method of data collection: with free-form diaries, patients may forget certain items, whereas with checklists, they are limited to the available options or may record symptoms that they would not otherwise have reported or may have forgotten.[14] We report one of the highest prevalence rates (85.3%). This may be due to our methodology: patients were able to add PSs that were not included on the provided checklist. A further detail that we deem relevant is the fact that time was specifically dedicated at the baseline consultation to performing a directed medical history interview and educating patients about PSs. Time constraints do not allow this at normal consultations. Therefore, patients often do not associate PSs with pain, as shown by the results of the survey, in which 47% of patients reported that they either had not recognized these symptoms or had not related them with migraine prior to the baseline interview. This argument supports the need of targeting the patients in a direct manner, as previously described in Jay and Barkin.[27]

We observed a mean of 4 PSs per event in our sample, whereas our literature review found that other researchers typically reported 3 PSs;[10,13] this contrast was probably also due to differences in the method of data collection. Other articles described events accompanied by seven or even 12 of these symptoms.[11,16] We also observed that the mean number of PSs reported per attack was lower for PSs reported prior to pain onset. This was probably because not all PSs are easily identified; predictive patients are more selective in recording PSs.

Various articles[9–13,15–17,28] described yawning, irritability, apathy, neck stiffness, photophobia, nausea, fatigue, and difficulty concentrating as the most frequent symptoms. In addition to these, we also found perceived changes in body temperature and increased thirst to be frequent PSs.

Although the ICHD-3 beta[29] definition stated that PSs may appear between 2 and 48 hours prior to pain, we found examples of PSs occurring later than 2 hours prior to pain onset. This issue has previously been discussed by Maniyar et al[30] These authors considered that the definition involved two aspects that required consideration: first, PSs do not precede or forewarn of migraine attacks; rather, they are a part of the attack itself. Second, these symptoms may present during the 2-hour interval before the onset of pain/aura. The reason for this time interval is to enable PSs to be clearly differentiated from aura; however, this gap does not truly exist, as has been shown by various prospective studies[15,31] and now by the present study, with patients describing non-headache symptoms even minutes before pain onset. Additionally, aura is clearly a distinct entity from a pathophysiological perspective. In the definitive version,[2] the specification of 2 hours has already disappeared and the PSs are considered possible part of the migraine attack.

In our sample, PSs occurred a mean time of 10 hours prior to pain onset; this is consistent with previous studies, which describe a mean time of 6–12 hours.[15,19] As other authors have found to be the case,[19] certain symptoms were typically observed to occur closer to pain onset (neck stiffness, nausea, apathy, difficulty concentrating, and fatigue), while others occurred earlier (perceived changes in body temperature, anxiety, osmophobia, yawning, allodynia, and tinnitus). Such authors as Waelkens[26] also describe these early symptoms. Other early PSs described in the literature include mood alterations such as euphoria and hyperactivity;[26] however, our results do not support this conclusion, as very few of the patients in our sample recognized these PSs; Giffin et al[15] reported similar findings. This variability in the time of onset of PSs is supported by neuroimaging studies, which reveal different brain activation patterns depending on the phase of the migraine. Maniyar et al[32] artificially induced migraine in patients and observed activations in specific areas at onset of the migraine attack, in accordance with the PSs reported by the patient. It should be noted that activation was different during the early and late premonitory phase. The activation of

areas including the hypothalamus, ventral tegmentum, periaqueductal gray, and putamen diminished nearer pain onset; the dorsal pons remained active in all phases, and the insula was activated nearer the time of pain onset. This is probably linked to the fact that certain PSs occur at the earliest moment of the premonitory phase, maintaining a constant intensity, and disappear before pain onset (non-evolutive symptoms), whereas others increase in intensity approaching pain onset (evolutive symptoms).[4,26]

As was mentioned earlier, the main study into patients' ability to predict pain in migraine attacks based on their PSs was conducted in 2003 by Giffin et al.[15] In this study, patients were required to record the different cognitive, sensory, and mood alterations they experienced, as well as any other symptoms. The researchers then analyzed whether symptoms changed in the days and hours before pain onset. Patients considered good predictors (n=97) were able to predict 72% of attacks; 82% of patients predicted more than half of their attacks. This stands in contrast with our findings (35% of our patients predicted more than half of their attacks), which can be explained by two facts. First, we included in our study any migraine patient and not only those considered as "good predictors", because the aim of our work was to evaluate the prediction capability of all our patients visiting for migraine diagnosis. Additionally, in the work of Giffin et al, it is related how the patients were instructed to fill a form upon a daily alarm, although spontaneous registers were also allowed. In that work, we can observe that most of the valid data (68%) were obtained right after the alarm. However, if we aim to advance the intake of the treatment before the pain starts, the patients must recognize these PSs. Therefore, we only allowed patients to register data spontaneously.

The most predictive PSs in the study of Giffin et al[15] were difficulty speaking, difficulty reading and writing, and yawning; these symptoms were also frequently recorded prior to pain onset in our study. In our study, the most relevant PSs (considering the number of times each PS was recorded, its predictiveness, and its PPV) were photophobia and drowsiness. These symptoms were also found to be predictive in the study of Giffin et al; other very relevant symptoms to be taken into account, based on the evaluation of both studies, are blurred vision, thirst, dizziness, perceived changes in body temperature (especially high temperature), food craving, and difficulty concentrating. Other symptoms did not aid patients in predicting attacks; examples are sadness and apathy. Regarding nausea and vomiting, the results of the two studies diverge: the present study found this to be a good predictor, while this was not in the case of the study of Giffin et al. As can be seen in the study of Giffin et al, although nausea and vomiting are registered a priori in many of the events, there is also a large percentage of prediction error related to these PSs. However, our study found that the PPV of these symptoms is 80.

Another interesting point is that the machine learning techniques used enabled us to tell patients with a precision of almost 80% whether their attacks may be predictable, based on the PSs they reported.

After reviewing the patient surveys, we observed that patients know whether they were able to predict some migraines, but were often mistaken regarding their self-identification as good predictors. We deem it important to verify this information as patients may under- or overestimate their ability to predict attacks.

The main limitations of this study are as follows: 1) the small sample size; 2) the fact that using a mobile application excludes those patients who do not have basic user-level understanding of smartphone-type devices, who often are aged patients; 3) the exclusion of patients who consistently recorded symptoms incorrectly; and 4) the fact that probably patients were more focused on recognizing their PSs than usual due to the 2-month study period. These limitations probably result in an overestimation in predictability. Despite this, we consider the study's strengths to be its real-time approach, the ability to study multiple migraines and baseline characteristics, and the machine learning analysis. In conjunction with the large amount of data and the application installed on patients' own telephones, this has afforded great reliability to the study's reflection of patients' everyday condition.

Conclusions

With appropriate training, a large majority of the patients in our study successfully identified their PSs and were able to predict at least one attack. However, a strategy of administering treatment during the premonitory phase, based only on prior recognition of symptoms, would benefit a very small percentage of patients. We found no baseline characteristic offering insight into a patient's status as a good predictor; analyzing the PSs itself was found to be more informative. Nonetheless, it should be stressed that patients who believed that they were experiencing a PS were correct in a large majority of cases; this effect was more pronounced for specific symptoms. We deem it fundamental for the future treatment of migraine attacks for researchers to continue to seek the best method of predicting pain onset.

Acknowledgments

We would like to thank all the participating patients, without whom this study would not have been possible. This project was funded by the Instituto Carlos III Healthcare Research Fund (PI15/01976). The project was co-financed by the European Regional Development Fund.

Author contributions

ABGV and JP conceived the project, participated in data analysis, participated in drafting the manuscript, and read and approved the final manuscript. KH, PH, and MIDO participated in data analysis and read and approved the final manuscript. NGG participated in data analysis, participated in drafting the manuscript, and read and approved the final manuscript. JLA and MS conceived the project, participated in drafting the manuscript, and read and approved the final manuscript. JV participated in drafting the manuscript and read and approved the final manuscript. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Blau JN. Migraine prodromes separated from the aura: complete migraine. *Br Med J*. 1980;281(6241):658–660.
2. Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders, 3rd edition.* Cephalalgia. 2018;38(1):1–211.
3. Maniyar FH, Sprenger T, Monteith T, Schankin CJ, Goadsby PJ. The Premonitory Phase of Migraine - What Can We Learn From It? *Headache*. 2015;55(5):609–620.
4. Gago-Veiga AB, Vivancos J, Sobrado M. The premonitory phase: a crucial stage in migraine. *Neurologia*. Epub 2017 Dec 22.
5. Waelkens J. Dopamine blockade with domperidone: bridge between prophylactic and abortive treatment of migraine? A dose-finding study. *Cephalalgia*. 1984;4(2):85–90.
6. Luciani R, Carter D, Mannix L, Hemphill M, Diamond M, Cady R. Prevention of migraine during prodrome with naratriptan. *Cephalalgia*. 2000;20(2):122–126.
7. Amery WK, Waelkens J, Vandenbergh V. Migraine warnings. *Headache*. 1986;26(2):60–66.
8. Santoro G, Bernasconi F, Sessa F, Venco A. Premonitory symptoms in migraine without aura: a clinical investigation. *Funct Neurol*. 1990;5(4):339–344.
9. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache*. 2004;44(9):865–872.
10. Schoonman GG, Evers DJ, Terwindt GM, van Dijk JG, Ferrari MD. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia*. 2006;26(10):1209–1213.
11. Schulte LH, Jürgens TP, May A. Photo-, osmo- and phonophobia in the premonitory phase of migraine: mistaking symptoms for triggers? *J Headache Pain*. 2015;16:14.
12. Karsan N, Prabhakar P, Goadsby PJ. Characterising the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service. *J Headache Pain*. 2016;17(1):94.
13. Laurell K, Artto V, Bendtsen L, et al. Premonitory symptoms in migraine: a cross-sectional study in 2714 persons. *Cephalalgia*. 2016;36(10):951–959.
14. Lipton RB, Pavlovic JM, Haut SR, Grosberg BM, Buse DC. Methodological issues in studying trigger factors and premonitory features of migraine. *Headache*. 2014;54(10):1661–1669.
15. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: an electronic diary study. *Neurology*. 2003;60(6):935–940.
16. Quintela E, Castillo J, Muñoz P, Pascual J. Premonitory and resolution symptoms in migraine: a prospective study in 100 unselected patients. *Cephalalgia*. 2006;26(9):1051–1060.
17. Wöber C, Brannath W, Schmidt K, et al. Prospective analysis of factors related to migraine attacks: the PAMINA study. *Cephalalgia*. 2007;27(4):304–314.
18. Hashizume M, Yamada U, Sato A, et al. Stress and psychological factors before a migraine attack: a time-based analysis. *Biopsychosoc Med*. 2008;2:14.
19. Houtveen JH, Sorbi MJ. Prodromal Functioning of Migraine Patients Relative to their interictal State – An Ecological Momentary Assessment Study. *PloS ONE*. 2013;16:8.
20. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res*. 2003;12(8):963–974.
21. Goldberg D, Bridges K, Duncan-Jones P, Grayson D. Detecting anxiety and depression in general medical settings. *BMJ*. 1988;297(6653):897–899.
22. Rami L, Valls-Pedret C, Bartrés-Faz D, et al. Cognitive reserve questionnaire. Scores obtained in a healthy elderly population and in one with Alzheimer's disease. *Rev Neurol*. 2011;52(4):195–201.
23. Nucci M, Mapelli D, Mondini S. Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clin Exp Res*. 2012;24(3):218–226.
24. Thongkam J, Xu G, Zhang Y. AdaBoost algorithm with random forests for predicting breast cancer survivability. In: IEEE International Joint Conference on Neural Networks (IEEE World Congress on Computational Intelligence); June 1–6, 2008; Hong Kong.
25. Russell MB, Rasmussen BK, Fenger K, Olesen J. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. *Cephalalgia*. 1996;16(4):239–245.
26. Waelkens J. Warning symptoms in migraine: characteristics and therapeutic implications. *Cephalalgia*. 1985;5(4):223–228.
27. Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. *Dis Mon*. 2017;63(11):308–338.
28. Cuvellier JC, Mars A, Vallée L. The prevalence of premonitory symptoms in paediatric migraine: a questionnaire study in 103 children and adolescents. *Cephalalgia*. 2009;29(11):1197–1201.
29. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629–808.
30. Maniyar FH, Sprenger T, Monteith T, Schankin CJ, Goadsby PJ. The premonitory phase of migraine--what can we learn from it? *Headache*. 2015;55(5):609–620.
31. Isler H-R. Frequency and time course of premonitory phemomena. In: Amery WK, Wauquier A, editors. *The Prelude to the Migraine Attack*. London: Balliere Tindall; 1986.
32. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*. 2014;137(Pt 1):232–241.