

Transient Visual Disturbance is Associated with Disability and Suicidal Risk in Patients with Migraine Without Aura

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Abstract

Background: Patients with migraine without aura frequently report transient visual disturbances (TVD) other than typical visual aura, but the clinical correlates are not determined.

Method: Patients with migraine without aura (MO) that attended the headache clinic were enrolled. Structured questionnaires were self-administered by the patients including headache profiles, comorbidities, lifetime suicidal ideation and attempts, six-item Headache Impact Test, Migraine Photophobia Score, Migraine Disability Assessment, Hospital Anxiety and Depression Scale, Beck Depression Inventory, and Pittsburgh Sleep Quality Index. A semi-structured visual phenomenon questionnaire was also used to assess the characteristics of TVDs. TVD is defined as any zigzag flashes, flickering dots/lines, or blurred/foggy vision associated with headache and with a Visual Aura Rating Scale < 4. Headache specialists interviewed with the participants for the ascertainment of diagnosis and verified of the questionnaires.

Result: MO patients (n = 7,200, female/male = 3.56, mean age: 40.1 ± 13.4 years) were divided into 2 subgroups based on the presence (n=2,488) or absence of TVDs (n= 4,712). Patients with TVD had higher headache-related disability, more psychiatric comorbidities and were more likely to be photophobic. Suicidal ideation and attempts were more common in patients with TVD than in those without (ideation: 31.9% vs. 18.1%, OR = 1.92 [95% CI: 1.71–2.15], $p < 0.001$; attempt: 8.2% vs. 3.5%, OR = 2.23 [95% CI: 1.80–2.75], $p < 0.001$). The associations remained after adjustment of confounding factors.

Conclusion: Presence of transient visual disturbance may suggest a higher migraine-related disability, higher level of photophobia and higher suicidal ideation/attempts in MO patients.

Introduction

Migraine aura is reversible visual, sensory, or language disturbances associated with headache, which develops gradually over more than 5 minutes and lasts between 5 and 60 minutes [1, 2]. Among these neurological symptoms, visual aura is the most common and occurs in 98% of patients with migraine with aura (MA) [3]. Flashes of bright light, foggy/blurred vision, zigzag/jagged lines are the most frequent visual aura symptoms [4]. In clinical practice, however, many patients with migraine without aura (MO) also reported different and complex transient visual disturbances (TVD) other than typical visual aura. Our previous field study in adolescents showed that almost half (48%) of migraine adolescents without characteristic migraine visual aura experienced TVD related to their headache attack [5]. Moreover, there are some migraine patients predominantly affected by the visual symptoms due to variable duration or complexity, such as photophobia and after-image [6, 7]. Even though these TVDs do not fulfill the criteria of visual aura proposed by the International Classification of Headache Disorders (ICHD)[1, 2], they are frequently reported by patients with MO. However, they are poorly characterized, often neglected, and related research is limited.

Previous studies have found connections between migraine aura and photophobia, which appear to be associated with cortical hypersensitivity [8]. Although the pathophysiology of TVD has not been fully investigated yet, we have found non-aura TVD is also associated with photophobia, implies the possibility of visual cortex hypersensitivity among patients with TVD [5]. On the other hand, studies have indicated that visual aura increased the odds of psychiatric comorbidities and suicide risk, possibly by alterations in the neuroendocrine system [9–11]. It is not known whether TVD could also be associated with psychiatric comorbidities and suicide risk among MO patients.

The aim of this study was to investigate the characteristics and clinical correlates of TVD among patients with migraine without visual aura, which may help understand the clinical significance of TVD and the complex neurobiology of migraine.

Material And Methods

Study participants and data collection

The headache specialists at the headache clinic of the Taipei Veterans General Hospital (TVGH) surveyed patients presented with headache during the period from May 2010 to July 2020. All participants completed a structured questionnaire to assess their headache profiles, comorbidities, mood, sleep, photophobic scale and suicidal ideation or attempts (see below) at their first visit. A semi-structured visual phenomenon questionnaire was used to assess the characteristics of TVDs. Later, they underwent a thorough clinical interview for the ascertainment of headache diagnosis as well as the questionnaires. Information collected from the questionnaires was de-identified and entered into the TVGH headache registry.

Ethics

This retrospective study analyzed these de-identified data included in the TVGH headache registry. Because this study involved secondary analysis of existing de-identified data, informed consent has been waived by the institutional review board of Taipei Veterans General Hospital, which approved the whole study protocol (TVGH IRB-2021-04-121-CC). The corresponding authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Diagnoses of migraine

The diagnoses of MA, MO, and chronic migraine (CM) were based on the International Classification of Headache Disorders, 2nd and 3rd edition (ICHD-2 and ICHD-3) criteria (MO: code 1.1; MA: code 1.2; CM: code 1.3) [1, 2], made through face-to-face interviews by experienced headache specialists. Patients with MA were excluded from this study.

Definition of TVD

TVDs were defined as transient visual phenomena related in time to the occurrence of a migraine headache attack, but not visual aura. All of the participants received the five items of the Visual Aura

Rating Scale (VARS) embedded in the questionnaires. The score is the weighted sum of the five-item scale: duration 5–60 minutes (three points), developing gradually ≥ 5 minutes (two points), scotoma (two points), zig-zag lines (two points) and unilateral visual field (one point). A cutoff VARS score of five or more points is reportedly highly sensitive and specific to diagnose MA [12]. In order to exclude potential aura, we also explored the VARS cutoff value in our cohort. MA diagnoses made by neurologists based on ICHD [1, 2] were used as the gold standard. Compared to physician diagnosis, a VARS score ≥ 5 had a sensitivity of 68.4% and a specificity of 88.7%, while a VARS score ≥ 4 had a sensitivity of 77.1% and a specificity of 79.9% to identify typical migraine aura. By using the criteria, i.e. a VARS score of ≥ 4 , the positive predictive value (PPV) was 0.29 and the negative predictive value (NPV) was 0.97 for MA. Hence, in this study, we included only MO patients (diagnosed by neurologists) with VARS < 4 to ensure that their TVDs are unlikely to be visual aura.

Questionnaires

Demographic data, including age, sex, occupation, education level, marital status, and medical history were collected. A validated headache questionnaire was used to specifically inquire headache frequency (days/ month), intensity (Numerical Rating Scale 0–10), duration, location, characteristics, accompanying symptoms, frequency of acute abortive medications usage (days/month), and disease duration of migraine (years), as well as TVD symptoms [13, 14]. To differentiate these visual symptoms from characteristic migraine aura defined in the ICHD, a visual phenomenon questionnaire was used to assess the TVDs, including patterns (zigzag flashes, flickering dots/lines, or blurred/foggy vision), laterality of the visual fields, colors, presence of movement, development time, duration and temporal relationship with headaches. The questions were:

1. Have you ever seen zigzag flashes before or during the headache?
2. Have you ever seen flickering dots or lines before or during the headache?
3. Before or when the headache started, did you have blurred or foggy vision?
4. What colors are these zigzag flashes, flickering dots or lines?
5. Do these TVDs (zigzag flashes, flickering dots or lines, or blurred vision) occur every time you have a headache?
6. Are these TVDs that you have seen unilateral, bilateral or different every time?
7. Did your TVDs move?
8. How long did your TVDs develop?
9. How long did your TVDs last?
10. Did these TVDs develop before, after or during the onset of the headache?

Afterwards, the MO patients were divided in to 2 subgroups based on the presence (MwTVD) or absence (MwoTVD) of TVDs. Additionally, the questionnaires also include the Migraine Disability Assessment (MIDAS), six-item Headache Impact Test (HIT-6), Migraine Photophobia Score (MPS), Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Perceived Stress Scale (PSS), and

Pittsburgh Sleep Quality Index (PSQI), presence of MOH, suicidal ideation and attempts to collect relevant clinical information.

The Migraine Disability Assessment (MIDAS) questionnaire assesses headache-related disability in a 3-month period and the six-item Headache Impact Test (HIT-6) measures the severity of headache pain and adverse impact of headache [15, 16]. Both MIDAS and HIT-6 have been well accepted and widely utilized to evaluate the disability and impact caused by migraine. Headache intensity influences HIT-6 score more than the MIDAS, whereas the MIDAS is influenced more by headache frequency [17]. Migraine Photophobia Score (MPS) is a self-administered, eight-question questionnaires to evaluate the scale of photophobia in migraine patients. Adding the total number of “yes” responses generates the MPS [18]. Hospital Anxiety and Depression Scale (HADS) is a self-administered instrument to detect psychiatric comorbidity in the setting of a hospital outpatient clinic [19]. Anxiety was defined as a HADS score ≥ 13 based on our previous study[20]. The Beck Depression Inventory (BDI) is a 21-item self-report measure that evaluates major depression symptoms according to diagnostic criteria listed in the Diagnostic and Statistical Manual for Mental Disorders [21], and moderate depression is defined as a BDI ≥ 20 [22, 23]. The Perceived Stress Scale (PSS) is a 14-item self-reported questionnaire that was designed to measure “the degree to which individuals appraise situations in their lives as stressful” [24, 25]. Pittsburgh Sleep Quality Index (PSQI) evaluates the quality and patterns of sleep in the past one month. Poor sleep quality was defined as a PSQI score of > 5 [26]. Suicidal ideation and attempts were evaluated by 2 separate directly asked questions: (1) whether they, once in their lifetime, had ideational thoughts of engaging in suicidal behavior, and (2) whether they had engaged in any self-injury behavior with the intent to die. Unanswered questionnaires were interpreted as missing data.

Migrainous features, the prevalence of visual disturbance, and the severity of photophobia

Migrainous features (including moderate to severe intensity; pulsating quality; unilaterality; aggravation by physical activity; nausea or vomiting; photophobia and phonophobia) of each subject were evaluated. The “yes” responses to each features were summed up to a total score of migrainous features, ranging from 0 to 6. To evaluate the migrainous feature in patients with photophobia, we re-calculated numbers of migrainous features ranged from 0 to 5, including the same features mentioned above except photophobia and phonophobia.

Statistical analysis

The descriptive data were presented as means \pm SDs or percentages. The Chi square test was used to test the difference in categorical data. Continuous data between groups were analyzed using Student’s t test with Bonferroni correction. For subgroup analysis, logistic regression was performed to test the interaction effect. The risks associated with comorbid suicidal ideation and attempts were predicted separately by 3 layers of models: (1) no controlling for any covariates; (2) controlling for demographics; (3) controlling for demographics and clinical characteristics. These models were performed stepwise. Demographics included patients’ age, sex, and marital status (married vs.

single/separated/divorced/widowed). Clinical characteristics included headache frequency (days/month), HIT-6 score, depression (BDI \geq 20), anxiety (HADS score \geq 13), poor sleep quality (PSQI > 5), MOH, and CM. The predictors were presented as odds ratio (OR) with 95% confidence interval. Results were considered significant for p value < 0.05. Statistical analyses were performed with R for Mac OS (Version 3.6.3; R Core Team, Vienna, Austria.)

Results

Prevalence of TVD

Totally 12,255 patients who visited our headache clinic during the 10-year study period were enrolled. Migraine was diagnosed in 9,966 patients, while the other 2,309 patients were excluded due to non-migraine headache. Among the migraineurs, 962 patients diagnosed with MA and 1,784 MO patients with VARS \geq 4 were excluded from the study. After excluding those with aura or high VARS, the remaining 7,200 patients with MO constituted the final sample. The MO patients (female/male 5,620 (78.1%)/1,580 (21.9%); mean age: 40.1 \pm 13.4 years) were divided into 2 subgroups based on the presence (MwTVD, $n = 2,488$, 34.6%) or absence (MwoTVD, $n = 4,712$, 65.4%) of TVD. A flow chart of the patient enrollment process is presented in Figure 1.

TVD characteristics and clinical features

Among the 2,488 MwTVD subjects, 865 (34.8%) patients reported more than one pattern of TVDs. The most common TVD was blurred or foggy vision ($n = 1,766$, 71.0%), followed by flickering dots/lines ($n = 1,332$, 53.5%) and zigzag flashes ($n = 279$, 11.2%). More than a quarter of the patients ($n = 683$, 27.5%) reported both positive TVDs (flickering dots /lines, or zigzag flashes) and negative TVDs (blurred/foggy vision). Most of the TVDs happened during the headache (74.1%), while 18.4% happened before headache and 7.5% after the headache. The onset of TVD was commonly quick (59.2% of VD occurred in \leq 30 seconds, 22.7% between 30 seconds to 1 minute, and 15.3% between 1-5 minutes), and the duration was also short (51.6% lasted \leq 30 seconds, 23.0% lasted for 30 seconds to 1 minute, and 15.8% lasted for 1-5 minutes). The detailed characteristics of the TVDs are shown in Table 1. The onset time, duration, and temporal relationships with headache are the three major different characteristics of TVD comparing with typical visual aura. To validate phenotype-based diagnosis of TVD, we compared these three characteristics between our MwTVD and MA groups. For visual symptoms that did not fulfill typical visual aura but had at least two of these three characteristics: A. Develops or spreads in less than 5 minutes; B. Lasts last than 5 minutes; C. Occurs during headache phase, the sensitivity and specificity to identify TVD were 96.38% and 64.03%. Both the PPV and NPV were 0.87.

Details of demographic data and clinical characteristics of MwTVD and MwoTVD are listed in Table 2. In general, MwTVD had worse clinical features than MwoTVD. The MwTVD group, compared with the MwoTVD group, had higher headache frequency, more severe headache-related disability, higher proportions of CM, MOH and psychiatric comorbidities, and were more likely to be photophobic.

TVD, photophobia and migrainous features

There is a trend for increasing TVD frequency with increasing migrainous features (Fig. 2A). While the TVD was reported in only 12.2% of MO patients with least migrainous features, its prevalence increased to 46.6% in those with all six migrainous features. To investigate whether patients with TVD were also more photophobic, we further compared the MPS between MwTVD and MwoTVD. Consistent with our speculation, MwTVD patients had higher MPS while comparing with MwoTVD (2.9 ± 2.0 vs. 1.6 ± 1.9 , $p < 0.001$, Table 1). Moreover, we found MPS was a predictor of TVD (unadjusted OR = 1.37, 95% CI = 1.32–1.42, $p < 0.001$), and the result remained after gender and age were adjusted (adjusted OR = 1.36, 95% CI = 1.31–1.41, $p < 0.001$). Similar to TVD, there is also a trend for increasing photophobia frequency with increasing migrainous features, expanding from 15.6% to 38.4% (Fig. 2B).

Suicide risk in patients with migraine with visual disturbance and photophobia

Because the percentages of suicidal ideation and attempts were much higher in the MwTVD group than those in the MwoTVD group (31.9% vs. 18.1%, $p < 0.001$ for suicidal ideation; 8.2% vs. 3.5%, $p < 0.001$ for suicide attempts, Table 2), we further explored whether TVD could be an independent risk factor for suicidal risk in patients with migraine without typical visual aura. Univariate analysis showed that TVD, photophobia, headache frequency and headache-related disability, CM, MOH, along with traditional risk factors including depression, anxiety, and poor sleep quality, were associated with higher risks of suicidal ideation and attempts in patients with migraine, while marriage had a protective effect in suicide ideation (Table 3). In multivariable analysis, TVD remained an independent risk factor for suicidal ideation and attempts even after controlling for demographics, headache frequency, headache-related disability, CM, MOH and psychiatric comorbidities (Table 4).

Discussion

Our study demonstrated that the prevalence of the non-aura TVD was as high as 34.6% among MO patients. Patients with TVD are predominately female, had worse headache-related disability, more psychiatric comorbidities, and were more likely to be photophobic compared with patients without TVD. Patients who exhibited more migrainous features were more likely to have a higher prevalence of TVD and photophobia, implying the clinical significance of non-aura visual symptoms in migraine. Moreover, the presence of TVD was positively correlated with increased suicidal ideation and attempts, even after the other suicide risk factors were adjusted. Based on these findings, we speculated that the presence of TVD might serve as a marker of disease severity and even a potential indicator of higher suicidal risk.

Blurred/foggy vision is the most common type of TVD, and more than a quarter of these patients (27.5%) also have seen flickers or zigzag flashes. This is similar to a previous study, stating that “blurred/foggy vision” was the most common visual symptom other than aura among MA patients [27]. The TVDs reported in our patients are mostly fixed, colorless, over non-specific fields, developing within 5 minutes, lasting less than 5 minutes, and occurring during the headache phase. This finding is consistent with our previous study indicating the transient TVDs are short in onset to development as well as the duration

and is common among adolescent patients with migraine [5]. The major differences between typical visual aura and TVD are the onset and duration of the symptoms, and the temporal relation with headache. Also, among our 9,946 migraine patients, one-fourth of them reported to have non-aura TVD (n=2,488) but only less than one-tenth of them have MA (n=962), showing that the prevalence of TVD is much higher than that of typical aura. We proposed that these non-classic visual symptoms should not be classified as atypical aura, and might be identified separately. We suggest non-aura TVD has crucial clinical implications and should be identified in clinical practice. Herein we proposed an operational criteria to characterize these migraine-associated TVD, the clinical utility of which needs to be validated in future studies (Table 5).

To our best knowledge, this is the first study that found TVD is related to higher migraine-related disability, higher level of photophobia, and higher suicidal ideation/attempts risk. Furthermore, the odds ratios of TVD and MPS on suicide are higher than HIT-6 and headache frequency, which were previously thought to be highly related to suicide risk [28]. This implies the impact of non-aura TVD on migraine might be underestimated. Also, both TVD and photophobia have a higher prevalence among those with more migrainous features than those without (Fig. 2). Although photophobia is known as one of the most disabling symptoms of migraine [29], the disabilities caused by TVD are seldom addressed. Therefore, we propose that TVD should be considered as one of the indicators to evaluate the prognosis of migraine.

The pathophysiology of TVD in patients with migraine is unknown. Typical aura is associated with abnormal cortical hyper-excitability, and visual percept of aura could change depends on the region of the occipital cortex involved [30]. Previous studies also found cortical hypersensitivity might be the link between migraine aura and photophobia [8]. Since patients with TVD were more photophobic than those without and that increased interictal visual sensitivity is present in both MA and MO [31], the TVD in some patients might also be linked to mechanisms similar to cortical hyper-excitability but involving a less eloquent visual cortex [32]. We speculate that our patients with TVD may have a hyperexcitable visual cortex, which contributes to non-aura TVD and more severe photophobia and may thus lead to worse migraine-related disability. Furthermore, we found non-aura TVD as an independent risk factor of increased suicidal ideation or attempts even after adjusting other potential confounders. Studies have reported that suicide survivors had lower oxytocin concentration both in serum and CSF [33, 34], and oxytocin is a potential biomarker of attempted suicide [35]. On the other hand, oxytocin released from paraventricular neurons (PVN) can suppress nociception of inflammatory pain [36]. Since PVN also channels the photic input from the retina [37], it is possible that oxytocin may be also related to migraine-type photophobia and worse headache-related disability. However, it is hypothetical and systematic studies should be conducted in the future.

There are several strengths in our study. First, our sample size is large, with more than 7,000 patients with MO enrolled consecutively in the ten-year study period. The large sample size increased the validity of this clinic-based study. Second, we have detailed and validated questionnaires to specifically inquire headache characteristics and TVD symptoms. The data from the questionnaires was highly qualified, and these questionnaires have been widely accepted as reliable neuropsychological instruments in many

studies [13, 14, 20]. Furthermore, the final diagnoses of MO and TVD were ascertained by experienced headache specialists made through face-to-face interview, which help to confirm the accuracy of our data. We also used VARS to exclude the potential inclusion of aura. Additionally, we provided our proposed TVD diagnostic criteria based the phenotype of the visual symptoms. Therefore, we believe our findings could have a practical implication for neurologists.

However, there are also some limitations in our study. First, all the patients were recruited from a tertiary medical center; thus, the patients we seen were at the worse end of the disease spectrum. Nevertheless, even in these patients, those with TVD still had much worse clinical features than those without. Second, the suicide risk was evaluated based on single-item direct questions, questioning of the suicidal ideation and attempts. Although the patients received face-to-face interview, detailed information regarding the potential etiologies of suicidal ideation or attempts was not systematically collected. However, the overall lifetime suicidal attempts in our MwoTVD was very close to previous cross-national, multicultural study (3.5% and 2.7%, respectively), indicating the reliability of our study [38]. As previous studies have shown that more than half of suicidal ideations transform into plan and attempt in one year, and suicide attempt is the best predictor of a completed suicide [39]. Last, we focused on psychiatric diseases and some other demographics factors since these are the strongest predictors of suicide while some other risk factors for suicide such as chronic pain disorders, fibromyalgia, major life events, and financial status were not controlled in the multivariable analysis [40, 41]. Further study to investigate these risk factors should be conducted in the future.

Conclusions

In this study, we found that non-aura TVD was associated with higher level of photophobia, higher migraine-related disability, and higher suicidal ideation/attempts. The odds ratio of TVD and MPS on suicide are higher than HIT-6 and headache frequency, implies the impact of non-aura TVD and photophobia on migraine might be underestimated. We suggested that TVD should be considered as one of the indicators to evaluate the prognosis of migraine, and proposed an operational criteria for TVD. Nevertheless, the exact pathophysiology is unknown and required further exploration.

Abbreviations

BDI: Beck Depression Inventory; CDH: Chronic daily headache; CI: Confidence interval; CM: Chronic migraine; HADS: Hospital Anxiety and Depression Scale; HAS: Hospital Anxiety Scale; HDS: Hospital Depression Scale; HIT-6: six-item Headache Impact Test; ICHD: The International Classification of Headache Disorders; MIDAS: Migraine Disability Assessment Scale; MOH: Medication-overuse headache; MPS: Migraine Photophobia Score; OR: Odds ratio; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; TVD: Transient visual disturbance.

Declarations

Ethics approval and consent to participate

This retrospective study analyzed these de-identified data included in the TVGH headache registry. Because this study involved secondary analysis of existing de-identified data, informed consent has been waived by the institutional review board of Taipei Veterans General Hospital, which approved the whole study protocol (TVGH IRB-2021-04-121-CC). The corresponding authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have declared no relevant conflict of interests.

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Authors' contributions

YCT and SPC conceived and designed the study, and completed the first draft. JLF, YFW, WTC, KLL, HYL and SJW acquired and analyzed the data. SPC and SJW participated in the discussion and critical revision of the manuscript. The authors have read and approved the manuscript

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Conflicts of interest:

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Tables

Table 1. Characteristics of TVDs

	n (%) ^a
Blurred /foggy vision	1,766 (71.0%)
Flickering dots or lines	1,332 (53.5%)
Zigzag flashes	279 (11.2%)
Hazy	227 (47.7%)
Wave-like	153 (32.1%)
Fortification spectra	58 (12.2%)
Reticular	38 (8.0%)
Colors	
Colorless	653 (38.6%)
Whitish	641 (37.9%)
Blackish	184 (10.9%)
Non-specific	94 (5.6%)
Yellowish	83 (4.9%)
Rainbow like	36 (2.1%)
Co-occurrence of VD and headache	
Not every time	2,167 (92.7%)
Every time	170 (7.3 %)
Laterality	
Non-specific	908 (36.4%)
Bilateral	688 (27.7%)
Unilateral	892 (35.9%)
Movable	
Yes	921 (40.4 %)
No	1,356 (59.6 %)
Time of development	
≤30 seconds	1,472 (59.2%)
0.5 - 1 minute	564 (22.7%)
1 - 5 minutes	380 (15.3%)

5 - 20 minutes	36 (1.4%)
≥20 minutes	36 (1.4%)
Duration	
≤30 seconds	1,285 (51.6%)
0.5 – 1 minute	571 (23.0%)
1 - 5 minutes	393 (15.8%)
5 - 30 minutes	20 (0.8%)
0.5 - 1 hour	13 (0.5%)
≥ 1 hour	206 (8.3%)
Temporal relationship with headache	
Before headache	397 (18.4%)
During headache	1,602 (74.1%)
After headache	162 (7.5%)

^aThe data represent the number of subjects who answered each questionnaire; unanswered questionnaires were interpreted as missing data; TVD: transient visual disturbance.

Table 2. Demographic data, headache characteristics and comorbidity in patients with migraine with (MwTVD) or without transient visual disturbance (MwoTVD)

	MwTVVD n = 2,488	MwoTVVD n = 4,712	p value
Age	38.2 ± 13.0	41.1 ± 13.5	<2e-16*
Gender (Female/Male); n (%)	2,023 (81.3) / 465 (18.7)	3,597 (76.3) / 1,115 (23.7)	1.242e-06*
Headache days/ month	13.0 ± 9.6	10.7 ± 9.3	<2.2e-16*
MPS	2.9 ± 2.0	1.6 ± 1.9	<2.2e-16*
MIDAS	31.8 ± 44.9	22.9 ± 35.9	<2.2e-16*
HIT-6	62.6 ± 6.6	60.7 ± 7.8	2.105e-14*
HADS	15.3 ± 7.6	12.30 ± 7.2	<2.2e-16*
HAS	8.8 ± 4.3	7.1 ± 4.1	<2.2e-16*
HDS	6.5 ± 4.1	5.3 ± 3.9	<2.2e-16*
BDI	13.1 ± 9.1	9.7 ± 7.5	<2.2e-16*
PSS	26.5 ± 9.2	23.8 ± 8.6	<2.2e-16*
PSQI	10.1 ± 4.2	8.6 ± 4.0	2.734e-15*
Chronic migraine	902 (36.3%)	1,327 (28.2%)	1.634e-12*
Medication overuse headache	469 (18.9%)	806 (17.1%)	0.06507
Suicidal ideation	793 (31.9%)	854 (18.1%)	4.437e-30*
Suicide attempt	203 (8.2%)	167 (3.5%)	2.969e-14*

Abbreviations: MIDAS, Migraine Disability Assessment; HIT-6, six-item Headache Impact Test; MPS, Migraine Photophobia Score; HDAS, Hospital Anxiety and Depression Scale; HDS, Hospital depression scale; HAS, Hospital Anxiety Scale; BDI, Beck Depression Inventory; PSS, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index. Data are presented as mean ± SD. * Significant after Bonferroni correction

Table 3. Association of suicide ideation/attempts with potential risk factors.

	Suicidal ideation		Suicide attempt	
	OR (95%CI)	<i>p</i> value	OR (95%CI)	<i>p</i> value
Depression	8.50 (7.30, 9.91)	< 0.001	6.59 (5.27, 8.24)	< 0.001
Anxiety	4.19 (3.69, 4.77)	< 0.001	4.08 (3.15, 5.35)	< 0.001
Poor sleep quality	2.99 (2.49, 3.62)	< 0.001	3.38 (2.28, 5.23)	< 0.001
CM	2.00 (1.78, 2.25)	< 0.001	2.64 (2.14, 3.26)	< 0.001
TVD	1.92 (1.71, 2.15)	< 0.001	2.23 (1.80, 2.75)	< 0.001
MOH	1.79 (1.56, 2.05)	< 0.001	2.95 (2.35, 3.68)	< 0.001
MPS	1.17 (1.13, 1.22)	< 0.001	1.20 (1.12, 1.29)	< 0.001
HIT-6	1.07 (1.05, 1.08)	< 0.001	1.08 (1.06, 1.11)	< 0.001
Headache days/month	1.04 (1.03, 1.04)	< 0.001	1.05 (1.04, 1.06)	< 0.001
Married	0.75 (0.67, 0.83)	< 0.001	0.88 (0.71, 1.09)	0.24

Abbreviations: OR, odds ratio; CI, confidence interval; TVD, transient visual disturbance; MPS, Migraine Photophobia Score; HIT-6, six-item Headache Impact Test.

Table 4. Different models for the association of suicide risk with TVD and MPS

	Suicidal ideation		Suicide attempt	
	OR (95%CI)	<i>p</i> value	OR (95%CI)	<i>p</i> value
TVD+ Demographics	1.86 (1.66, 2.09)	< 0.001	2.17 (1.75, 2.69)	< 0.001
TVD+ Demographics +Confounders	1.44 (1.19, 1.73)	< 0.001	2.18 (1.53, 3.14)	< 0.001
MPS+ Demographics	1.16 (1.11, 1.20)	< 0.001	1.19 (1.11, 1.18)	< 0.001
MPS+ Demographics+ Confounders	1.08 (1.03, 1.13)	0.001	1.07 (0.98, 1.16)	0.1155

Abbreviations: OR, odds ratio; CI, confidence interval; TVD, transient visual disturbance; MPS, Migraine Photophobia Score; HIT-6, six-item Headache Impact Test.

Demographics = age, gender, marital status; Confounders = depression, anxiety, poor sleep quality, HIT-6 score, headache frequency (days/ month), chronic migraine, medication overuse headache

Table 5. Proposed operational criteria to characterize these migraine-associated transient visual disturbance

A. Transient visual disturbance not fulfilling 1.2.1 migraine with typical aura;

B. At least two of the following three characteristics:

1. Transient visual disturbance develops or spreads in <5 mins.

2. Transient visual disturbance lasts < 5 minutes.

3. Transient visual disturbance occurs during headache phase.

Figures

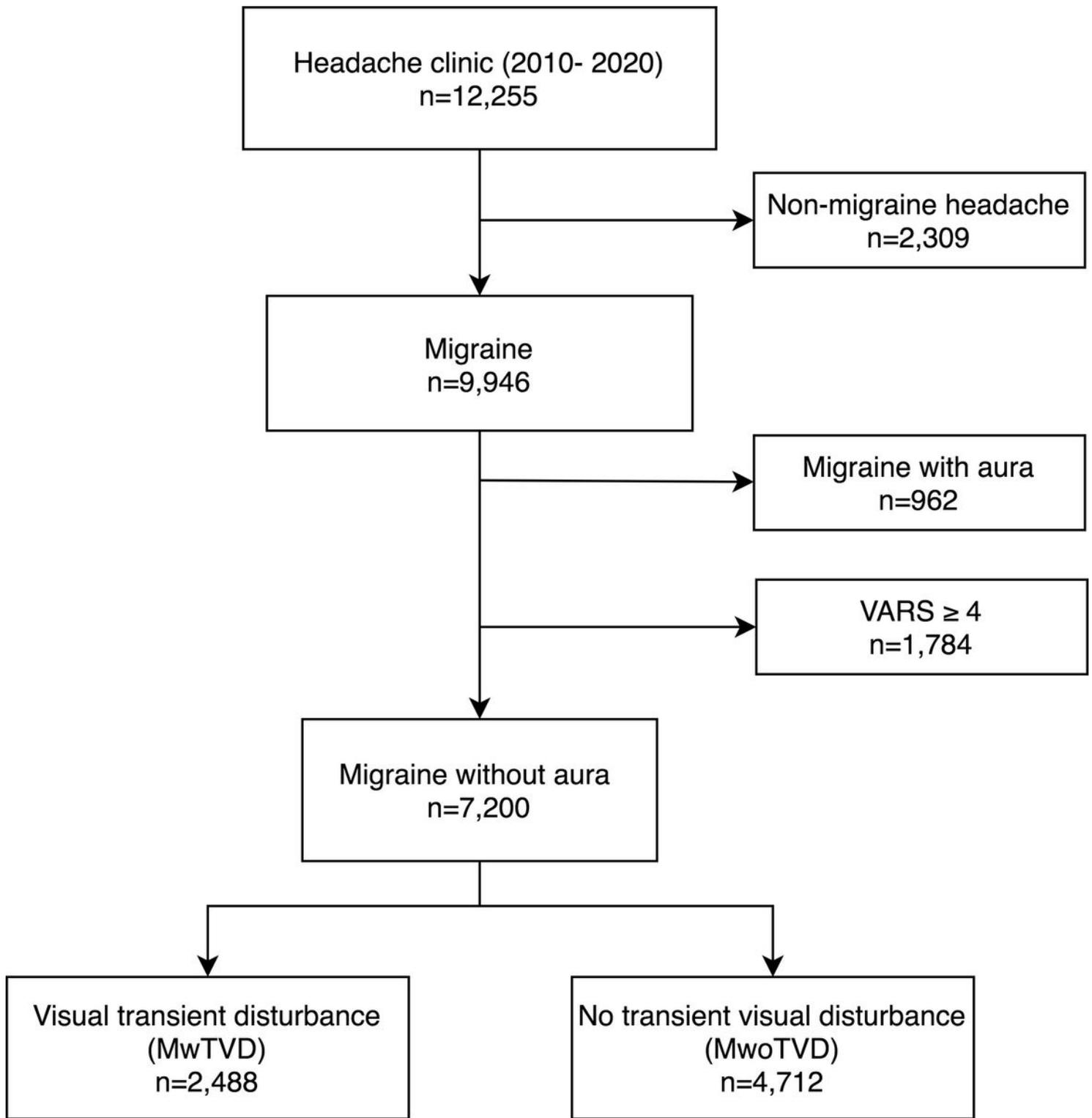


Figure 1

A flow chart of the patient enrollment process

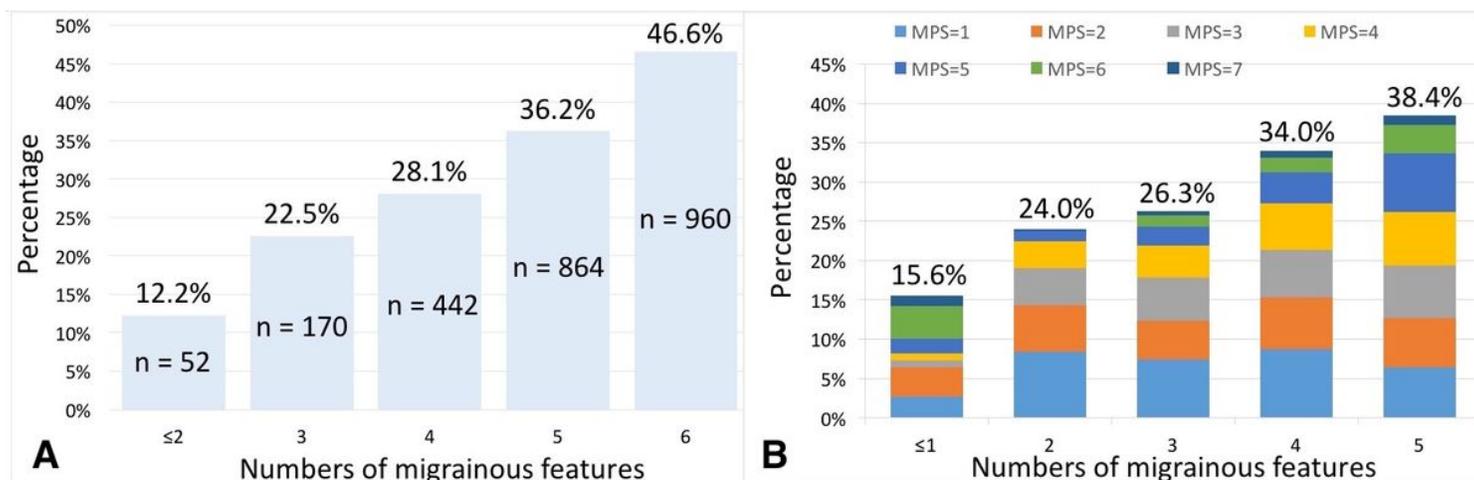


Figure 2

There is a trend for increasing TVD frequency with increasing migrainous features (Fig. 2A). While the TVD was reported in only 12.2% of MO patients with least migrainous features, its prevalence increased to 46.6% in those with all six migrainous features. To investigate whether patients with TVD were also more photophobic, we further compared the MPS between MwTVD and MwoTVD. Consistent with our speculation, MwTVD patients had higher MPS while comparing with MwoTVD (2.9 ± 2.0 vs. 1.6 ± 1.9 , $p < 0.001$, Table 1). Moreover, we found MPS was a predictor of TVD (unadjusted OR = 1.37, 95% CI = 1.32–1.42, $p < 0.001$), and the result remained after gender and age were adjusted (adjusted OR = 1.36, 95% CI = 1.31–1.41, $p < 0.001$). Similar to TVD, there is also a trend for increasing photophobia frequency with increasing migrainous features, expanding from 15.6% to 38.4% (Fig. 2B).