Transient Visual Disturbance is Associated With Disability And Suicidal Risk In Patients With Migraine Without Aura

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Abstract

Objectives: To investigate the characteristics and clinical correlates of transient visual disturbances (TVDs) in patients with migraine without aura (MO).

Background: Patients with MO frequently report TVD other than typical visual aura, but the clinical significance of the TVDs is not determined.

Method: Patients with MO that attended our headache clinics were enrolled. Headache profiles, disability, comorbidities, lifetime suicidal ideation and attempts were acquired with structured questionnaires. A semi-structured visual phenomenon questionnaire was also used to assess the characteristics of TVDs. Headache specialists interviewed with the participants for the ascertainment of diagnosis and verified 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 photophobic. Suicidal ideation and attempts were more common in patients with TVD than in those without (ideation: OR = 1.92 [95% CI: 1.71–2.15], $p < 0.001$; attempt: OR = 2.23 [95% CI: 1.80–2.75], $p < 0.001$).

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 significance of TVD among patients with migraine without visual aura, which may help understand the clinical significance of TVD and the complex neurobiology of migraine. We hypothesized that non-aura TVD might be related to increased migraine disease burden or suicidal risk in patients with migraine. This is a post-hoc study implementing secondary analysis of previously collected data in the Taipei Veterans General Hospital (TVGH) headache registry. Several studies adopting part of the dataset have been published previously [12,13]

Material And Methods

Study participants and data collection

The headache specialists at the headache clinic of the 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. No *a priori* statistical power calculation was conducted and the sample size was based on the available data.

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 retrospective cohort 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 [14]. In order to exclude potential aura, we also explored the VARS cutoff value in our cohort. MA diagnoses made by neurologists based on

ICHD [1,15] were used as the gold standard. Compared to physician diagnosis, a VARS score ≥ five 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 [13,16]. 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 (HAS, HDS), 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. Suicidal ideation and attempts were evaluated by 2 separate directly asked questions: 1. Have you ever had ideational thoughts of engaging in suicidal behavior? 2. Have you ever had engaged in any self-injurious behavior with the intent to die? Unanswered questionnaires were interpreted as missing data. The responses to these questions were validated by experienced headache specialists with face-to-face interview.

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 [17,18]. 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 [19]. 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 [20]. Hospital Anxiety and Depression Scale is a self-administered instrument to detect psychiatric comorbidity in the setting of a hospital outpatient clinic. Anxiety was defined as a Hospital Anxiety Scale (HAS) score $\geq$ 11, and depression was defined as Hospital Depression Scale (HDS) score $\geq$ 11 [21]. 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 [22]. 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” [23]. 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 [24]. 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 photophobia) 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 ± SDs or percentages. The Chi square test was used to test the difference in categorical data. Normality was checked with histograms before conducting

parametric tests. Continuous data between groups were analyzed using two-tailed independent sample t-test. Mann–Whitney U test was used to compare variables that were not distributed normally, including headache frequency, disease duration, BDI, HDS, MIDAS, and MPS. Bonferroni correction was done for the 16 variables (i.e., age, gender, disease duration of migraine (years), headache frequency (days/month), MPS, MIDAS, HIT-6, HAS, HDS, BDI, PSS, PSQI, chronic migraine, medication overuse headache, suicidal ideation, and suicide attempt). For post-hoc subgroup analysis, logistic regression was performed to test the interaction effect. The risks associated with comorbid suicidal ideation and attempts were analyzed separately by 3 layers of models: (1) no controlling for any covariates; (2) controlling for demographics; (3) controlling for demographics and clinical characteristics. These 3 layers of models were performed with “Enter” method. That is, the independent variables in each layer were fitted in the regression model simultaneously. Demographics included patients’ age, sex, and marital status (married vs. single/separated/divorced/widowed). Clinical characteristics included headache frequency (days/month), disease duration, HIT-6 score, depression (HDS score ≥ 11), anxiety (HAS score ≥ 11), poor sleep quality (PSQI >5), PSS, MOH, and CM. The risk factors 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.)

Ethical 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 TVGH, which approved the whole study protocol (TVGH IRB-2021-04-121-CC). The study was performed using ethical principles for medical research involving human subject in accord with the Declaration of Helsinki. 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.

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 ≥ 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%); female/male = 3.6, mean age: 40.1 ± 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 Fig. 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 ≤ 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 ≤ 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.

Table 1
Characteristics of TVDs in MwTVD patients, n=2,488

MwTVD patients, n=2,488	n (%) [a]
Blurred /foggy vision	1,766 (71.0%)
Flickering dots or lines	1,332 (53.5%)
Zigzag flashes	279 (11.2%)
Patterns of zigzag flashes	
Hazy	227 (81.4%)
Wave-like	153 (54.8%)
Fortification spectra	58 (20.8%)
Reticular	38 (13.6%)
Colors [b]	
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 TVD and headache [c]	
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 [d]	

a The data represent the number of subjects who answered each questionnaire; unanswered questionnaires were interpreted as missing data and were excluded from analysis; [b] 798 patients did not have data for colors of TVD; [c] 151 patients did not have data for co-occurrence of TVD; [d] 211 patients did not have data for movability of TVD; [e] 327 patients did not have data for temporal relationship with headache and TVD; TVD: transient visual disturbance.

MwTVD patients, n=2,488	n (%) [a]
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 [e]	
Before headache	397 (18.4%)
During headache	1,602 (74.1%)
After headache	162 (7.5%)

a The data represent the number of subjects who answered each questionnaire; unanswered questionnaires were interpreted as missing data and were excluded from analysis; [b] 798 patients did not have data for colors of TVD; [c] 151 patients did not have data for co-occurrence of TVD; [d] 211 patients did not have data for movability of TVD; [e] 327 patients did not have data for temporal relationship with headache and TVD; TVD: transient visual disturbance.

Details of demographic data and clinical characteristics of MwTVD and MwoTVD are listed in Table 2. In general, patients with MwTVD had worse clinical features than those without TVD. 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.

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

	MwTVD **n = 2,488**		**MwoTVD** **n = 4,712**		***p* value**
	Mean (SD)	Median [25th, 75th]	Mean (SD)	Median (25th, 75th)	
Age	38.2 (13.0)	36.7 [28.2, 47.3]	41.1 (13.5)	40.5 (30.7, 50.7)	<0.001*
Female/Male; n (%)	2,023 (81.3%) / 465 (18.7%)		3,597 (76.3%) / 1,115 (23.7%)		<0.001*
Disease duration of migraine (years)	17.4 (11.5)	15.4 [8.5, 24.4]	19.2 (12.2)	17.2 [9.8, 26.9]	<0.001*
Headache days/ month	13.0 (9.6)	10 [5, 20]	10.7 (9.3)	7 [4, 15]	<0.001*
MPS	2.9 (2.0)	3 [1, 5]	1.6 (1.9)	1 [0, 3]	<0.001*
MIDAS	31.8 (44.9)	16 [6, 39]	22.9 (35.9)	11 [2, 28]	<0.001*
HIT-6	62.6 (6.6)	63 [59, 66]	60.7 (7.8)	61[57, 65]	<0.001*
HAS	8.8 (4.3)	9 [6, 12]	7.1 (4.1)	7 [4, 10]	<0.001*
HDS	6.5 (4.1)	6 [3, 9]	5.3 (3.9)	5 [2, 8]	<0.001*
BDI	13.1 (9.1)	11 [6, 18]	9.7 (7.5)	8 [4, 14]	<0.001*
PSS	26.5 (9.2)	27 [21, 33]	23.8 (8.6)	24 [18, 29]	<0.001*
PSQI	10.1 (4.2)	10 [7, 13]	8.6 (4.0)	8 [6, 11]	<0.001*
Chronic migraine; n (%)	902 (36.3%)		1,327 (28.2%)		<0.001*
Medication overuse headache; n (%)	469 (18.9%)		806 (17.1%)		0.065
Suicidal ideation; n (%)	793 (31.9%)		854 (18.1%)		<0.001*

Abbreviations: MIDAS, Migraine Disability Assessment; HIT-6, six-item Headache Impact Test; MPS, Migraine Photophobia Score; 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

	MwTVD n = 2,488	MwoTVD n = 4,712	*p* value
Suicide attempt; n (%)	203 (8.2%)	167 (3.5%)	<0.001*

Abbreviations: MIDAS, Migraine Disability Assessment; HIT-6, six-item Headache Impact Test; MPS, Migraine Photophobia Score; 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

TVD, photophobia and migrainous features

There is an 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 that MPS was associated with 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 an increasing photophobia frequency with increasing migrainous features, expanding from 15.6–38.4% (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, the covariates associated with suicidal risk were fitted in the regression model first by controlling for demographics, and then by controlling for both demographics and clinical characteristics. TVD remained an independent risk factor for suicidal ideation and attempts even after controlling for demographics, headache frequency, disease duration, headache-related disability, CM, MOH and psychiatric comorbidities (Table 4).

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

	Suicidal ideation		Suicide attempt	
	OR (95%CI)	p value	OR (95%CI)	p value
Depression (HDS ≥ 11)	4.0 (3.48, 4.7)	< 0.001	4.5 (3.59, 5.7)	< 0.001
Anxiety (HAS ≥ 11)	3.67 (3.26, 4.1)	< 0.001	3.10 (2.51, 3.83)	< 0.001
Poor sleep quality (PSQI > 5)	2.99 (2.49, 3.62)	< 0.001	3.38 (2.28, 5.2)	< 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
PSS	1.11 (1.09, 1.12)	< 0.001	1.09 (1.07, 1.12)	< 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
MIDAS	1.01 (1.00, 1.01)	< 0.001	1.01(1.01, 1.01)	< 0.001
Disease duration of migraine (years)	1.01 (1.00, 1.01)	0.004	1.01 (1.00, 1.02)	0.013
Married	0.75 (0.67, 0.83)	< 0.001	0.88 (0.71, 1.09)	0.237

Abbreviations: OR, odds ratio; CI, confidence interval; HDS, Hospital depression scale; HAS, Hospital Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index; TVD, transient visual disturbance; MPS, Migraine Photophobia Score; PSS, Perceived Stress Scale; HIT-6, six-item Headache Impact Test; MIDAS, Migraine Disability Assessment.

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

	Suicidal ideation		Suicide attempt	
	OR (95%CI)	p value	OR (95%CI)	p value
TVD+ Demographics	1.86 (1.66, 2.09)	< 0.001	2.17 (1.75, 2.69)	< 0.001
TVD+ Demographics +Confounders	1.47 (1.21, 1.78)	< 0.001	2.16 (1.50, 3.13)	< 0.001
MPS+ Demographics	1.16 (1.11, 1.20)	< 0.001	1.19 (1.11, 1.18)	< 0.001
MPS+ Demographics+ Confounders	1.07 (1.02, 1.12)	0.009	1.07 (0.99, 1.17)	0.097
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), disease duration of migraine, PSS, chronic migraine, medication overuse headache				

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 associated 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. Foggy vision, the most common TVD, could be a cranial autonomic symptom, e.g. a problem of accommodation or a corneal edema. This is similar to a previous study, stating that “blurred/foggy vision” was the most common visual symptom other than aura among MA patients [25]. 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 be validated in future studies (Table 5).

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.

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 [26]. 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 [27], 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 [28]. 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 [29], the TVD in some patients might also be linked to mechanisms similar to cortical hyper-excitability but involving a less eloquent visual cortex [30]. 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 [31,32], and oxytocin is a potential biomarker of attempted suicide [33]. On the other hand, oxytocin released from paraventricular neurons (PVN) can suppress nociception of inflammatory pain [34]. Since PVN also channels the photic input from the retina [35], 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, the large sample size increased the precision of the estimates of this clinic-based study. Second, we have detailed questionnaires to specifically inquire headache characteristics and TVD symptoms. Although the validity of the questionnaires used for TVD needs further examinations, the other questionnaires are widely accepted neuropsychological instruments and are considered both valid and reliable in previous studies [12,13]. 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 [36]. 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 [37].Third, this is a retrospective study analyzing a pre-existing dataset not specifically designed to establish the reliability of TVD and the validity of questionnaires assessing TVD has not been examined before. It is still possible that there was some occasional aura misdiagnosed as TVD. In addition, the use of migrainous features as a scaled construct is arbitrary and could increase chances of undiagnosed MA. However, considering that we have excluded a reasonable proportion of patients with MA with a prevalence comparable to our previous field studies and the prevalence of TVDs identified in this study was much higher than that of MA, we speculated that undiagnosed aura might only account for a small proportion of TVDs defined in this study. Nevertheless, further prospective studies are needed to interrogate these potential confounding issues. Also, our findings were confined to one population in one hospital only. Therefore, future prospective studies with more than one clinician evaluating each patient to ensure inter-rater reliability when diagnosing MO vs TVD are needed to see if the findings could be replicated in different setting, different populations or countries. Last, we focused on psychiatric disorders such as depression and anxiety since these factors are strongly related to suicide. However, there were some other psychiatric conditions and sociodemographic factors that were related to suicide but not controlled in the multivariable analysis, such as bipolar disorder, borderline personality, traumatic brain injury, chronic pain disorders, fibromyalgia, educational level, employment status, housing status, major life events, and financial status [12,38]. 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, implying that 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 operational criteria for TVD. Nevertheless, the exact pathophysiology is unknown and required further exploration.

Declarations

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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DECLARATION OF CONFLICTING INTERESTS

The authors have declared no relevant conflict of interests.

AUTHOR CONTRIBUTIONS

Conception and Design: SJW, SPC. Acquisition of Data: YFW, JLF, WTC, KLL, HYL, SJW, SPC. Analysis and Interpretation of Data: YCT, SPC. Drafting the Manuscript: YCT, SPC. Revising It for Intellectual Content: SPC, SJW. Final Approval of the Completed Manuscript SPC, SJW.

References

1. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* **24 Suppl 1**, 9-160, doi:10.1111/j.1468-2982.2003.00824.x (2004).
2. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* **33**, 629-808, doi:10.1177/0333102413485658 (2013).
3. Viana, M. *et al.* Clinical features of migraine aura: results from a prospective diary-aided study. *Cephalalgia* **37**, 979–989 (2017).
4. Viana, M., Tronvik, E. A., Do, T. P., Zecca, C. & Hougaard, A. Clinical features of visual migraine aura: a systematic review. *J Headache Pain* **20**, 64, doi:10.1186/s10194-019-1008-x (2019).
5. Liu, H. Y. *et al.* Transient visual disturbances in adolescents: migrainous feature or headache-accompanied phenomenon? *Cephalalgia* **32**, 1109–1115, doi:10.1177/0333102412460777 (2012).
6. van Dongen, R. M. & Haan, J. Symptoms related to the visual system in migraine. *F1000Res* **8**, doi:10.12688/f1000research.18768.1 (2019).
7. Luedtke, K., Schulte, L. H. & May, A. Visual processing in migraineurs depends on the migraine cycle. *Ann Neurol* **85**, 280–283, doi:10.1002/ana.25398 (2019).
8. Hayne, D. P. & Martin, P. R. Relating Photophobia, Visual Aura, and Visual Triggers of Headache and Migraine. *Headache* **59**, 430–442, doi:10.1111/head.13486 (2019).
9. Purselle, D. C. & Nemeroff, C. B. Serotonin transporter: a potential substrate in the biology of suicide. *Neuropsychopharmacology* **28**, 613–619, doi:10.1038/sj.npp.1300092 (2003).
10. Wang, S. J., Fuh, J. L., Juang, K. D. & Lu, S. R. Migraine and suicidal ideation in adolescents aged 13 to 15 years. *Neurology* **72**, 1146–1152, doi:10.1212/01.wnl.0000345362.91734.b3 (2009).
11. Radat, F. & Swendsen, J. Psychiatric comorbidity in migraine: a review. *Cephalalgia* **25**, 165–178, doi:10.1111/j.1468-2982.2004.00839.x (2005).
12. Liu, H. Y., Fuh, J. L., Lin, Y. Y., Chen, W. T. & Wang, S. J. Suicide risk in patients with migraine and comorbid fibromyalgia. *Neurology* **85**, 1017–1023, doi:10.1212/wnl.0000000000001943 (2015).
13. Wang, Y. F., Yu, C. C., Kuan, A. S., Chen, S. P. & Wang, S. J. Association between suicidal risks and medication-overuse headache in chronic migraine: a cross-sectional study. *J Headache Pain* **22**, 36, doi:10.1186/s10194-021-01248-0 (2021).
14. Eriksen, M. K., Thomsen, L. L. & Olesen, J. The Visual Aura Rating Scale (VARS) for migraine aura diagnosis. *Cephalalgia* **25**, 801–810, doi:10.1111/j.1468-2982.2005.00955.x (2005).
15. (IHS), H. C. C. o. t. I. H. S. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* **38**, 1-211, doi:10.1177/0333102417738202 (2018).
16. Hung, C. I., Liu, C. Y., Yang, C. H. & Wang, S. J. The Impacts of Migraine among Outpatients with Major Depressive Disorder at a Two-Year Follow-Up. *PLoS One* **10**, e0128087, doi:10.1371/journal.pone.0128087 (2015).
17. Stewart, W. F. *et al.* An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology* **53**, 988–994, doi:10.1212/wnl.53.5.988 (1999).

18. Kosinski, M. *et al.* A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* **12**, 963–974, doi:10.1023/a:1026119331193 (2003).
19. Sauro, K. M. *et al.* HIT-6 and MIDAS as measures of headache disability in a headache referral population. *Headache* **50**, 383–395, doi:10.1111/j.1526-4610.2009.01544.x (2010).
20. Choi, J. Y. *et al.* Usefulness of a photophobia questionnaire in patients with migraine. *Cephalalgia* **29**, 953–959, doi:10.1111/j.1468-2982.2008.01822.x (2009).
21. Zigmond, A. S. & Snaith, R. P. The hospital anxiety and depression scale. *Acta Psychiatr Scand* **67**, 361–370, doi:10.1111/j.1600-0447.1983.tb09716.x (1983).
22. Association, A. P. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. (American Psychiatric Pub, 2013).
23. Lee, E. H. Review of the psychometric evidence of the perceived stress scale. *Asian Nurs Res (Korean Soc Nurs Sci)* **6**, 121–127, doi:10.1016/j.anr.2012.08.004 (2012).
24. Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* **28**, 193–213, doi:10.1016/0165-1781(89)90047-4 (1989).
25. Queiroz, L. P. *et al.* Characteristics of migraine visual aura. *Headache* **37**, 137–141, doi:10.1046/j.1526-4610.1997.3703137.x (1997).
26. Lin, Y. K. *et al.* Association of Suicide Risk With Headache Frequency Among Migraine Patients With and Without Aura. *Front Neurol* **10**, 228, doi:10.3389/fneur.2019.00228 (2019).
27. Walters, A. B. & Smitherman, T. A. Development and Validation of a Four-Item Migraine Screening Algorithm Among a Nonclinical Sample: The Migraine-4. *Headache* **56**, 86–94, doi:10.1111/head.12716 (2016).
28. Hansen, J. M., Baca, S. M., Vanvalkenburgh, P. & Charles, A. Distinctive anatomical and physiological features of migraine aura revealed by 18 years of recording. *Brain* **136**, 3589–3595, doi:10.1093/brain/awt309 (2013).
29. Cucchiara, B., Datta, R., Aguirre, G. K., Idoko, K. E. & Detre, J. Measurement of visual sensitivity in migraine: Validation of two scales and correlation with visual cortex activation. *Cephalalgia* **35**, 585–592, doi:10.1177/0333102414547782 (2015).
30. Schankin, C. J., Viana, M. & Goadsby, P. J. Persistent and Repetitive Visual Disturbances in Migraine: A Review. *Headache* **57**, 1–16, doi:10.1111/head.12946 (2017).
31. Jahangard, L. *et al.* Serum oxytocin concentrations in current and recent suicide survivors are lower than in healthy controls. *Journal of Psychiatric Research* **128**, 75–82, doi:https://doi.org/10.1016/j.jpsychires.2020.05.014 (2020).
32. Jokinen, J. *et al.* Low CSF oxytocin reflects high intent in suicide attempters. *Psychoneuroendocrinology* **37**, 482–490, doi:10.1016/j.psyneuen.2011.07.016 (2012).
33. Parris, M. S. *et al.* Attempted suicide and oxytocin-related gene polymorphisms. *J Affect Disord* **238**, 62–68, doi:10.1016/j.jad.2018.05.022 (2018).

34. Nersesyan, Y. *et al.* Oxytocin Modulates Nociception as an Agonist of Pain-Sensing TRPV1. *Cell Rep* **21**, 1681–1691, doi:10.1016/j.celrep.2017.10.063 (2017).
35. Mikkelsen, J. D. *et al.* Gating of retinal inputs through the suprachiasmatic nucleus: role of excitatory neurotransmission. *Neurochem Int* **27**, 263–272, doi:10.1016/0197-0186(95)00039-b (1995).
36. Nock, M. K. *et al.* Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry* **192**, 98–105, doi:10.1192/bjp.bp.107.040113 (2008).
37. Mościcki, E. K. Identification of suicide risk factors using epidemiologic studies. *Psychiatr Clin North Am* **20**, 499–517, doi:10.1016/s0193-953x(05)70327-0 (1997).
38. Yuodelis-Flores, C. & Ries, R. K. Addiction and suicide: A review. *Am J Addict* **24**, 98–104, doi:10.1111/ajad.12185 (2015).

Figures

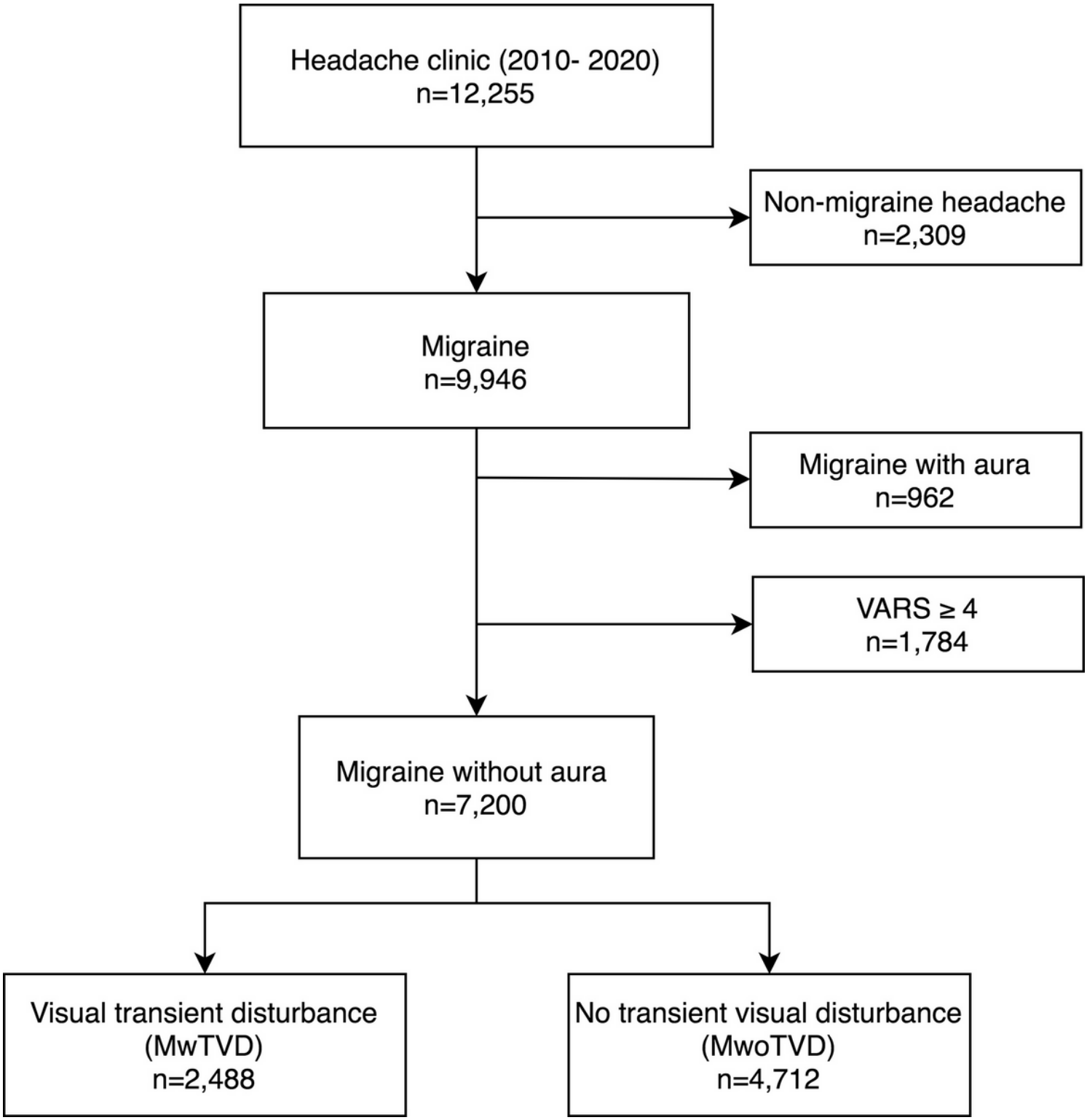

Figure 1

Flow chart depicting the patient selection. For all patients visited our headache clinic, patients with non-migraine headache and patients with migraine with aura and Visual Aura Rating Scale (VARS) more than 4 were excluded from the study. Patients with migraine without aura were divided into two subgroups base on the presence of transient visual disturbance (MwTVD vs. MwoTVD).

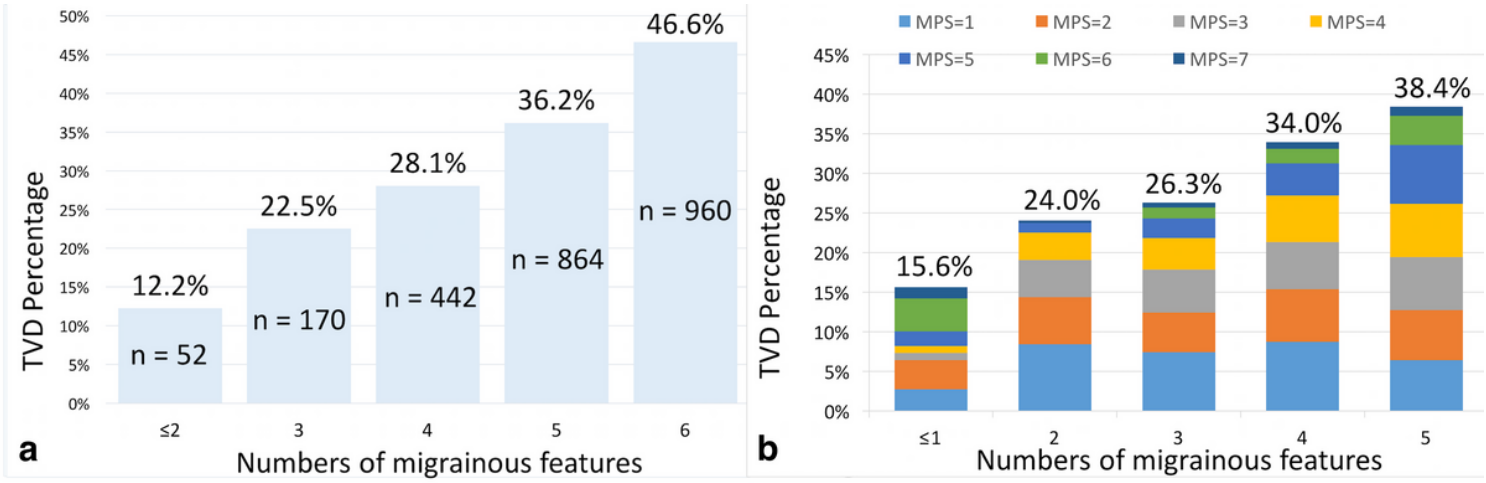

Figure 2

Numbers of migrainous features are positively associated with prevalence of transient visual disturbance and photophobia. (a) The prevalence of transient visual disturbance in subjects with different numbers of migrainous features (including moderate to severe intensity, pulsating quality, unilateral, aggravation by physical activity, nausea or vomiting, photophobia and phonophobia; range of numbers: 0–6). (b) The Migraine Photophobia Score (MPS) in subjects with different numbers of migrainous features (range of numbers: 0–5; note that photophobia and phonophobia were not taking into account as migrainous features).