J Chin Med Assoc

ORIGINAL ARTICLE

Transient visual disturbances are associated with disability and suicide risk in patients with migraine without aura

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Abstract

Background: To investigate the characteristics and clinical correlates of transient visual disturbances (TVDs) in patients with migraine without aura (MO). Patients with MO frequently report TVDs, which differ from typical visual aura, but the clinical significance of these TVDs has not been determined.

Methods: Patients with MO who attended our headache clinics were enrolled. Structured questionnaires were used to acquire data on participants' headache profiles, disability, comorbidities, and lifetime suicidal ideation and suicide attempts. A semistructured visual phenomenon questionnaire was used to characterize TVDs. Headache specialists interviewed the participants for diagnosis and the verification of questionnaire responses.

Results: Patients with MO (n = 7200; female/male ratio = 3.56, mean age 40.1 ± 13.4 years) were divided into two groups based on the presence (n = 2488) or absence (n = 4712) of TVDs. Patients with TVDs had more headache-related disability, psychiatric comorbidities, and photophobia than did those without TVDs. Suicidal ideation and suicide attempts were more common among patients with than among those without TVDs [ideation: odds ratio (OR) = 1.92, 95% confidence interval (CI) 1.71-2.15, $p < 0.001$; suicide attempt: OR = 2.23, 95% CI 1.80-2.75, $p < 0.001$].

Conclusion: The presence of TVDs may imply greater migraine-related disability, photophobia, and suicidal ideation/suicide attempt risk in patients with MO.

Keywords: Migraine without aura; Photophobia; Suicide risk; Transient visual disturbance

1. INTRODUCTION

Migraine aura refers to reversible visual, sensory, and language disturbances associated with headache, which develop gradually >5 minutes and last 5 to 60 minutes.[1,2] Visual aura is the most common of these neurological symptoms, occurring in 98% of patients with migraine with aura (MA).[3] Flashes of bright light, foggy or blurred vision, and zigzag or jagged lines are the most frequent visual aura symptoms.[4] In clinical practice, however, many patients with migraine without aura (MO) report complex transient visual disturbances (TVDs) of variable duration and complexity that differ from typical visual aura, such as photophobia and after-image.[5–7] In a field study, we determined that nearly half (48%) of adolescents with migraine without characteristic visual aura experienced TVDs related to their headache attacks.[5] TVDs do not fulfill the visual aura criteria proposed in the International Classification of Headache Disorders (ICHD),[1,2] and they are poorly characterized, often neglected, and under-researched.

Previous studies have revealed connections between migraine aura and photophobia, which appear to be associated with cortical hypersensitivity.[8] Although the pathophysiology of TVDs has not been investigated fully, we have found that nonaura TVDs are also associated with photophobia, raising the possibility of visual cortex hypersensitivity in patients who experience them.[5] Furthermore, visual aura has been found to increase the odds of psychiatric comorbidities and the suicide risk, possibly due to neuroendocrine alterations.[9–11] Whether TVDs are associated with these risks among patients with MO remains unknown.

The aim of this study was to investigate the characteristics and clinical significance of TVDs among patients with migraine without visual aura, to aid the understanding of the complex neurobiology of migraine. We hypothesized that nonaura TVDs

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Conflicts of interest: Dr. Shuu-Jiun Wang, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2023) 86: 557-564.

Received August 18, 2022; accepted January 31, 2023.

doi: 10.1097/JCMA.0000000000000912.

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would be related to increased migraine disease burden and/or suicidal risk. This post-hoc study involved the secondary analysis of data collected previously from the Taipei Veterans General Hospital (TVGH) headache registry. Several other studies of parts of this dataset have been published.[12,13]

2. METHODS

2.1. Study participants and data collection

The headache specialists at the TVGH headache clinic surveyed patients presenting with headache during the period of May 2010 to July 2020. All participants completed a structured questionnaire assessing their headache profiles, comorbidities, mood, sleep, photophobia, and suicidal ideation or suicide attempts at their first visits. A semistructured visual phenomenon questionnaire was used to assess TVDs characteristics. Later, each participant underwent a thorough clinical interview to establish a headache diagnosis and completed questionnaires. Headache specialists diagnosed MA, MO, and chronic migraine (CM) based on the criteria of the second and third editions of the International Classification of Headache Disorders (ICHD-2 and ICHD-3, respectively; MO, code 1.1; MA, code 1.2; CM, code 1.3).[1,2] Patients with MA were excluded from this study. Information collected from the questionnaires was de-identified and entered into the TVGH headache registry. No a priori statistical power calculation was conducted for this study; the sample size was based on data availability.

2.2. Ethical considerations

The institutional review board of TVGH approved the protocol for this retrospective secondary analysis of de-identified data from the TVGH headache registry, with a waiver of the informed consent requirement (TVGH IRB-2021-04-121-CC). The corresponding authors had full access to all study data and assumed final responsibility for the decision to submit this report for publication.

2.3. TVDs definition

TVDs were defined as transient visual phenomena related in time to the occurrence of a migraine headache attack without visual aura. They were characterized using the five items of the visual aura rating scale (VARS). The total VARS score is the weighted sum of the five-item scale: duration 5 to 60 minutes (three points), developing gradually over ≥5 minutes (two points), scotoma (two points), zigzag lines (two points), and unilateral visual field (one point). Scores ≥ 5 are highly sensitive and specific for the diagnosis of MA.[14] To exclude patients with potential aura, we explored the VARS cutoff value in our cohort using MA diagnoses made by neurologists based on the ICHD[1,15] as the gold standard. Compared to physician diagnoses, VARS scores ≥ 5 had a 68.4% sensitivity and 88.7% specificity, and those ≥4 had 77.1% sensitivity and 79.9% specificity for the identification of typical migraine aura. For VARS scores ≥ 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 patients with neurologist-diagnosed MO and VARS scores < 4 to ensure that their TVDs were unlikely to be visual aura.

2.4. Questionnaires

Data on participants' demographic characteristics, including their age, sex, occupation, education level, and marital status, and their medical histories were collected. A validated headache questionnaire was used to determine their headache frequency (days/month), intensity (numerical rating scale, 0-10), duration, location, characteristics, accompanying symptoms, frequency of acute abortive medication usage (days/month), and duration of migraine (years), as well as TVDs symptoms.[13,16] A visual phenomenon questionnaire was used to assess the TVDs, including patterns (zigzag flashes, flickering dots or lines, and blurred or foggy vision), visual field laterality, 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 take to develop?
9. How long did your TVDs last?
10. Did these TVDs develop before, after, or during the onset of the headache?

The patients with MO were divided into two groups based on the presence (MwTVDs) or absence (MwoTVDs) of TVDs. Other questionnaires administered were the Migraine Disability Assessment (MIDAS), six-item Headache Impact Test (HIT-6), Migraine Photophobia Score (MPS), Hospital Anxiety and Depression Scales (HADS), Beck Depression Inventory (BDI), Perceived Stress Scale (PSS), and Pittsburgh Sleep Quality Index (PSQI). The presence of medication-overuse headache (MOH) and suicidal ideation and suicide attempts (Have you ever had ideational thoughts of engaging in suicidal behavior? Have you ever had engaged in any self-injurious behavior with the intent to die?) were also determined. Unanswered items were treated as missing data. Headache specialists validated participants' questionnaire responses during the face-to-face interviews. The whole process lasted ≤30 minutes, with a 10-minute break to reduce the effect of fatigue.

The MIDAS assesses headache-related disability during a 3-month period, and the HIT-6 measures the severity of headache pain and the adverse impact of headache.[17,18] They are well accepted and widely utilized to evaluate migraine disability and impacts. Headache intensity and frequency predominantly influence the HIT-6 and MIDAS scores, respectively.[19] The MPS is determined using a self-administered eight-item questionnaire on the degree of photophobia in patients with migraine. The total MPS is the sum of "yes" responses.[20] The HADS is a self-administered instrument used to detect psychiatric comorbidity in the setting of a hospital outpatient clinic. Anxiety and depression were defined by hospital anxiety scale (HAS) and hospital depression scale (HDS) scores ≥ 11, respectively.[21] The BDI is a 21-item self-reported measure of major depression symptoms according to the diagnostic criteria listed in the Diagnostic and Statistical Manual for Mental Disorders.[22] The 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] The PSQI is used to characterize the quality and patterns of sleep in the past month. Poor sleep quality was defined as PSQI scores > 5.[24]

2.4.1. Characterization of migrainous features, prevalence of visual disturbances, and severity of photophobia

Each participant's migrainous features (moderate-to-severe intensity, pulsating quality, unilaterality, aggravation by physical

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activity, nausea or vomiting, and photophobia and phonophobia) were evaluated. "Yes" responses were summed to obtain total scores ranging from 0 to 6. To evaluate the migrainous features of patients with photophobia, we calculated scores ranging from 0 to 5, excluding photophobia and phonophobia.

2.5. Statistical analysis

The descriptive data are presented as means ± standard deviations or percentages. The chi-squared test was used to assess differences in categorical data between study groups. The normality of data distributions was checked with histograms before conducting parametric tests. Continuous data were compared between the study groups using the two-tailed independent-sample *t* test. The Mann-Whitney *U* test was used to compare variables that were not distributed normally (headache frequency; disease duration; BDI, HDS, and MIDAS scores; and MPS). Bonferroni correction was performed for the 16 study variables (age, gender, migraine duration, headache frequency, MPS, MIDAS, HIT-6, HAS, HDS, BDI, PSS, and PSQI scores; CM; MOH; suicidal ideation; and suicide attempts). For post-hoc subgroup analysis, logistic regression was performed to identify interaction effects. The risks associated with comorbid suicidal ideation and suicide attempts were analyzed separately with models with no controlling for any covariate, control for demographic characteristics, and control for demographic and clinical characteristics. These models were performed using the "enter" method, that is, with simultaneous fitting of the independent variables in each model. Risks are characterized by odds ratios (ORs) with 95% confidence intervals (CIs). Results were considered significant at $p < 0.05$. The statistical analyses were performed using R for Mac OS (version 3.6.3; R Core Team, Vienna, Austria).

3. RESULTS

3.1. Prevalence of TVDs

Of 12 255 patients who visited our headache clinic during the 10-year study period, migraine was diagnosed in 9946 patients. Of these patients, 962 with MA and 1784 with MO and VARS scores ≥ 4 were excluded, yielding a final sample of 7200 patients with MO. The female:male ratio was 3.6 [5620 (78.1%) females and 1580 (21.9%] males) and the mean age was 40.1 ± 13.4 years The MwTVDs and MwTVDs groups contained 2488 (34.6%) and 4,712 (65.4%) patients, respectively. A flow chart of patient enrollment is presented as Fig. 1.

3.2. TVDs characteristics and clinical features

In total, 865 (34.8%) patients in the MwTVDs group reported >1 TVD pattern. The most common pattern was blurred or foggy vision [n = 1766 (71.0%)], followed by flickering dots or lines [n = 1332 (53.5%)] and zigzag flashes [n = 279 (11.2%)]. More than one-quarter [n = 683 (27.5%)] of the patients reported both positive (flickering dots or lines or zigzag flashes) and negative (blurred or foggy vision) TVDs. Most (74.1%) of the TVDs occurred during the participants' headaches; 18.4% occurred before and 7.5% occurred after headaches. TVDs onset were commonly quick (59.2% in ≤30 seconds, 22.7% in 30-60 seconds, and 15.3% in 1-5 minutes), and the TVDs duration were commonly short (51.6% for ≤30 seconds, 23.0% for

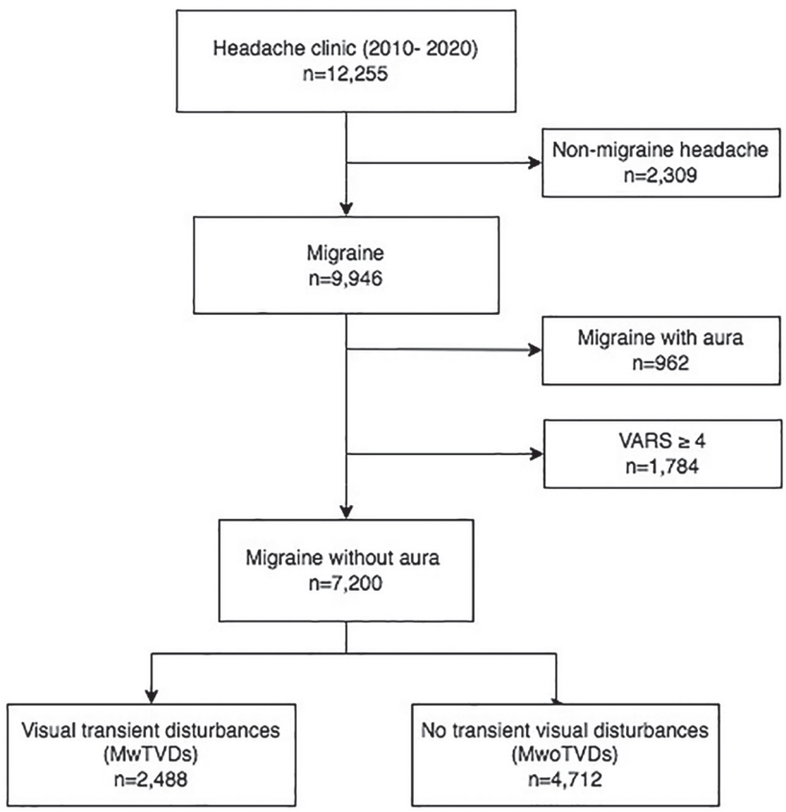

Fig. 1 Flow of patient selection. From all patients who visited our headache clinic, those with nonmigraine headache and patients with migraine with aura and Visual Aura Rating Scale (VARS) scores > 4 were excluded from the study. Patients with migraine without aura were divided into two groups based on the presence and absence of transient visual disturbances (MwTVDs and MwoTVDs, respectively).

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30-60 seconds, and 15.8% for 1-5 minutes; Table 1). The onset time, duration, and temporal relationship with headache are the three major differences between TVDs and typical visual aura. To validate the phenotype-based TVDs diagnoses, we compared these characteristics between the MwTVDs and MA groups. For visual symptoms that did not fulfill the criteria for typical visual aura but had at least two of three characteristics assessed (develops or spreads in <5 minutes, lasts <5 minutes, and occurs during the headache phase), the sensitivity and specificity of TVDs identification were 96.38% and 64.03%, respectively, and the PPV and NPV were 0.87.

The demographic and clinical characteristics of the MwTVDs and MwoTVDs groups are summarized in Table 2. In general, patients with MwTVDs had worse clinical features than did those with MwoTVDs. Compared with the MwoTVDs group, the MwTVDs group had more frequent headaches; more severe headache-related disability; more CM, MOH, and psychiatric comorbidity diagnoses; and a greater likelihood of being photophobic (Supplementary Tables 1, 2).

3.3. TVDs, photophobia, and migrainous features

The frequency of TVDs increased with that of migrainous features, from 12.2% in patients with MO and the fewest features to 46.6% in those with all six features (Fig. 2A). Patients with MwTVDs had higher MPSs than did those with MwoTVDs (2.9 ± 2.0 vs 1.6 ± 1.9, $p < 0.001$, Table 1). In addition, the MPS was associated with TVDs (unadjusted OR = 1.37, 95% CI = 1.32-1.42, $p < 0.001$), including in an analysis adjusted for gender and age (adjusted OR = 1.36, 95% CI = 1.31-1.41, $p < 0.001$). Similar to that of TVDs, the frequency of photophobia increased with that of migrainous features, from 15.6% to 38.4% (Fig. 2B).

3.4. Suicide risk in patients with MwTVDs and photophobia

Because the percentages of suicidal ideation and suicide attempts were much higher in the MwTVDs group than in the MwoTVDs group (31.9% vs 18.1%, $p < 0.001$ and 8.2% vs 3.5%, $p < 0.001$, respectively; Table 2), we further explored whether TVDs constituted an independent suicide-related risk factor in patients with MO. Univariate analysis showed that TVDs, photophobia, headache frequency, headache-related disability, CM, MOH, and traditional risk factors (depression, anxiety, and poor sleep quality) were associated with greater risks of suicidal ideation and suicide attempts in patients with migraine, whereas marriage had a protective effect against suicidal ideation (Table 3). In the multivariable analysis controlled for demographic characteristics, headache frequency, disease duration, headache-related disability, CM, MOH, and psychiatric comorbidities, TVDs remained an independent risk factor for suicidal ideation and suicidal attempts (Table 4).

4. DISCUSSION

This study demonstrated that the prevalence of nonaura TVDs was as high as 34.6% among patients with MO. Patients with TVDs were predominately female, had worse headache-related disability and more psychiatric comorbidities, and were more likely to be photophobic than were those without TVDs. Patients who exhibited more migrainous features were more likely to have TVDs and photophobia, implying the clinical significance of nonaura visual symptoms in migraine. Moreover, the presence of TVDs was associated with increased suicidal ideation and suicide attempts, even after adjustment for other suicide risk factors. Based on these findings, we propose that the presence of TVDs can serve as a marker of disease severity and even a potential indicator of greater suicide risk.

Table 1

Characteristics of TVDs in MwTVDs patients, n = 2488

MwTVDs patients, n = 2488	n (%)[a]
Blurred/foggy vision	1766 (71.0%)
Flickering dots or lines	1332 (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%)
Nonspecific	94 (5.6%)
Yellowish	83 (4.9%)
Rainbow like	36 (2.1%)
Co-occurrence of TVDs and headache[c]	
Not every time	2167 (92.7%)
Every time	170 (7.3 %)
Laterality	
Nonspecific	908 (36.4%)
Bilateral	688 (27.7%)
Unilateral	892 (35.9%)
Movable[d]	
Yes	921 (40.4 %)
No	1356 (59.6 %)
Time of development	
≤30 s	1472 (59.2%)
0.5–1 min	564 (22.7%)
1–5 min	380 (15.3%)
5–20 min	36 (1.4%)
≥20 min	36 (1.4%)
Duration	
≤30 s	1285 (51.6%)
0.5–1 min	571 (23.0%)
1–5 min	393 (15.8%)
5–30 min	20 (0.8%)
0.5–1 h	13 (0.5%)
≥1 h	206 (8.3%)
Temporal relationship with headache[e]	
Before headache	397 (18.4%)
During headache	1602 (74.1%)
After headache	162 (7.5%)

TVDs = transient visual disturbances.

[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]Seven hundred ninety-eight patients did not have data for colors of TVDs.

[c]One hundred fifty-one patients did not have data for co-occurrence of TVDs.

[d]Two hundred eleven patients did not have data for movability of TVDs.

[e]Three hundred twenty-seven patients did not have data for temporal relationship with headache and TVDs;

Blurred or foggy vision was the most common type of TVD, and more than one-quarter of affected patients also saw flickers or zigzag flashes. Similarly, blurred or foggy vision was the most common visual symptom other than aura among patients with MA in a previous study.[25] Foggy vision, the most common TVD, may be an autonomic cranial symptom, that is, an accommodation problem attributed to the alteration of the autonomic trigeminal reflex.[26,27] Most TVDs reported by our patients were fixed, colorless, over nonspecific fields, developing within 5 minutes, lasting <5 minutes, and occurring during the headache phase. These results are consistent with our previous finding that

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Table 2

Demographic data, headache characteristics, and comorbidity in patients with migraine with (MwTVDs) or without transient visual disturbance (MwoTVDs)

	MwTVDs, n = 2488		MwoTVDs, n = 4712		*p*
	Mean (SD)	Median [25th, 75th]	Mean (SD)	Median [25th, 75th]	
Age, y	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 (%)	2023 (81.3%)/465 (18.7%)		3597 (76.3%)/1115 (23.7%)		<0.001*
Disease duration of migraine (y)	17.4 (11.5)	15.4 [8.5, 24.4]	19.2 (12.2)	17.2 [9.8, 26.9]	<0.001*
Headache days/mo	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*
Suicide attempt, n (%)	203 (8.2%)		167 (3.5%)		<0.001*

Data are presented as mean ± SD.

BDI = Beck depression inventory; HAS = hospital anxiety scale; HDS = hospital depression scale; HIT-6 = six-item headache impact test; MIDAS = migraine disability assessment; MPS = migraine photophobia score; PSQI = Pittsburgh sleep quality index; PSS = perceived stress scale.

*Significant after Bonferroni correction.

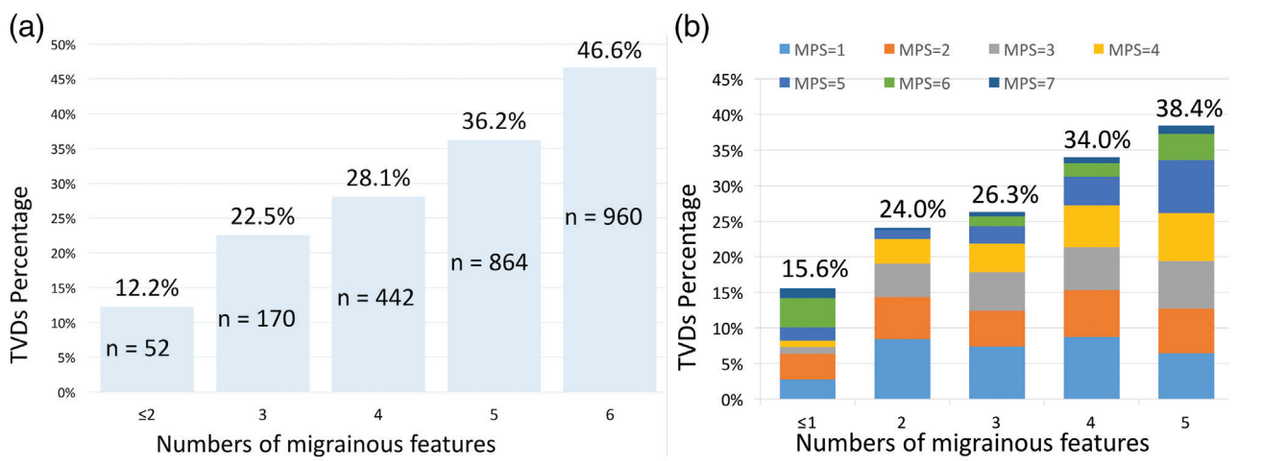

Fig. 2 Associations of the number of migrainous features (moderate-to-severe intensity, pulsating quality, unilaterality, aggravation by physical activity, nausea or vomiting, photophobia and phonophobia) with the prevalence of transient visual disturbances (A) and photophobia (based on the Migraine Photophobia Score; B). For (B), photophobia and phonophobia were not included as migrainous features.

TVDs have short onset-to-development and overall durations and are common among adolescent patients with migraine.[5] The major differences between typical visual aura and TVDs are the symptom onset and duration and the temporal relationship to headache. In addition, TVDs were much more prevalent than typical aura in the present study, affecting one-fourth and less than one-tenth, respectively, of patients with migraine. We propose that these non-classical visual symptoms be classified not as atypical aura, but as separate phenomena. We emphasize the importance of identifying TVDs in clinical practice, given their crucial clinical implications. We propose operational criteria for the characterization of migraine-associated TVDs, the clinical utility of which needs be validated in future research (Table 5).

To our knowledge, this study is the first to show that TVDs in patients with migraine are related to greater migraine-related disability, photophobia, and suicidal ideation and suicide attempt risks. The ORs for suicide-related risk of TVDs and the MPS were larger than those for the HIT-6 score and headache frequency, previously reported to be related strongly to suicide risk.[28] Thus, the impact of nonaura TVDs on patients with migraine may have been underestimated. In addition, TVDs and photophobia were more prevalent among those with more migrainous features. Photophobia is known to be one of the most disabling symptoms of migraine,[29] but the disability caused by TVDs is seldom addressed. Thus, we propose that TVDs be considered not only as indicators of migraine-related disability, but also as prognostic factors for migraine.

The pathophysiology of TVDs in patients with migraine is unknown. Typical aura is associated with abnormal cortical hyperexcitability, and its visual perception may differ depending on the region of the occipital cortex involved.[30] Cortical

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Table 3

Association of suicide ideation/attempts with potential risk factors

	Suicidal ideation		Suicide attempt	
	OR (95% CI)	*p*	OR (95% CI)	*p*
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
TVDs	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/mo	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 (y)	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

CI = confidence interval; HAS = hospital anxiety scale; HDS = hospital depression scale; HIT-6 = six-item headache impact test; MPS = migraine photophobia score; MIDAS = migraine disability assessment; OR = odds ratio; PSQI = Pittsburgh sleep quality index; PSS = perceived stress scale; TVDs = transient visual disturbances.

Table 4

Different models for the association of suicide risk with TVDs and MPS

	Suicidal ideation		Suicide attempt	
	OR (95% CI)	*p*	OR (95% CI)	*p*
TVDs+ Demographics	1.86 (1.66, 2.09)	<0.001	2.17 (1.75, 2.69)	<0.001
TVDs+ 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

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.

HIT-6 = six-item headache impact test; CI = confidence interval; MPS = migraine photophobia score; OR = odds ratio; TVDs = transient visual disturbances.

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 min
2. Transient visual disturbance lasts < 5 min
3. Transient visual disturbance occurs during headache phase

hypersensitivity may be the link between migraine aura and photophobia.[8] As patients with TVDs were more photophobic than were those without TVDs and increased interictal visual sensitivity is present in both MA and MO,[31] some patients' TVDs may be linked to mechanisms similar to cortical hyperexcitability but involving a less-eloquent visual cortex.[32] We speculate that our patients with TVDs had hyperexcitable visual cortices that contributed to the TVDs and more severe photophobia, resulting in worse migraine-related disability. Furthermore, we found that TVDs constituted an independent risk factor for increased suicidal ideation and suicide attempts in an analysis adjusted for potential confounders. Suicide survivors have lower serum and cerebrospinal fluid oxytocin concentrations,[33,34] and oxytocin is a potential biomarker of attempted suicide.[35] On the other hand, oxytocin released from paraventricular neurons (PVNs) can suppress the nociception of inflammatory pain.[36] As PVNs also channel photic input from the retina,[37] oxytocin may also be related to migraine-type photophobia and worse headache-related disability. This possibility needs to be investigated in systematic studies.

This study has several strengths. First, the examination of data from a large clinical sample increased the precision of the estimates. Second, we used detailed questionnaires to specifically characterize participants' headaches and TVDs symptoms. Although the validity of the questionnaires used to assess TVDs needs to be examined further, the other questionnaires administered are widely accepted valid and reliable neuropsychological instruments.[12,13] Furthermore, experienced headache specialists made final diagnoses of MO and TVDs through face-to-face interviews, which helped to confirm the accuracy of our data. We used the VARS to exclude patients with potential aura. Additionally, we propose phenotype-based diagnostic criteria for TVDs. Thus, we believe that our findings could have practical implications for neurologists.

However, the study also has some limitations. First, all patients were recruited from a tertiary medical center, and thus were at the worse end of the disease spectrum. Nevertheless, patients in this sample with TVDs had much worse clinical features than did those without TVDs. Second, we evaluated participants' suicide risk using direct single-item questions. Although we verified participants' responses in face-to-face interviews, we did not collect detailed information about the potential etiologies of suicidal ideation and suicide attempts. However, the overall lifetime prevalence of suicide attempts in the MwoTVDs group was very similar to that obtained in a cross-national multicultural study (3.5% and 2.7%, respectively),[38] indicating that our findings are reliable. More than half of suicidal ideations are transformed into suicide planning and attempts within 1 year, and attempted

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suicide is the best predictor of completed suicide.[39] Third, this retrospective study involved the analysis of a pre-existing dataset that was not specifically designed to establish the reliability of TVDs, and the validity of the TVDs questionnaires used has not been examined. Some cases of aura in our sample may have been misdiagnosed as TVDs. However, considering that we excluded a proportion of patients with MA comparable to those excluded in our previous field studies and the prevalence of TVDs identified in this study was much higher than that of MA, we believe that possible undiagnosed cases of aura would account for a small proportion of TVDs cases in our sample. Nevertheless, further prospective studies are needed to explore these potential confounding issues. In addition, our study population was derived from a single hospital. Prospective studies involving patient evaluation by more than one clinician and the confirmation of the inter-rater reliability of MO and TVDs diagnoses are needed to determine whether our study findings can be replicated in different settings and with different populations. Finally, we focused on the psychiatric disorders of depression and anxiety, which are strongly related to suicide. We did not control for other suicide-related psychiatric conditions and sociodemographic factors (ie, bipolar disorder, borderline personality disorder, traumatic brain injury, chronic pain disorders, fibromyalgia, educational level, employment status, housing status, major life events, and financial status) in the multivariable analysis.[12,40] Further research on the effects of these potential risk factors is needed.

In conclusion, we found that non-aura TVDs were associated with greater photophobia, migraine-related disability, and suicidal ideation and suicide attempts in patients with migraine. The suicide-related ORs for TVDs and the MPS were greater than those for the HIT-6 score and headache frequency, suggesting that the impacts of nonaura TVDs and photophobia in patients with migraine have been underestimated. We recommend that TVDs be considered an indicator in the determination of migraine prognosis, and we propose operational criteria for TVDs. Nevertheless, the exact underlying pathophysiology and associations with treatment outcomes remain unclear; further exploration is required.

ACKNOWLEDGMENTS

This work was supported by the Brain Research Center, National Yang Ming Chiao Tung University, under The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project of Taiwan's Ministry of Education (to S.J.W. and S.P.C.); the Ministry of Science and Technology of Taiwan [MOST-107-2314-B-010-021, 108-2314-B-010 -022 -MY3, 110-2326-B-A49A-501-MY3, and 111-2321-B-A49-004 (to S.P.C.) and MOST 108-2321-B-010-014-MY2, 108-2321-B-010-001, 108-2314-B-010-023-MY3, 110-2321-B-010-005, and 111-2314-B-A49-069-MY3 (to S.J.W.)]; the National Science and Technology Council [NSTC-111-2634-F-A49-014 (to S.J.W.)]; the Ministry of Health and Welfare of Taiwan (MOHW107-TDU-B-211-123001 and MOHW 108-TDU-B-211-133001 to S.J.W.), and Taipei Veterans General Hospital [VGH-106-D9-001-MY2-2 (to SJW) and V110C-102, V109D52-001-MY3-2, VGHUST110-G1-3-1 (to S.P.C.)]. The funders had no role in the study design, data collection or analysis, decision to publish, or preparation of the manuscript.

The authors would like to thank the study participants for their contributions.

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