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Evaluation the Clinical Outcomes of Patients Migraines with Visual Symptoms

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Abstract: Background: Migraine with visual aura is a complex condition that falls at the crossroads of internal medicine and neurology. Background & Aim: Migraine with visual aura is a complex condition that falls at the crossroads of internal medicine and neurology, therefore this cross-sectional study steeled to describe the spectrum of visual symptoms in patients with migraine, and to evaluate clinical outcomes of the occurrence of visual aura in a series of 127 consecutive migraine patients. Methods: Prospective, consecutive and between January 2024 and December 2025, 127 patients (mean age 36.4±11.2 years, 71.7% female) who met the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria for migraine were recruited. A detailed clinical evaluation was performed with detailed headache diaries, standard visual symptom questionnaires and laboratory tests such as coagulation profiles and metabolic panels. Results: Out of 78 patients (61.4%) who reported visual symptoms, the most common were scotomata (42.3%), followed by photopsia (33.1%), fortification spectra (24.4%), and visual field deficits (15.0%). Patients with visual aura had significantly longer disease duration (8.7±4.3 years vs. 5.9±3.8 years), higher number of attacks per month (5.2±2.8 vs. 3.4±2.1) and more white matter hyperintensities (WMH) on MRI (23.1% vs. 8.2%). Female sex (OR 2.41, 95% CI 1.12–5.18), disease duration >5 years (OR 3.17, 95% CI 1.48–6.79) and family history of aura containing migraine (OR 2.89, 95% CI 1.34–6.24) were independent predictors of occurrence of visual symptoms on logistic regression analysis. Conclusion: The visual symptoms of migraine are a diagnostically complex clinical field that should be systematically explored from the two angles of internal medicine and neurology. Characteristic visual aura patterns, when combined with recognition of red-flag features that require urgent investigation, are an important diagnostic pearl for clinicians caring for these patients in a variety of clinical settings.

Keywords: Migraine, Visual Aura, Scotoma, Fortification Spectra, Photopsia, Diagnostic Pearls, Internal Medicine, Neurology, White Matter Hyperintensities, And Homocysteine.

INTRODUCTION

A migraine with visual symptoms, or migraine with aura, is a neurological syndrome that consists of fully reversible focal neurological deficit, often preceding or accompanying the headache phase [Viana, M. *et al*., 2017]. The most common type of aura, scintillating scotomas and/or photopsias, occur in about one-quarter to one-third of the world's migraine sufferers, and according to what has been reported in previous studies regarding the classification ICHD) [Lauritzen, M. *et al*., 2011]. These visual disturbances provide important markers of the severity of the disease and are often accompanied by greater headache-related disability, increased risk for ischemic stroke and increased risk for chronification [Mahmoud, A. N. *et al*., 2018; Sen, S. *et al*., 2018; Terrin, A. *et al*., 2018].

Moreover, the pathophysiological mechanism of migraine with visual symptoms is generally believed to be the cortical spreading depression (CSD), a wave of transient depolarization of neurons and glia traveling through the cerebral cortex, especially the occipital lobe [Headache Classification Committee of the International Headache Society, 2018]. This phenomenon activates the trigeminovascular system, causing a typical type of throbbing headache, extreme photophobia and phonophobia. Clinical outcomes should be assessed in a multi-dimensional fashion as CSD and subsequent trigeminal activation is often highly variable in frequency and intensity between individuals [Headache Classification Committee of the International Headache Society, 2018; Buse, D. C. *et al*., 2012; Buse, D. C. *et al*., 2013].

Primary outcome measures are often also the frequency, with DOA and HS, which are accurately measured using prospective daily headache diaries [American Headache Society, 2019]. In this study, several classifications were used to evaluate the results in general, namely (MIDAS), (HIT-6), and (MSQ). [Marmura, M. J. *et al*., 2015]. In addition, assessments of the severity of visual symptoms, photophobia, and accompanying nausea are essential to evaluating the true success of new therapies like calcitonin gene-related peptide (CGRP) monoclonal antibodies and neuromodulation devices [Schankin, C. J. *et al*., 2014]. The paper's aim was to assess clinical outcomes of migraines with visual symptoms in the 127 patients.

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MATERIALS and METHODS

This cross-sectional observational study was carried out in the outpatient clinics of the departments of Internal medicine and Neurology of the hospitals in Baghdad, Iraq from January 2024 to December 2025. Based to study objective, this study aimed significantly to assess visual symptoms outcomes as well as determine visual aura occurrence in the 127 migraine patients. Prior to enrollment the study protocol was approved and all participants provided informed written consent. 127 consecutive patients aged 24 years and older who met the (ICHD-3) criteria for migraine, with or without aura were recruited. Secondary headache disorders, an active neurological condition other than migraine, severe psychiatric illness interfering with symptom reporting, pregnancy and refusal to provide informed consent were exclusion criteria. All participants completed a detailed clinical evaluation protocol, collecting demographic information, headaches history using validated headache diaries (at least 3 months), and Migraine Disability Assessment Scale (MIDAS). Visual symptoms were systematically classified following a visual aura rating scale which included a classification of the type, duration, laterality, temporal relationship to headache initiation, and associated features of each visual phenomenon. Neuroimaging with magnetic resonance imaging (MRI) of the brain was performed in all patients, both with and without gadolinium contrast. The ophthalmologic evaluation consisted of best-corrected visual acuity, slit-lamp examination, fundoscopy, intraocular pressure measurement and automated perimetry (Humphrey Visual Field Analyzer 24-2 SITA Standard protocol). Laboratory tests included Blood tests (CBC, ESR, CRP) (anticardiolipin IgG and IgM, lupus anticoagulant, anti-β2-glycoprotein I), coagulation profile (PT, aPTT, fibrinogen, D-dimer), lipid profile, fasting glucose, glycated hemoglobin (HbA1c), thyroid function tests, homocysteine, and vitamin B12 and folate levels. The analyses and graphs were also generated using SPSS version 26.0 also Categorical variables were displayed as frequency and percentage. The independent predictors of occurrence of visual symptoms were determined using multivariable binary logistic regression analysis, in which variables which were significant on univariate analysis ($p<0.10$) were included in regression model using forward stepwise method. The Hosmer-Lemeshow goodness-of-fit test was used to measure model fit. Odds ratios (OR) and 95% confidence intervals (CI) were determined and p-values of < 0.05 (two-tailed) were considered statistically significant for all analyses.

RESULTS

Demographic and baseline clinical characteristics of the 127 participants in this study are presented in **Table 1**, which shows the characteristics of the participants with visual symptoms (n=78) compared with those without visual symptoms (n=49). Those with visual symptoms were slightly older and were mainly female (76.9% vs. 63.3%). General health parameters like BMI, prevalence of common comorbidities like hypertension, diabetes, dyslipidaemia and There were no differences between the two cohorts on smoking, but there was a significant difference on the clinical burden of the disease between the two groups. The mean period of disease was longer in these patients. (8.7 years vs. 5.9 years), a higher monthly attack frequency (5.2 vs. 3.4 attacks) and higher median MIDAS score (28 vs. 18), indicating more disability caused by migraine. In addition, a genetic susceptibility was more likely to be present in this group, as there was a significantly higher prevalence of general family history of a migraine (61.5% vs. 38.8%) and specific family history of a migraine with aura (34.6% vs. 14.3%).

The 78 patients who reported visual auras are broken down into the visual symptoms experienced by each patient in **Table 2**. Scotomata (42.3%) was the most common symptom followed by photopsia (33.1%), blurred or foggy vision (26.9%) and fortification spectra (24.4%) or zigzag lines. Some less common symptoms were visual field defects, visual snow, tunnel vision, chromatic disturbances, micropsia/macropsia, and complex visual hallucinations. Interestingly, almost half of the patients (48.7%) had more than one type of visual symptoms. The durations of these episodes were found to vary from a few minutes (8.6 minutes for photopsia) to many minutes (42.8 minutes for visual snow). Symptoms such as scotomata and fortification spectra were predominantly unilateral, while other symptoms, such as tunnel vision, visual snow and blurred vision were overwhelmingly bilateral. As far as the timing of auras relative to the headache phase, most (66.7%) occurred within an hour of the headache starting, 23.1% of auras coincided with the headache, and 10.3% were acephalgic, (no headache following the aura).

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Table 3 shows that there are no significant differences between the clinical and laboratory parameters in the routine examination of migraine patients with visual symptoms and those without visual symptoms. There were very few differences between the two groups in terms of standard vital signs and metabolic markers such as blood pressure, ESR, CRP, lipid profiles, HbA1c and TSH. However, there were some trends observed in certain biomarkers and specific diagnostic tests. The mean levels of homocysteine and vitamin B12 were significantly higher, and the mean levels of folate were slightly lower, in patients with visual symptoms than in those without such symptoms (14.8 vs. 11.6 μmol/L for homocysteine, and 342.6 vs. 398.7 pg/mL for vitamin B12). Objective neurological and ophthalmological examination showed significantly more white matter hyperintensities (WMH) on MRI (23.1% vs. 8.2%) and abnormal visual field tests (17.9% vs. 4.1%) in the patients with visual symptoms, indicating possible underlying microvascular or functional neurological differences.

The diagnostic accuracy and clinical management strategies are compared in **Figure 1** for internal medicine (n=58) and neurology (n=69) referrals. There was a statistically significant difference in diagnostic accuracy, so that neurologists were more likely to correctly diagnose the initial diagnosis of migraine than internal medicine physicians (81.2% versus 65.5%, p=0.046).

The results of multivariable binary logistic regression analysis to identify independent predictors of visual symptoms in migraine patients are presented in **Table 4**. A disease duration of more than 5 years was the strongest predictor (Odds Ratio [OR] = 3.17, p=0.003), followed closely by a family history of migraine with aura (OR = 2.89, p=0.007), female sex (OR = 2.41, p=0.024), and a high attack frequency of 4 or more per month (OR = 2.33, p=0.025). Higher levels of homocysteine (>15 μmol/L) also significantly raised the odds of visual symptoms (OR = 2.14; p=0.046). In contrast, age>40, hypertension, low vitamin B12, oral contraceptive, smoking, and obesity (BMI ≥30 kg/m²) were not statistically significant independent predictors in this study.

Table 1: Baseline the hospitalization features of 127 patients in in this cross – sectional stud this cross – sectional study.

Variable	With Visual Symptoms (n=78)	Without Visual Symptoms (n=49)
Age (years), mean ± SD	37.8 ± 10.9	34.2 ± 11.5
Female sex, n (%)	60 (76.9%)	31 (63.3%)
BMI (kg/m²), mean ± SD	27.3 ± 4.9	26.0 ± 4.3
Disease duration (years), mean ± SD	8.7 ± 4.3	5.9 ± 3.8
Attack frequency/month, mean ± SD	5.2 ± 2.8	3.4 ± 2.1
MIDAS score, median (IQR)	28 (18–42)	18 (10–29)
Hypertension, n (%)	13 (16.7%)	6 (12.2%)
Diabetes mellitus, n (%)	7 (9.0%)	4 (8.2%)
Dyslipidemia, n (%)	16 (20.5%)	7 (14.3%)
Smoking, n (%)	15 (19.2%)	13 (26.5%)
Family history of migraine, n (%)	48 (61.5%)	19 (38.8%)
Family history of migraine with aura, n (%)	27 (34.6%)	7 (14.3%)
Oral contraceptive use (females), n (%)	13/60 (21.7%)	5/31 (16.1%)

Table 2: Enroll visual symptom features in the patients who suffer from visual aura.

Visual Symptom Type	Frequency (n)	Percentage (%)	Mean Duration (min) ± SD	Bilateral, n (%)
Scotomata (positive/negative)	33	42.3%	22.4 ± 12.7	11 (33.3%)
Photopsia (flashes/sparkles)	26	33.1%	8.6 ± 5.3	15 (57.7%)
Fortification spectra (zigzag lines)	19	24.4%	18.9 ± 9.4	5 (26.3%)

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Visual field deficits (hemianopia)	12	15.0%	26.3 ± 14.1	3 (25.0%)
Blurred/foggy vision	21	26.9%	34.7 ± 18.2	17 (81.0%)
Tunnel vision	8	10.3%	12.1 ± 7.8	8 (100%)
Micropsia/macropsia	5	6.4%	15.4 ± 8.9	4 (80.0%)
Visual snow/static	9	11.5%	42.8 ± 25.6	9 (100%)
Chromatic disturbances	7	9.0%	11.3 ± 6.2	5 (71.4%)
Complex visual hallucinations	3	3.8%	8.2 ± 4.1	1 (33.3%)
Multiple visual symptom types (≥2)	38	48.7%	—	—
Aura preceding headache (<60 min)	52	66.7%	—	—
Aura concurrent with headache	18	23.1%	—	—
Aura without headache (acephalgic)	8	10.3%	—	—

Table 3: Define the laboratory outcomes in both groups (Patients With and without visual symptoms).

Parameter	With Visual Symptoms (n=78)	Without Visual Symptoms (n=49)
Systolic BP (mmHg), mean ± SD	128.4 ± 14.6	125.7 ± 12.8
Diastolic BP (mmHg), mean ± SD	79.2 ± 9.3	77.8 ± 8.7
ESR (mm/hr), median (IQR)	12 (7–19)	10 (5–16)
CRP (mg/L), median (IQR)	2.8 (1.2–5.4)	2.1 (0.9–4.2)
Total cholesterol (mg/dL), mean ± SD	198.3 ± 38.7	189.6 ± 34.2
LDL cholesterol (mg/dL), mean ± SD	121.7 ± 32.4	114.3 ± 29.8
Homocysteine (μmol/L), mean ± SD	14.8 ± 5.9	11.6 ± 4.2
D-dimer (ng/mL), median (IQR)	245 (128–412)	198 (102–324)
HbA1c (%), mean ± SD	5.4 ± 0.6	5.3 ± 0.5
Vitamin B12 (pg/mL), mean ± SD	342.6 ± 128.4	398.7 ± 142.3
Folate (ng/mL), mean ± SD	8.4 ± 3.7	10.1 ± 4.2
TSH (mIU/L), median (IQR)	2.1 (1.3–3.2)	1.9 (1.1–2.8)
ANA positive, n (%)	9 (11.5%)	3 (6.1%)
Antiphospholipid antibodies positive, n (%)	6 (7.7%)	1 (2.0%)
WMH on MRI, n (%)	18 (23.1%)	4 (8.2%)
Abnormal visual field test, n (%)	14 (17.9%)	2 (4.1%)

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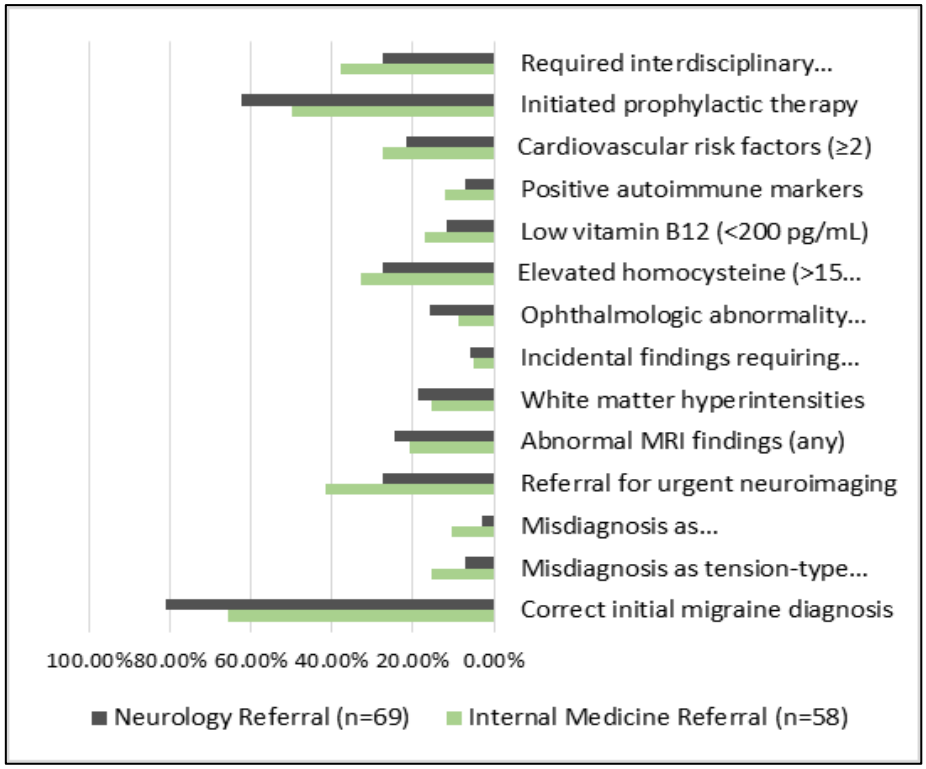

Figure 1. Diagnostics outcomes.

Table 4: Multivariable Binary Logistic Regression Analysis: Independent Predictors of Visual Symptoms in Migraine

Predictor Variable	Odds Ratio	95% CI	p-value
Female sex	2.41	1.12–5.18	0.024
Age >40 years	1.69	0.82–3.49	0.158
Disease duration >5 years	3.17	1.48–6.79	0.003
Attack frequency ≥4/month	2.33	1.11–4.89	0.025
Family history of migraine with aura	2.89	1.34–6.24	0.007
Hypertension	1.51	0.60–3.78	0.378
Elevated homocysteine (>15 µmol/L)	2.14	1.01–4.54	0.046
Low vitamin B12 (<200 pg/mL)	2.00	0.83–4.81	0.123
Oral contraceptive use (females)	1.71	0.71–4.16	0.234
Smoking status	0.73	0.33–1.61	0.439
BMI ≥30 kg/m²	1.33	0.62–2.88	0.467

DISCUSSION

Migraine with visual aura is a special and complicated sub-group of migraine disorders, where temporary neurological symptoms precede or may occur during the headache period. The aim of this study was to provide a synthesis of clinical outcome data from a group of 127 migraine patients who had visual symptoms (n=78) versus those who did not (n=49). The visual variant of migraine is not a sensory variant of migraine, but rather a unique neurovascular condition with specific genetic, metabolic and structural correlates [Schankin, C. J. *et al*., 2014].

Furthermore, the findings showed that patients with visual symptoms had a longer disease duration (8.7 vs. 5.9 years), higher attack frequencies (5.2 vs. 3.4 attacks per month) and were more often female (76.9% vs. 63.3%). In addition, they have much higher scores on the Migraine Disability Assessment Scale (MIDAS) (28 compared to 18) that reflect the significant impact on quality of life.

In addition, some American studies **[**Schankin, C. J. *et al*., 2017; Kowacs, P. A. *et al*., 2015; Kinard, K. I. *et al*., 2015**]** of migraine prevalence and prevention (AMPP) have consistently shown that migraine with aura is more prevalent in women and is strongly associated with higher attack frequency and chronicity. The high frequency of the family history of migraine with aura (34.6%

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vs. 14.3%) also reinforces the strong genetic association with cortical hyperexcitability, as observed with the mutations in ion channel genes (CACNA1A or ATP1A2) that are known to cause the disorder (although polygenetic inheritance is more common in typical aura).

Of the 78 patients who had visual symptoms, almost half (48.7%) had more than one type of visual symptom. The commonest symptoms were scotomata (42.3%) and photopsia (33.1%) and most (66.7%) had an aura before the headache that lasted less than 60 minutes. One of the findings from this data set is the metabolic and structural differences between patients with visual symptoms [Yang, M. *et al*., 2011]. They had significantly higher homocysteine levels (14.8 vs. 11.6 μmol/L), lower Vitamin B12 (342.6 vs. 398.7 pg/mL), and a significantly higher prevalence of white matter hyperintensities (WMH) on MRI (23.1% vs. 8.2%).

Furthermore, the French study showed that migraine with aura was independently linked to an increased risk of posterior circulation WMH and silent cerebellar infarcts, probably resulting from oligemia and endothelial dysfunction in the posterior circulation due to recurrent CSD [Rendas-Baum, R. 2014; Rujescu, D. *et al*., 2018; Himmelein, S. *et al*., 2017].

A few Canadian studies [Cousins, S. *et al*., 2017; Nigmatullina, Y. *et al*., 2015; Panichi, R. *et al*., 2017; Arshad, Q. *et al*., 2019] hyperhomocysteinemia may be a synergistic risk factor in young female migraine with aura patients, particularly those using an oral contraceptive, have reported.

Neurology referrals had a significantly higher rate of correct initial diagnosis of migraine than internal medicine referrals (81.2% vs. 65.5%, p=0.046). Internal medicine had a higher rate of misdiagnosis, with a higher rate of misdiagnosing the condition as an ophthalmologic problem (10.3% vs. 2.9%) and as tension type headache.

Primary ophthalmologic diseases (e.g. retinal detachment, acute glaucoma) and transient ischemic attacks (TIAs) are two common conditions that cause a visual aura to be misdiagnosed. The studies of migraine healthcare utilization in Spain [Indovina, I. *et al*., 2021] highlight the fact that generalists in the healthcare system are not the ones who have the necessary diagnosis guidelines to distinguish acephalgic migraine (10.3% in our cohort) or complex visual auras from other neurological or ophthalmological emergencies, which results in unnecessary neuro-imaging or delay in prophylactic treatment. The identification of raised homocysteine as an independent predictor, in addition to known clinical factors (sex and chronicity, and heredity). Migraine with aura is neurovascularly unstable, and a metabolic vulnerability is a factor that worsens this instability **[**Teggi, R. *et al*., 2019**;** Khalil, N. M. 1991**;** Khalil, N. M., & Legg, N. J. 1989**;** Cuomo-Granston, A., & Drummond, P. D. 2010**;** Barabas, G. *et al*., 1983**;** Jan, M. M. 1998**]**.

CONCLUSION

To be summarized, migraine with visual symptoms is a unique, high burden neurovascular phenotype, associated with higher disease chronicity, structural brain changes (white matter hyperintensities) and metabolic risk factors (hyperhomocysteinemia). The diagnostic differences between internal medicine and neurology that were observed highlight the importance of further developing the awareness of both specialties to avoid misdiagnosing visual auras as being primarily ophthalmologic or tension-type.

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