Objective: To examine short-wavelength sensitivity in patients with migraine using short-wavelength automated perimetry (SWAP) and Stiles 2-color increment threshold procedures.

Methods: Twenty-five subjects with migraine with (n=11) and without (n=14) aura and 20 age-matched headache-free subjects underwent testing. All subjects underwent standard automated perimetry (SAP) and SWAP (using a Humphrey field analyzer; 24-2 presentation pattern). In 2 migraine patients (one with and another without aura), the 2-color increment threshold procedure was used to determine whether sensitivity losses were specific to short-wavelength sensitivity pathways or a generalized loss to multiple pathways.

Results: No statistically significant differences between migraine patients and controls were found for mean deviation (MD) or pattern-standard deviation (PSD) for SAP. However, for SWAP, MD and PSD were worse for the migraine group (P = .04). Twelve migraine patients had more than 4 locations with sensitivity worse than the 5% probability level (reference value). Increment threshold determinations in the 2 selected migraine patients indicated a selectively greater loss for short-wavelength sensitivity mechanisms.

Conclusions: Approximately 50% of subjects with migraine (with or without aura) demonstrate SWAP sensitivity losses, at times between migraine events. These findings, in conjunction with previous results for SAP and flicker perimetry, suggest that migraine patients should be excluded from normative databases of visual function, and warrant further investigations of the relationship between migraine and glaucoma.

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Between migraine events, the visual fields of many individuals with migraine (hereafter described as migraine patients) are abnormal, with deficits being demonstrated for achromatic perimetry and temporal modulation (flicker) perimetry. Because the symptoms of migrainous visual aura are consistent with a cortical origin and are accompanied by changes in blood flow within cortical areas responsible for vision, other visual field deficits associated with migraine would be expected to be cortical. Although reports of homonymous deficits exist, these are the exception. Most deficits are reported to be unilateral and nonhomonymous, which implies involvement of the prestriate visual pathways. Functional deficits have also been identified in migraine patients using psychophysical methods that measure prestriate function.

The potential significance of visual field loss in migraine patients should be considered in light of evidence of an increased prevalence of migraine in patients with glaucoma. However, this finding has not been universal. Vasospastic disorders, including migraine, have been suggested to be more common in individuals with glaucoma, and these conditions may share etiologic factors such as abnormalities in vascular regulation.

Although a relationship between migraine and glaucoma may exist, prestriate visual field deficits have been demonstrated between migraine attacks in young migraine patients with normal intraocular pressures and optic disc appearance.

Although visual field deficits have been demonstrated in migraine patients using standard achromatic perimetry (SAP), more substantial visual field loss has been identified using flicker perimetry, a technique that has also been shown to be effective in detecting glaucomatous visual field loss. These tests are designed to assess the magnocellular pathways, which are likely to be sensitive for early loss because these cells are sparse (approximately 10%-20% of ganglion cells). Therefore, if even a small proportion of neurons are affected by disease, a deficit may be manifest owing to reduced redundancy.
PATIENTS AND METHODS

Twenty-five individuals with a history of migraine participated in the study. Migraines were classified as with (n=11) and without (n=14) aura to meet the classification criteria of the International Headache Society.34 All subjects in the aura group had visual symptoms. The test protocol was approved by the Institutional Review Board of Legacy Health Systems, Portland, Ore, and all subjects gave written informed consent before commencement of the test procedures, in accordance with the tenets of the Declaration of Helsinki.

The control group consisted of 20 subjects free of headache as established by means of a questionnaire and a clinical interview. Subjects were aged 18 to 40 years. No statistically significant difference was found among the mean (±SD) ages of the 3 groups (migraine patients with aura, 32.4±5.9 years; migraine patients without aura, 27.7±6.5 years; and controls, 29.9±5.6 years; analysis of variance, P=.16). Migraine patients and controls were recruited from within Legacy Health Systems or by means of advertisement in local newspapers. Three migraine patients (2 patients with aura and 1 without), and 4 controls were recruited from within our laboratory. Only these subjects had previous SAP experience. Only 1 subject had previous SWAP experience.

A routine eye examination was performed to ensure that all subjects had normal optic disc appearance, intraocular pressure of less than 21 mm Hg, results of slitlamp examination within the reference range, visual acuity of 20/20 or better, and refractive errors of less than 6.00 diopters (D) sphere and 2.00 D cylinder. Subjects were required to be free of systemic disease and systemic medications known to affect visual function. None of the migraine patients was receiving preventive drug therapy.

Migraine patients underwent testing at least 4 days after a migraine to minimize possible transient effects on performance due to medications, nausea, or postmigraine fatigue.

Other visual mechanisms that are sparsely represented may also manifest deficits in migraine patients, particularly the short-wavelength sensitivity (SWS) pathways. The SWS deficits have been demonstrated in glaucoma,32-35 diabetes,34-38 and retinitis pigmentosa.34,35 The SWS pathways may be sensitive to damage, as SWS photoreceptors are particularly susceptible to vascular insult and light damage.30,36 However, the presence of SWS pathway deficits in a wide variety of diseases implies receptor and postreceptor (involving the SWS neural pathways) sites of damage. Psychophysical evidence of damage at postreceptor sites has been measured in diabetic patients.41 Alternatively, a non–SWS-specific loss may be manifest earlier in the sparsely represented SWS system owing to reduced redundancy.31 The sensitivity of the SWS pathway is commonly assessed in glaucoma using short-wavelength automated perimetry (SWAP).32,33 This method has been shown to be superior to SAP for detection of early functional glaucomatous damage.32,42,44

In this study, SWAP was used to measure the sensitivity of the SWS pathway across the central visual field. In 2 migraine patients who demonstrated SWAP deficits, the sensitivities of SWS (blue/pi-1) and middle-wavelength sensitivity (MWS) (green/pi-4) pathways were compared using the Stiles 2-color increment threshold technique40 to determine whether a selective loss of SWS pathway sensitivity or losses in MWS pathway sensitivity were present. Two-color increment thresholds have been used previously to demonstrate selective losses of SWS pathway sensitivity in early diabetic retinopathy34,36 and deficits in MWS and SWS pathway sensitivity in glaucoma and retinitis pigmentosa.34,36

RESULTS

Figure 2 presents the MD and PSD values for SAP and SWAP for the migraine (with and without aura) patient and control groups. The significance level of the t tests after adjustment by means of the Hochberg procedure are also given in Figure 2. No significant difference was found between the group means for MD or PSD for SAP. However, for SWAP, significant differences were present between the combined migraine and the control groups for MD and PSD.
Individual migraine subject performance was also analyzed on a pointwise basis, using the control group to determine a 95% confidence interval for each point in the visual field. If the thresholds at individual points are independent (which they may not be), the probability that n points (from a total of N) fall below the lower confidence limit (CL) is determined using the following equation46:

\[ N_{\alpha,n} = (1 - \alpha)N - n \]

where \( \alpha \) is the probability an individual point will fall outside the control CL (\( \alpha = 0.025 \)), and \( N_{\alpha,n} \) is the binomial coefficient that determines the number of uniquely different ways in which a subset of \( n \) points may be chosen from a larger set of \( N \) points and is equivalent to \( N!/[n!(N-n)!] \). The factorial expansion is signified by \( \alpha \), which determines the number of ways that a set of numbers can be ordered and is equal to \( N = N \times (N-1) \times (N-2) \times (N-3) \times \ldots \times 3 \times 2 \times 1 \), where \( N \) is a positive integer.

For the 2×2 test pattern, the number of test points is 14. The points above and below the blind spot were excluded from analysis, resulting in 52 points. From equation 1, visual fields were judged to be abnormal (\( P < 0.05 \)) if they had 4 or more points below our lower CL (\( P = 0.025 \) for a single point) determined from the control data.

We used a modified Humphrey field analyzer I to perform a Stiles 2-color increment threshold procedure to assess SWS (blue) and MWS (green) pathway sensitivity. We measured thresholds using a Goldmann size V blue target superimposed on a yellow background (Schott OG530 filter).55 Conditions were selected to measure Stiles pi-4 (MWS) and pi-1 (SWS) mechanisms.45 This concept has been described in detail by Demirel and Johnson.45 For low-luminance yellow backgrounds, detection of a large blue target is mediated by MWS pathways (or rods if very low luminances). For the SWS mechanism to become responsible for detection of the blue target, sensitivity of the MWS mechanism must be reduced. This reduction is achieved by displaying a bright yellow background. Adaptation to the bright yellow background reduces the sensitivity of the MWS pathway, and the SWS mechanism becomes responsible for detection of the blue target. If sensitivity to the blue target is measured at a range of yellow background intensities (from dim to very bright), a characteristic 2-branch curve is obtained as illustrated schematically in Figure 1. It is well documented that the lower branch represents detection by MWS mechanisms, and the upper branch, detection by SWS mechanisms.45

Thresholds to the blue target were measured at 16 adapting field intensities, beginning at 0.1 cd/m². After 10 minutes of dark adaptation, thresholds were measured at 2 locations (one of normal SWAP sensitivity, and the other of reduced SWAP sensitivity at the same eccentricity) using the Humphrey full-threshold algorithm. Thresholds were measured twice at each location for each background intensity, and the mean of both measurements was taken as the final threshold. After each increment in background intensity, 2 minutes of adaptation to the new background was required before measuring thresholds.

The background intensity levels and the mean thresholds provided by the Humphrey field analyzer at each background intensity were converted to quantum units (quanta·sec⁻¹·degree⁻²) as recommended by Wyszecki and Stiles,65 using the method detailed by Sample et al.67 The threshold-vs-intensity (TVI) curves were the best fit of the following equation56,57:

\[ \Delta I = A[I(I+1)]/P \]

where \( \Delta I \) is the increment threshold; \( A \), the ordinate intercept; \( I \), the background intensity; \( I \), the background intensity where the TVI curve begins to adapt; and \( n \), the exponent that describes the slope of the function.

For SAP, 5 (20%) of 25 migraine patients had 4 or more points outside the lower bounds of the control group 95% CL. Within this group of 5 subjects, 3 had bilateral and 2 had unilateral involvement. The bilateral involvement was not homonymous and not obviously consistent with a cortical origin. For SWAP, 12 (48%) of 25 migraine patients had 4 or more points outside the lower bounds of the control group 95% CL. Of this group of 12 patients, 6 had unilateral and 6 had bilateral deficits. Six of the subjects had the depressed locations clustered in the superior arcuate nerve-fiber bundle region, 3 had abnormal locations clustered in the inferior arcuate nerve-fiber bundle region, and 3 had scattered locations of loss. None of the subjects had bilateral homonymous deficits. None of the controls had 4 or more points outside the 95% CLs for SAP or SWAP.

The Table shows the number of subjects in each migraine group with abnormal performance measured on a pointwise basis for SAP and SWAP. Inspection of the Table shows similar involvement in both migraine groups. No significant difference was found between the migraine groups for MD or PSD on SAP or SWAP (t test, \( P > 0.05 \)). This result should be viewed with caution, as our limited sample size (11 migraine patients with and 14 without aura) results in a power of 0.70 to detect a difference of 2 dB. Nevertheless, no trend for different performance was found between the migraine groups.

We measured TVI curves for 2 migraine patients, one with and one without aura, who had abnormal performance on SWAP. Both subjects demonstrated normal thresholds for SAP.

The migraine patient with aura was a 28-year-old woman with a typical migraine frequency of 2 weeks. Her initial SWAP visual field assessment was conducted 9 days after migraine (Figure 3A). She returned on 2 further occasions for measurement of TVI curves. These visits were performed 24 hours and 14 days after the same migraine. On both occasions, increment threshold data were collected for her left eye at a relatively depressed visual field location (3° nasal and 9° superior) and a location of normal sensitivity at the same eccentricity (3° nasal and 9° inferior). The increment threshold data collected at 24 hours after migraine is displayed in Figure 3B and at 14 days after migraine in Figure 3C.
The migraine patient without aura was an 18-year-old woman with a typical migraine frequency of 1 month. Her initial SWAP visual field was measured 2 weeks after migraine. She returned for 2 further examinations to measure increment threshold data, at 6 days and 3 weeks after the same migraine. Increment thresholds were measured at 3° nasal and 9° superior and at 3° temporal and 9° inferior in her left eye. The increment threshold data collected at 6 days after migraine is displayed in Figure 4B and at 3 weeks after migraine in Figure 4C.

Both migraine patients show sensitivity losses for MWS and SWS pathways; however, the relative loss of SWS pathway function was greater than that of the MWS pathway. The logarithm decrease in sensitivity at background intensities of 7 quanta·sec⁻¹·degree⁻² (a measure of MWS pathway function) and 9 quanta·sec⁻¹·degree⁻² (a measure of SWS pathway function) for the affected location of visual field is plotted in Figure 5. For each subject, the data presented are the mean of the 2 visits. Figure 5 demonstrates the relatively greater loss of SWS pathway function in these 2 individuals.

**COMMENT**

The SWS deficits were common in migraine patients (12/25 [48%]) when compared with a group of headache-free subjects of similar age. The visual field loss was suggestive of prestriate rather than cortical involvement, as
there was an absence of bilateral homonymous deficits. This does not necessarily exclude cortical involvement; however, we found no direct evidence of such involvement in our subject group. Migraine patients with and without visual aura showed similar degrees of loss (Table and Figures 3 and 4), suggesting that the visual field deficits are independent of the cortical involvement present during the aura phase of the attack.

Migraine patients are reported to demonstrate increased susceptibility to glare and ocular discomfort between attacks, and these hypersensitivities may arise owing to interruptions in cortical inhibition.\textsuperscript{38-60} No evidence of hypersensitivity was found in our migraine group, and subjects did not report excessive discomfort during assessment. As our experiments were not designed specifically to consider these issues, we cannot rule out the possibility of heightened aversive responses in our migraine group resulting in losses of concentration and elevated thresholds. Visual discomfort in migraine patients has been demonstrated previously for foveal viewing using gratings stimuli of 3 to 4 cycles per degree.\textsuperscript{59,60} However, our measures were for spot targets in the periphery, and we think cortical hypersensitivity to illusory stimuli was unlikely to be a significant factor in the visual dysfunction measured in this study.

The mechanism and site of SWS loss in migraine remains to be elucidated. Increment threshold data from 2 subjects (Figures 3 and 4) suggest that the SWS pathway is more affected than the MWS pathway, although a larger cohort of subjects must undergo testing. The SWS pathways are particularly vulnerable to retinal disease, with evidence of dysfunction of the photoreceptors and postreceptor sites. In diabetes, metabolic abnormalities and hypoxia are thought to contribute to the selective SWS pathway deficits in early diabetic retinopathy.\textsuperscript{34} Abnormalities in ocular vascular
regulation may be present in migraine, as abnormalities in cold-induced vascular regulation in the finger have been reported in migraine patients.\textsuperscript{61,62} Although recent studies of cortical function find no evidence of ischemia during migraine events,\textsuperscript{63,64} similar studies have not been performed to verify the presence or absence of peripheral hypoxia during the course of a migraine or at other times.

What is the clinical significance of SWS loss in migraine? Although visual dysfunction in migraine likely arises owing to attrition caused by disease, at present no data support or reject this hypothesis. Longitudinal data are required to determine whether such visual field deficits are transient or permanent, or whether they are progressive. A relationship between time after migraine and visual field deficit severity has been reported using kinetic perimetry,\textsuperscript{3} and using flicker perimetry for several individual patients.\textsuperscript{3,65}

Most estimates of migraine prevalence range from 12% to 15%, with the prevalence for women being about twice that for men.\textsuperscript{66-68} Although visual field studies have only been conducted on small samples of migraine patients, reports suggest that 20% to 40% demonstrate visual field deficits for SAP,\textsuperscript{1,3,11} approximately 67% for flicker perimetry,\textsuperscript{3} and about 48% (12/25) for SWAP (present study). If these estimates are representative of migraine patients, we predict that 2.5% to 7% of the general population may demonstrate some form of visual field abnormality in association with migraine.

The possibility of large numbers of migraine patients demonstrating abnormal visual fields raises several interesting issues. First, migraine patients should be excluded from normative databases of visual performance. The high prevalence of SWAP sensitivity loss in migraine patients may account for part of the greater inaccuracy of SWAP compared with SAP.\textsuperscript{66-68} Second, a challenge remains in determining the relationship, if any, between prestriate visual dysfunction in migraine and glaucoma. Migraine has been suggested as a vascular risk factor for glaucoma\textsuperscript{20-24}, however, the relationship between these conditions is not a simple one. Primary open-angle glaucoma affects approximately 3% of the population older than 40 years.\textsuperscript{69,70} Within this glaucomatous population, estimates of migraine prevalence vary, but most range from 17% to 25%.\textsuperscript{14,15,19,71} Hence, approximately 0.6% of the general population has glaucoma and migraine. Within the general population, 2.5% to 7% may have visual field dysfunction in association

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Figure 4. Left eye short-wavelength automated perimetry visual field performance measured 2 weeks after migraine in a patient with migraine without aura (A). Increment threshold data were measured 6 days (B) and 3 weeks (C) after migraine in the left eye of the same subject. Solid symbols represent thresholds measured at a location of normal sensitivity (3° nasal and 9° superior); open symbols, thresholds for a location of depressed sensitivity (3° temporal and 9° inferior). MD indicates mean deviation; PSD, pattern-standard deviation.
with migraine in the presence of normal optic nerve appearance and normal intraocular pressure. Whether this group of patients has a higher risk for glaucoma is currently unknown.

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