Title page

Clinical impact of migraine for the management of glaucoma patients

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Article highlights (3-5 points, max 85 characters including spaces per point)

- People with migraine show visual abnormalities in between attacks
- These abnormalities are detectable using standard clinical tests for glaucoma
- Glaucoma evaluation is potentially confounded by the presence of migraine

Abstract

Migraine is a common and debilitating primary headache disorder that affects 10-15% of the general population, particularly people of working age. Migraine is relevant to providers of clinical eye-care because migraine attacks are associated with a range of visual sensory symptoms, and because of growing evidence that the results of standard tests of visual function necessary for the diagnosis and monitoring of glaucoma (visual fields, electrophysiology, ocular imaging) can be abnormal due to migraine. These abnormalities are measureable in-between migraine events (the interictal period), despite patients being asymptomatic and otherwise healthy. This picture is further complicated by epidemiological data that suggests an increased prevalence of migraine in patients with glaucoma, particularly in patients with normal tension glaucoma. We discuss how migraine, as a comorbidity, can confound the results and interpretation of clinical tests that form part of contemporary glaucoma evaluation, and provide practical evidence-based recommendations for the clinical testing and management of patients with migraine who attend eye-care settings.

Keywords

Migraine, glaucoma, perimetry, electrophysiology, imaging

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Contents

1 Introduction

Migraine is a common, debilitating primary headache disorder affecting 10-15% of people worldwide, particularly people of working age (Stovner et al. 2007). It is ranked in the top 20 most disabling conditions worldwide (Leonardi and Raggi 2013, World Health Organisation 2001), with 90% of migraine sufferers reporting significant impairment to activities of daily living (Lipton et al. 2001a). Attacks of migraine are episodic. The asymptomatic periods in between acute events are known as the interictal period. Typical migraines are characterised by headache, nausea and/or vomiting, sensitivity to light (photophobia) and sound (phonophobia) (International Headache Society 2013), and are associated with transient sensory symptoms that are predominantly visual. For example, many people experience mild blurring of vision during attacks (Hupp et al. 1989, Vincent et al. 1989), and approximately 30% of migraine sufferers experience a neurological aura as part of their migraine events, with over 90% of these being visual in nature (Kelman 2004a, Russell and Olesen 1996).

Given the prevalence of migraine in the general population (Stovner et al. 2007) and the predominance of visual symptoms within this group, clinicians in eyecare settings will regularly encounter patients with migraine. Often patients will seek eye examinations because of the visual symptoms associated with their migraine headaches, and in some cases, may not be aware that their symptoms are consistent with migraine. Approximately 50% of migraine sufferers have never consulted a physician nor received a formal diagnosis of migraine (Cooke and Becker 2010, Diamond et al. 2007, MacGregor et al. 2003). Moreover, migraine can occasionally be accompanied by permanent neurological changes such as paralysis (previously referred to as ‘complicated’ migraine). It is therefore imperative that clinicians are able to recognise migraine characteristics, differentiate the danger signs, and consider other more sinister causes of neurological dysfunction, which have been discussed in detail by others (Corbett 1983, Friedman 2004, Hupp et al. 1989, Maxner and Moeller 2005, Shams and Plant 2011) and are not covered here.

Alternatively, patients may present for routine eye-care for reasons unrelated to their migraines. In these instances, it is likely that they will present during the interictal period, whilst migraine-free and asymptomatic. However, during this period of apparent normality, visual and ocular abnormalities can be detected using standard,

clinical tests of vision – namely visual fields, electrophysiology, and ocular imaging. These tests are the very tests used commonly in research and clinical practice for the diagnosis and management of glaucoma. The picture is further complicated by epidemiological data suggesting that migraine is significantly more common (~30%) in patients with glaucoma than in non-glaucoma controls (~10-15%), particularly in patients with normal tension glaucoma (Corbett et al. 1985, Cursiefen et al. 2000, Phelps and Corbett 1985). Thus, migraine, as a co-morbidity, has the potential to confound the interpretation of clinical test results that form part of contemporary glaucoma assessment. Here, we provide an overview of the currently available technologies and clinical tests for glaucoma evaluation that have been applied to the study of migraine patients, and discuss the challenges in interpreting the test results of patients who suffer from migraines.

2 Definition and diagnosis of migraine

2.1 The International Classification of Headache Disorders

Migraine is diagnosed purely by its symptomatology, as detailed in the International Classification of Headache Disorders (ICHD), which were first published in 1988 and most recently updated in 2013 (International Headache Society 2013). Previously, migraine was classified using a range of terminology (e.g. ‘classic’, ‘common’, ‘complicated’, ‘hemicrania simplex’, ‘hemiparaesthetic’). The ICHD classifications are the result of a concerted effort to consolidate terminology into a single comprehensive resource and to provide quantitative methods for the diagnosis of headache-related conditions for clinical and research purposes. Therefore, this review will primarily discuss findings of studies that have explicitly classified migraine patients according to these recognised guidelines, where possible (i.e. after 1988).

2.2 Diagnostic criteria for migraine with and without aura

The two most common subtypes of migraine are ‘migraine without aura’ (MO, Table 1) and ‘migraine with aura’ (MA, Table 2), affecting 50% and 30% of migraine sufferers, respectively (Rasmussen and Olesen 1992). The distinguishing factor between MO and MA is the presence of aura, which consists of transient neurological disturbances of sight, speech, or tingling/numbness of the face or body. The majority of migraine auras are associated with headache, known as ‘typical aura with migraine headache’ (International Headache Society 2013), which will be referred to herein as

the more general term ‘migraine with aura’. Less commonly, aura can be associated with migraine headaches that do not fulfil the ICHD diagnostic criteria for MO as listed in Table 1 (known as ‘typical aura with non-migraine headache’), or can occur without headache (‘typical aura without headache’), which are not discussed here. Similarly, rarer forms of migraine that are excluded from studies of migraine are not discussed in this review (e.g. familial hemiplegic migraine, sporadic hemiplegic migraine, basilar-type migraine), but are described in detail in the ICHD (International Headache Society 2013).

The symptoms of a migraine attack generally occur in sequential phases (the ictal period), although not all of these phases are present at every episode (Charles 2013). Up to 48 hours before the headache, people may experience prodromal symptoms such as irritability, food cravings, and difficulty concentrating (Becker 2013, Kelman 2004b). During attacks of migraine with aura, the neurological disturbances of aura last between 5 and 60 minutes and subside before the onset of headache (Kelman 2004a, Rasmussen and Olesen 1992, Russell and Olesen 1996); although in some cases, aura symptoms may accompany rather than precede the headache (International Headache Society 2013). The duration of the headache phase of both MO and MA is 4-72 hours and is characterised by photophobia, phonophobia, and nausea and/or vomiting (International Headache Society 2013). After the headache, people may experience postdromal symptoms that last on average 24 hours, including lethargy and moodiness (Blau 1991, Kelman 2006). Once symptoms have subsided, the person is typically asymptomatic (during the interictal period) until the next attack occurs.

Table 1. Diagnostic criteria for 'migraine without aura' (MO) according to the most recent International Classification of Headache Disorders (International Headache Society 2013). MO is characterised by headache with specific features and associated symptoms, which must all be present (Items A-E) to be diagnosed and coded as 'MO'.

A	At least 5 attacks fulfilling criteria B-D
B	Headache lasting 4 to 72 hours (untreated, or unsuccessfully treated)
C	Headache has at least <u>two</u> of the following characteristics: (1) unilateral location (2) pulsating quality (3) moderate or severe pain intensity (4) aggravation by, or causing avoidance of, routine physical activity (e.g. walking or climbing stairs)
D	During headache, at least <u>one</u> of the following: (1) nausea and/or vomiting (2) photophobia and phonophobia
E	Not attributed to another disorder

Table 2. Diagnostic criteria for 'typical aura with migraine headache' (migraine with aura, MA) according to the most recent International Classification of Headache Disorders (International Headache Society 2013). MA is characterised by an 'aura' consisting of fully reversible visual and/or sensory and/or speech symptoms, which usually precede or sometimes accompany the headache. The headache of MA must fulfil the diagnostic criteria for MO (Table 1), and items A-E must all be present to be diagnosed and coded as 'MA'.

A	At least 2 attacks fulfilling criterion B-D and Migraine aura fulfilling criteria B and C
B	Aura consisting of at least <u>one</u> of the following, but no motor weakness: (1) fully reversible visual symptoms including positive features (e.g. flickering lights, spots, or lines) and/or negative features (i.e. loss of vision) (2) fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness) (3) fully reversible dysphasic speech disturbances
C	At least <u>two</u> of the following: (1) homonymous visual symptoms and/or unilateral sensory symptoms (2) at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes (3) each symptom lasts ≥ 5 and ≤ 60 minutes
D	Headache fulfilling criteria B-D for migraine without aura (Table 1) begins: (1) during the aura, or (2) follows aura within 60 minutes
E	Not attributed to any other disorder

2.3 Screening for migraine

We have provided the ICHD diagnostic criteria for MO and MA (International Headache Society 2013) because migraine research typically differentiates between these two most common subtypes. However, whether MO and MA are separate conditions remains a point of controversy (e.g. see Manzoni and Torelli 2008 versus Purdy 2008). Apart from the presence of aura, MO and MA share the same clinical characteristics: headache, photophobia, phonophobia, nausea/vomiting, and prodromal and postdromal symptoms. An added complexity is that over a lifetime, approximately 8% of migraine sufferers can alternate between MO and MA attacks (Rasmussen and Olesen 1992). For the purpose of this review, we limit our discussion to people who suffer typical migraine headaches in general, which encompass both MO and MA as the most common subtypes. Table 3 describes a three-item questionnaire ('ID Migraine', Table 3), which has 81% sensitivity and 75% specificity for migraine headache when a person scores positively on any two out of the three items (Lipton et al. 2003). The three item questionnaire can be supplemented by reference to the specific ICHD diagnostic criteria (Tables 1 and 2) to classify migraine sufferers into those with MO or MA. In some cases, patients may have frequent attacks of migraine with aura but also some attacks without aura, in which case the person is diagnosed as having both MO and MA (International Headache Society 2013).

Table 3. 'ID Migraine' screening tool for migraine headache (Lipton et al. 2003)

	During the last 3 months, did you have the following with your headaches?
1	Felt nauseated or sick to your stomach? □ Yes □ No
2	Light bothered you (a lot more than when you don't have headaches)? □ Yes □ No
3	Your headaches limited your ability to work, study, or do what you needed to do? □ Yes □ No

3 Pathophysiology of migraine

There is general consensus for cortical pathophysiology in migraine (Charles 2013, Pietrobon and Moskowitz 2013, Schwedt and Dodick 2009, Vecchia and Pietrobon 2012). For example, the classically described visual aura – the scintillating scotoma (Alvarez 1960, Grusser 1995, Hupp et al. 1989, Kelman 2004a, Lashley 1941, Queiroz et al. 1997, Schott 2007) – is homonymous and hemianopic, implying a cortical origin. The physiological substrate for visual aura is a neural phenomenon known as 'cortical spreading depression' (Charles and Baca 2013, Pietrobon and Moskowitz 2014, Schwedt and Dodick 2009), which is a slowly propagating wave of neuronal depolarisation across the brain (Leao 1944) with associated changes in local cerebral blood flow (Heeger and Ress 2002). Waves of reduced regional blood flow have been shown to spread across the visual cortex at the same rate (approximately 3 mm/min) and correspond in size to the progression of visual aura during a migraine attack (Cao et al. 1999, Grusser 1995, Hadjikhani et al. 2001, Lauritzen et al. 1983, Olesen et al. 1981). Susceptibility to cortical spreading depression, and to the triggering of a migraine attack, is believed to arise from cortical excitatory/inhibitory imbalance (Vecchia and Pietrobon 2012).

Further, evidence for the cortical pathophysiology of migraine is being pieced together by knowledge gained from advanced structural and functional neuroimaging (Schwedt et al. 2015, Schwedt and Dodick 2009, Tedeschi et al. 2013), transcranial magnetic stimulation (Brighina et al. 2013, Brigo et al. 2013, Cosentino et al. 2014), transcranial direct current stimulation (Brighina et al. 2013, Cosentino et al. 2014), and electrophysiology (Ambrosini et al. 2003, de Tommaso et al. 2014, Magis et al. 2007, Magis et al. 2013). There is also evidence for altered visual perception in between migraine attacks that is consistent with changes to cortical function (Antal et al. 2005, Battista et al. 2010, Battista et al. 2011, Ditchfield et al. 2006, McColl and Wilkinson 2000, McKendrick et al. 2011, Shepherd 2001, Shepherd 2006, Thabet et al. 2013, Wilkinson et al. 2008). We will not discuss this extensive literature base further in this review, which demonstrates clear cortical involvement in migraine both ictally and in between events. Rather, we will concentrate on findings that are relevant and potentially confounding with respect to glaucoma diagnosis and management.

4 Relevance of migraine to glaucoma

4.1 Potential epidemiological link between migraine and glaucoma

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy characterised by retinal ganglion cell degeneration and apoptosis (Nickells 1996, Weinreb et al. 2014). Global estimates of POAG prevalence in people aged 40-80 years are approximately 3.5% (Tham et al. 2014). Migraine affects 10-15% of the general population (Stovner et al. 2007), with the highest prevalence among the working age demographic (25-55 years) (Bigal and Lipton 2009, Stewart et al. 1994, Stovner et al. 2007). Clearly, the difference in prevalence rates means that not all migraine sufferers will develop glaucoma. Indeed, some studies find no significant difference in migraine prevalence between glaucoma and non-glaucoma control groups (Klein et al. 1993, Orgul and Flammer 1994, Usui et al. 1991).

However, other epidemiological reports find migraine is more common (~30%) in patients with glaucoma relative to the general population (10-15%) (Perruccio et al. 2007, Pradalier et al. 1998, Wang et al. 1997), which suggests migraine is an added risk factor for developing glaucoma. The Australian Blue Mountains Eye Study stratified data by age and found a greater likelihood (odds ratio: 2.5, 95% CI 1.2–5.2) of developing POAG in elderly patients aged 70-79 years with a past self-reported history of migraine, compared to people who had never experienced a migraine in their lives (Wang et al. 1997). The Glaucoma Inheritance Study additionally found that a past history of migraine was significantly associated with familial glaucoma (positive family history of POAG) compared to those with sporadic glaucoma (no known or identified relative affected with POAG) (Hewitt et al. 2010), implying that systemic co-morbidities such as migraine are important heritable factors contributing to susceptibility to glaucoma.

4.2 Potential pathophysiological link between migraine and glaucoma

Migraine is a disorder of the central nervous system, with both neural and vascular involvement as part of its pathophysiology (Charles 2013, Pietrobon and Moskowitz 2013, Schwedt and Dodick 2009, Vecchia and Pietrobon 2012). The pain of a migraine headache is attributed to the activation and sensitisation of the trigeminovascular system (reviewed by Noseda and Burstein 2013). Activation of nociceptors innervating the intracranial vasculature and the meninges leads, in part, to

the release of vasoactive peptides such as calcitonin gene-related peptide (Ho et al. 2010) and pro-inflammatory mediators that act directly on cerebral blood vessels to modulate vascular diameter during an acute attack (Noseda and Burstein 2013).

Transient, abnormal changes in blood vessel diameter are not, however, confined to cranial vessels during the attack period, but can also occur during the interictal period in peripheral organs such as the finger (Gasser and Meienberg 1991, Hegyalijai et al. 1997) and the eye of individuals with migraine (Abdul-Rahman et al. 2011, Flammer et al. 2013, Killer et al. 2003). These changes in blood vessel calibre are considered indicative of vasospasm, or more broadly referred to as 'vascular dysregulation' (Flammer et al. 2013). Indeed, epidemiological studies suggest that migraine is more prevalent in people with peripheral vasospastic disorders such as Raynaud's phenomenon (O'Keeffe et al. 1993, Takats et al. 2012, Zahavi et al. 1984) and angina (Rose et al. 2004).

Vascular factors also play a major role in the pathophysiology of glaucoma (Flammer and Orgul 1998, Flammer et al. 2002, Yamamoto and Kitazawa 1998). A particular form of glaucoma, normal tension glaucoma (NTG), is associated with retinal vascular dysregulation (Broadway and Drance 1998) and poor blood flow at the optic nerve head (Plange et al. 2003). Accordingly, several authors have posited a common vasospastic mechanism between NTG and migraine (Flammer et al. 2013, Flammer et al. 2001, Gasser et al. 1990). This hypothesis is supported by epidemiological reports of increased prevalence of migraine particularly amongst patients with NTG (Corbett et al. 1985, Cursiefen et al. 2000, Phelps and Corbett 1985).

The potential for retinal dysregulation in migraine sufferers is problematic because it may lead to irreversible visual and ocular abnormalities. Episodes of retinal vasospasm could plausibly underlie the case reports of retinal vascular occlusions in migraine sufferers (e.g. Gutteridge et al. 2007). In relation to glaucoma, Broadway and Drance found that the presence of vasospasm and migraine was higher in glaucoma patients with focal ischaemia of the optic nerve head and subsequent focal loss of neuroretinal rim than those with other types of glaucomatous damage (Broadway and Drance 1998). The Low Pressure Glaucoma Treatment Study reported that a history of migraine constituted a significant and independent risk factor for optic disc haemorrhages (Furlanetto et al. 2014), which are commonly seen in NTG and have been shown to increase the risk of onset and progression of the disease

(reviewed by Suh and Park 2014). Furthermore, visual field defects in patients with NTG are more likely to progress if there is a concurrent history of migraine (Drance et al. 2001). The hypothetical link between migraine and glaucoma has led to increasing numbers of studies investigating the potential for 'glaucomatous-like' dysfunction in people with migraine using common clinical tests of vision.

5 Clinical tests for glaucoma likely to be abnormal in patients with migraine

Glaucoma is a progressive optic neuropathy characterised by degeneration and loss of retinal ganglion cells and their axons (Nickells 1996), accompanied by structural changes in the optic nerve head and functional changes in visual field sensitivity (reviewed by Weinreb et al. 2014). There is no single test that can diagnose the condition or monitor its progression in isolation. Rather, current clinical practice relies on a combination of clinical measures of retinal structure and function using perimetry, electrophysiology, and ocular imaging for diagnosis and management. The potential for these test results to be abnormal in people with migraine will be discussed next as the main emphasis of this review.

5.1 Visual field tests

Assessment of contrast sensitivity across the visual field using perimetry remains the mainstay of clinical evaluation of visual function in glaucoma. To aid in the interpretation of visual field loss, global indices are determined relative to each perimeter's proprietary age-matched normative database, providing single summary statistics to describe visual field performance. Typical indices include a metric of global sensitivity, such as Mean Defect on the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, California, United States) or Average Defect on the Medmont perimeter (Medmont International Pty Ltd., Melbourne, Australia), while localised losses are described by Pattern Defect on the Medmont perimeter, Pattern Standard Deviation on the Humphrey Field Analyzer, or Loss Variance on the Octopus perimeter (Haag-Streit AG, Koeniz, Switzerland). In addition to these global indices, some studies of visual field performance in people with migraine have also recruited a specific age-matched non-headache control group for comparison. Under both circumstances, visual field defects have consistently been identified in people with migraine during the interictal period. Similar to glaucoma, these visual field defects have been found using a range of different visual stimuli and perimetric techniques

that rely on visual processing at various stages along the retinogeniculate (pre-cortical) pathways

5.1.1 Visual field defects in people with migraine identified using different perimetric techniques

5.1.1.1 White-on-white perimetry

Static automated perimetry (SAP) is the most common clinical perimetric tool and has been widely used to measure visual performance in people with migraine. The test measures sensitivity to an achromatic, briefly presented stimulus that is non-selective for pre-cortical visual pathways (Swanson et al. 2011). SAP has identified visual field defects in 20-60% of migraine sufferers in between their attacks (Figure 1) (De Natale et al. 1993, Dersu et al. 2013, Lewis et al. 1989, McKendrick et al. 2000, Nguyen et al. 2014, Nizankowska et al. 1997). Visual field sensitivity can also be mapped by kinetic perimetry using a similar achromatic but moving target. Kinetic perimetry has identified reductions in visual field extent in people with migraine, one day to one week after an attack (Drummond and Anderson 1992).

When studies have specifically compared people with migraine to age-matched non-headache controls, substantial numbers of subtle visual field defects (20-50% of migraine participants) are identified (Drummond and Anderson 1992, McKendrick et al. 2000, Nguyen et al. 2014). While these visual field deficits may not be classified as abnormal using standard clinical criteria based on the perimeter's global indices, this may partially reflect the contamination of the commercial normative dataset with people who have migraine. Given the prevalence of migraine worldwide (10-15%, Stovner et al. 2007), the inclusion of some migraine sufferers in the normative database is highly likely. This has prompted the suggestion of excluding regular migraine sufferers from normative perimetric databases to increase the likelihood of detecting abnormal results (McKendrick and Badcock 2004b, McKendrick et al. 2000), which is especially important when trying to differentiate glaucomatous damage from visual field loss associated with migraine.

Note that it is unlikely that people with migraine show worse visual field sensitivity than their control counterparts because they are poorer performers. Neither control nor migraine groups are more experienced at visual field testing, as all participants are recruited as naïve observers using the same selection criteria. Neither is the quality of

the visual field tests different between groups. Reliability indices (fixation loss, false positive rate, false negative rate) of all visual field test results are required to meet standard clinical criteria to be included. Moreover, several studies have explicitly ensured that migraine participants are not tested when unwell and are not medicated at the time of testing to minimise possible effects of migraine or migraine medications on concentration or fatigue (McKendrick and Badcock 2004a, McKendrick and Badcock 2004b, McKendrick et al. 2002, McKendrick et al. 2000, Nguyen et al. 2014).

5.1.1.2 Flicker and blue-on-yellow perimetry

Certain perimetric techniques are customised to bias the assessment of specific pre-cortical visual pathways, such as the fast-flickering luminance-pedestal targets of temporal modulation perimetry (TMP), or flicker perimetry, that preferentially test the magnocellular pathway (Vingrys et al. 1994), or the blue-on-yellow stimuli of short wavelength automated perimetry (SWAP), which preferentially tests the koniocellular pathway (Sample and Weinreb 1990). Both TMP (McKendrick and Badcock 2004a, McKendrick and Badcock 2004b, McKendrick et al. 2000, Nguyen et al. 2014) and SWAP (McKendrick et al. 2002, Nguyen et al. 2014, Yenice et al. 2006, Yucel et al. 2005) have identified visual field defects in up to 50% of migraine cohorts. Note that these findings should not be interpreted as evidence for migraine producing a selective loss of one type of processing pathway, as dysfunction in both the magnocellular and parvocellular pathways has been demonstrated in people with migraine using perceptual stimuli designed to assess these channels separately (McKendrick and Badcock 2003, McKendrick and Sampson 2009). Likewise, glaucomatous damage is similarly non-selective, with magnocellular, parvocellular, and koniocellular visual pathways being affected (Yucel et al. 2003). Rather, visual field defects can be apparent on perimetric tasks like TMP and SWAP if there is reduced neuronal redundancy, as is thought to be the case in glaucoma (Johnson 1994). A similar theory can likely explain the losses in migraine.

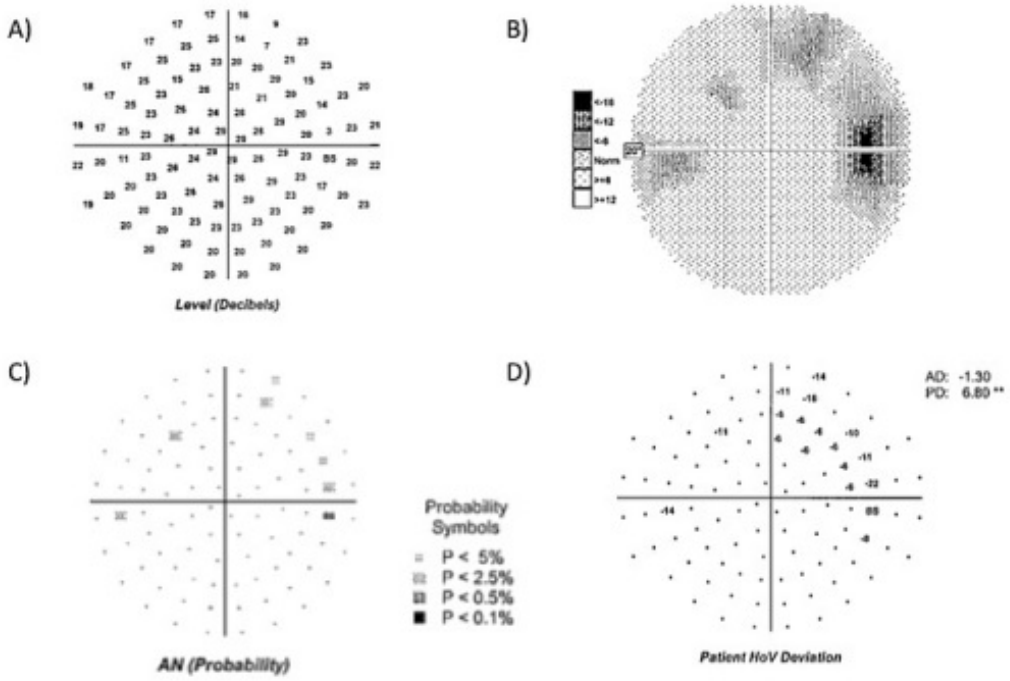

Figure 1. Example visual field result of a migraine sufferer. A 23-year-old patient with migraine without aura (MO) was tested using standard automated perimetry (SAP) on the Medmont M700 perimeter (Medmont International Pty Ltd., Melbourne, Australia) during the interictal period, 4 days after a migraine. The right eye results are shown. (A) Plot showing visual field sensitivity in decibels at each tested location. (B) Greyscale plot showing darker regions that indicate worse performance relative to the age-matched normative database. (C) Age-normal probability plot indicating locations with visual field sensitivity outside the lower confidence limit of age-matched performance (D) Difference plot indicating locations that deviate in visual field sensitivity from the person's hill of vision (HoV). This migraine sufferer showed normal generalised sensitivity, as indicated by the unflagged Average Defect (AD) index that is generated by the Medmont perimeter. However, the Pattern Defect (PD) index was flagged as abnormal at $p < 0.01$ (**) relative to the perimeter's normative database, indicating an area of localised visual field loss (spatially clustered deviations from the person's HoV). The pattern of the defect and the fact that the other eye returned normal results (not shown) implies a pre-cortical origin for the visual field defect.

A challenge for clinicians and researchers using perimetry to assess visual function is that there is no single perimetric algorithm or machine that is universally used. Given the range of different perimetric tests and algorithms available for visual field testing, a pertinent question is whether certain tests are more likely to detect abnormalities in migraine. We tested 45 migraine (26 MO, 19 MA) and 30 non-headache participants using SAP and TMP (Medmont perimeter) and SWAP (Octopus perimeter) on the same day. The migraine participants were tested during the interictal period at least 7 days after a migraine. These sample sizes are typical of the numbers of observers recruited in other studies of visual performance in migraine (20-30 in each group/subgroup), and these visual field tests are examples of the many different test algorithms that are commercially available for perimetry. As people with migraine are not excluded from proprietary normative databases, we used our control group data to determine an empirical lower limit of sensitivity (6^{th} percentile) at each visual field location as a criterion of abnormality (McKendrick et al. 2000). Visual fields were judged to be abnormally depressed ($p < 0.05$) if there were at least 7 locations with sensitivity below the control group 6^{th} percentile ($p < 0.03$ for a single location) out of a total 101 test points on SAP, 5 of 73 locations on TMP, and 4 of 50 locations on SWAP. Using these criteria, 70% of control participants (21 of 30 participants) returned normal results for every eye and every visual field task. On the other hand, 31 of 45 migraine participants (69%) showed abnormal visual field results in at least one eye and on at least one visual field test (chi-square test of proportions: $p < 0.001$). The Venn diagram in Figure 2 indicates the number of individuals with migraine with an abnormal visual field result for each perimetric test (SAP, TMP, SWAP), and combination of tests. There is no consistent loss specific to one visual field testing paradigm during this interictal period, indicating that any one, or combination of perimetric techniques, can uncover deficits in visual field sensitivity in people with migraine, as is also the case in glaucoma (Casson et al. 1993). The prospect for a flicker specific loss of sensitivity under certain conditions will be considered next.

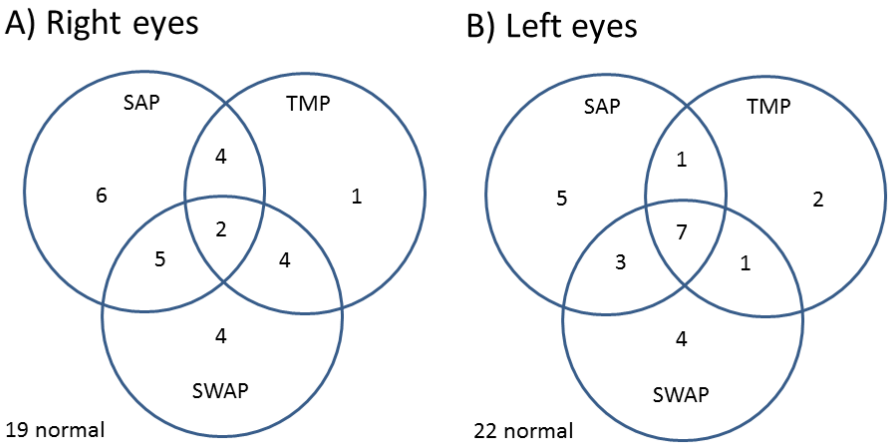

Figure 2. Number and overlap of visual field tests identified as abnormal in people with migraine. The Venn diagram indicates the number of visual field results of (A) right eyes and (B) left eyes of 45 migraine participants (26 MO, 19 MA) considered statistically abnormal ($p < 0.05$). Abnormal sensitivity was determined at each visual field location (one-sided test, $p < 0.03$) against the range of sensitivities measured in 30 non-headache control participants. Static automated perimetry (SAP), temporal modulation perimetry (TMP), and short-wavelength automated perimetry (SWAP) were completed on the same day during the interictal period at least one week after a migraine event.

5.1.1.3 Temporal tuning of visual field defects

Migraine patients typically report aversion and discomfort to flickering stimuli (Karanovic et al. 2011, Thabet et al. 2013, Wilkinson et al. 2008). Convergent evidence from psychophysical studies shows that temporally modulated stimuli have a particular potential to uncover visual deficits in migraine (Antal et al. 2005, Battista et al. 2010, Battista et al. 2011, Ditchfield et al. 2006, Drummond and Anderson 1992, Karanovic et al. 2011, McKendrick and Badcock 2003, McKendrick and Badcock 2004a, McKendrick and Badcock 2004b, McKendrick and Badcock 2004c, McKendrick et al. 2000, McKendrick et al. 2001, Shepherd 2006, Shepherd et al. 2012, Thabet et al. 2013), including flickering stimuli that are thought to be processed pre-cortically (Coleston et al. 1994, McKendrick et al. 2001, McKendrick and Badcock 2003). Such abnormal responses to flickering stimuli in migraine might be relevant to the potential link between migraine and glaucoma, given evidence for temporal processing anomalies in glaucoma (Casson et al. 1993, Eisner and Samples 1991, O'Hare et al. 2012).

Although Figure 2 demonstrates that abnormal visual field results can be found using any combination of SAP, TMP, and SWAP, our other work has shown that flickering targets are more sensitive than static targets for the detection of visual field loss in people with migraine (McKendrick and Badcock 2004b, McKendrick et al. 2002, McKendrick et al. 2000). McKendrick et al (1998) reported a patient who, at 24 hours after a migraine event, returned a substantial arcuate visual field defect on flicker perimetry (Pattern Defect = 13.56 dB). Further testing of this person with precise psychophysical methods found a selective loss of spatio-temporal sensitivity in the area of visual field loss that was tuned to 16 Hz, 0.5 cycles/degree, whereas testing with a 4 cycles/degree and 2 Hz stimulus gave normal outcomes in that same region. Three months later, the arcuate defect had significantly resolved and the Pattern Defect was within age-matched expected values (3.68 dB). This case suggests that flicker sensitivity for relatively fast temporal modulation (16 Hz) compared to slow temporal rates (static or 2 Hz) can be more affected in migraine. Furthermore, the dissociation between responses to static and temporally modulated stimuli appears to change as a function of the recency of headache, in this case being pronounced at 24 hours and near normal 3 months later. Differences in the timing of the test visit in relation to the last migraine attack may therefore influence whether visual dysfunction is evident on flicker perimetry.

Temporal frequency tuning of visual field loss was also confirmed in another study of a subset of four migraine sufferers (3 MA, 1 MO) who had well-defined scotomata on testing with TMP (McKendrick et al. 2000). This subset was taken from a larger cohort of migraine sufferers (n =16) who, on average, demonstrated abnormal visual field results when tested with flickering targets, yet normal results using static stimuli (SAP). Figure 3 shows the Pattern Defect of each individual (n = 4) of the subset when tested at fixed temporal frequencies (4, 6, 9, 12, and 16 Hz). Pattern Defect remained within normal limits (< 2.8 dB) according to the proprietary normative database for frequencies lower than 6 Hz. However, three of the observers demonstrated an increase in Pattern Defect for stimuli modulated at greater than 9 Hz, whereas one observer showed a deficit at frequencies greater than 6 Hz, which raises the possibility that the visual dysfunction in some people with migraine depends on the temporal frequency of visual stimulation. The mechanism for this is unclear; however, one possibility is that flicker is known to increase local metabolic demands

and increase local blood flow in the brain (Pastor et al. 2003) and at the retina and optic nerve (Kiryu et al. 1995, Riva et al. 2005). Some authors have therefore posited that disrupted neurovascular coupling is a key pathophysiological mechanism of migraine (reviewed by Fabjan et al. 2015), whereby for a given level of neural activity, the vascular response is disproportionate to that of non-migraine controls (Zaletel et al. 2005). A similar logic may apply to those patients with NTG, whose glaucomatous damage is believed to be associated with retinal vascular dysregulation (Flammer et al. 1999, Grieshaber et al. 2007), thus providing a common aetiology to explain such deficits.

5.1.2 Spatial characteristics of visual field defects in people with migraine

Occasionally, there have been case reports of homonymous visual field defects in individuals with migraine (e.g. Razeghinejad et al. 2009, Wakakura and Ichibe 1992). In general, no lesions can be found on structural brain scans to account for the visual field loss, but photon emission tomography in one case did detect decreased cerebral blood flow and possible ischaemia in the occipital area (Wakakura and Ichibe 1992). This suggests that cortical visual field defects in people with migraine may be vascular in origin. There is evidence to support an increased susceptibility to ischaemic cerebrovascular events in migraine sufferers, including a greater risk of stroke (Katsarava et al. 2008, Kurth et al. 2012), increased prevalence of rare physiological causes of cerebral infarct such as arterial dissections (Rist et al. 2011) and patent foramen ovale (Schwedt et al. 2008), and increased prevalence of vascular risk factors such as pro-thrombotic factors or markers of blood vessel wall dysfunction (Tietjen and Khubchandani 2015). All of these factors could contribute to clinical and sub-clinical brain lesions seen in migraine sufferers using magnetic resonance imaging (reviewed by Schwedt and Dodick 2009), and, if the occipital region is involved, could potentially explain the occurrence of homonymous visual field losses in people with migraine. However, homonymous defects comprise the minority of cases of visual field defects in people with migraine.

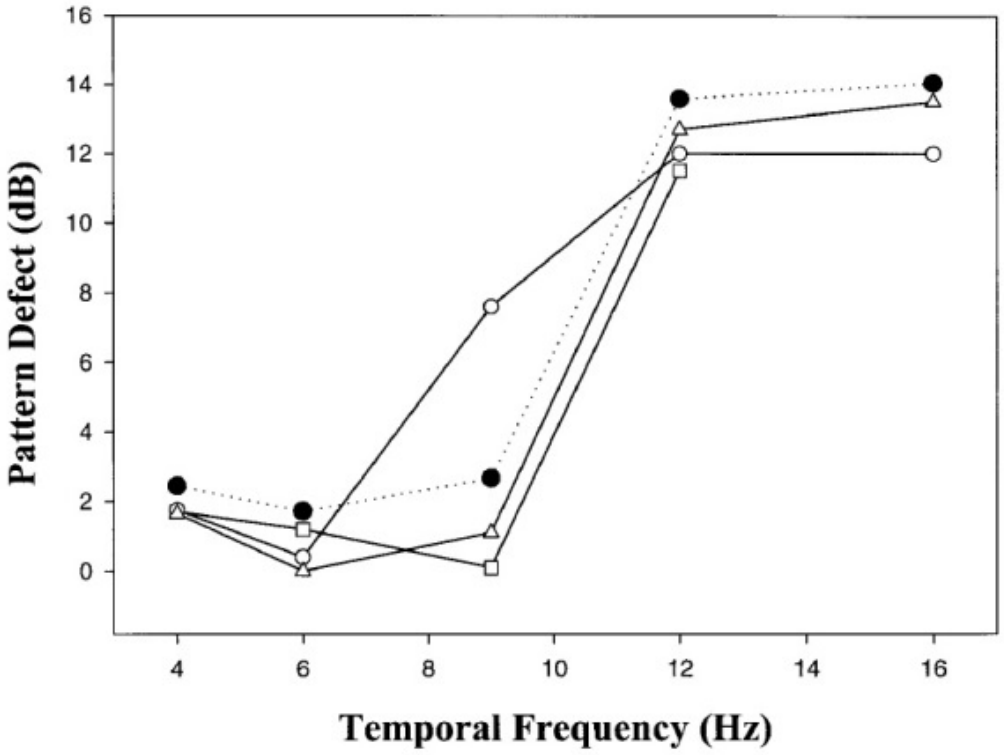

Figure 3. Temporal tuning of flicker perimetry defects in people with migraine. From a larger cohort of migraine sufferers (n = 16) who, on average, demonstrated abnormal visual field loss on temporal modulation perimetry (TMP) but not static automated perimetry (SAP), a subset of four people with migraine (3 MA: unfilled symbols, 1 MO: filled symbols) were tested on the Medmont M600 perimeter (Medmont International Pty Ltd., Melbourne, Australia). These migraine sufferers previously showed well-defined localised visual field loss during the interictal period on TMP, and so were tested again at least 7 days after a migraine to investigate whether visual field loss was dependent on temporal frequency. Five discrete temporal frequencies were tested (4, 6, 9, 12, and 16 Hz). With increasing temporal frequency of the flickering stimulus (above 6 Hz), the Pattern Defect increased. Pattern Defect values above 2.8 dB are flagged as abnormal ($p < 0.05$) by the Medmont perimeter, relative to the proprietary normative database. From: McKendrick, A.M., Vingrys, A.J., Badcock. D.R, and Heywood, J.T. "Visual field losses in subjects with migraine headaches." *Investigative Ophthalmology and Visual Sciences* 2000; 41: 1239-1247, copyright © 2000 by and reprinted with permission of The Association for Research in Vision and Ophthalmology.

Rather, of more common concern to clinicians faced with the challenge of managing glaucoma and its associated changes in visual field sensitivity is the fact that interictal visual field defects in migraine sufferers are mostly monocular and non-homonymous (e.g. Figure 1) (Comoglu et al. 2003, De Natale et al. 1993, Drummond and Anderson 1992, Lewis et al. 1989, McKendrick and Badcock 2004a, McKendrick and Badcock 2004b, McKendrick and Badcock 2004c, McKendrick et al. 2002, McKendrick et al. 2000, Nguyen et al. 2014, Nizankowska et al. 1997, Yenice et al. 2006, Yucel et al. 2005), implying a pre-chiasmal and possibly retinal ganglion cell origin. Monocular defects identified in people with migraine can involve mild generalised depression in visual field sensitivity, as reflected by a reduction in the perimetric global indices, Average and Mean Defect (Dersu et al. 2013, Lewis et al. 1989, McKendrick and Badcock 2004a, Yenice et al. 2006). Alternatively, monocular visual field deficits can be localised, which has been demonstrated by an increase in the global indices for visual field asymmetry, Pattern Defect, Pattern Standard Deviation, and Loss Variance (McKendrick and Badcock 2004a, McKendrick and Badcock 2004b, McKendrick and Badcock 2004c, McKendrick et al. 2002, McKendrick et al. 2000, Nguyen et al. 2014, Yenice et al. 2006). Sometimes the localised losses are arcuate in pattern (for example, see Figure 1), which has prompted some authors to refer to these as ‘glaucomatous-like’ (Comoglu et al. 2003, Nizankowska et al. 1997). Note that these monocular visual field defects are unlikely to be remnants of visual aura, because they can occur in individuals who have never experienced an aura as part of their migraine attacks (Figure 1), and because defects are indistinguishable between MO and MA groups (Comoglu et al. 2003, De Natale et al. 1993, McKendrick and Badcock 2004a, McKendrick and Badcock 2004b, McKendrick and Badcock 2004c, McKendrick et al. 2002, McKendrick et al. 2000, Nguyen et al. 2014).

5.1.3 Changes in visual field sensitivity in people with migraine over time

Most visual field studies in migraine are cross-sectional reports that measure visual field sensitivity at a single moment in time. However, repeated visual field testing is desirable because longitudinal data can demonstrate the time-course of visual field loss after an acute event. In our previous report (McKendrick et al. 2000), the visual field performance of one MO sufferer was followed at regular intervals over the course of 75 days after migraine offset, and up until the next migraine event. This person demonstrated a monocular visual field defect that improved over time. In this

case, the improvement was unlikely due to a learning effect, given the person's prior experience in psychophysical observation and the relative stability of the fellow eye (McKendrick et al. 2000). Similar findings of gradual improvement in visual field performance after migraine events have also been reported by studies involving larger groups of people with migraine (Drummond and Anderson 1992, McKendrick and Badcock 2004b, Nguyen et al. 2014).

Testing at known times after a migraine also provides information about whether acute migraine events affect visual field performance. If so, it is important to ascertain and record when the most recent migraine attack occurred, relative to the date of testing. Patients with migraine are far more likely to know the duration of time since their last migraine event, whereas it is close to impossible for people to know of an impending attack unless they can recognise non-specific prodromal symptoms, in which case the migraine is likely to occur within the next 48 hours (Becker 2013, Kelman 2004b). Drummond and Anderson (1992) mapped visual fields using kinetic perimetry in a group of MA sufferers and found defects were worst 24 hours post-migraine and were resolved 7-10 days later. Similarly, McKendrick and Badcock (2004b) noted sensitivity losses in MO and MA sufferers were worst the day after migraine offset, compared to one week post-migraine. It might be argued that loss of visual field sensitivity the day after migraine may be associated with headache-related factors such as fatigue or poor concentration. However, this confound was minimised by scheduling test visits after the offset, and not the onset, of migraine symptoms and ensuring there was enough time (at least 24 hours) for migraine medication washout (McKendrick and Badcock 2004a, McKendrick and Badcock 2004b, McKendrick et al. 2002, McKendrick et al. 2000, Nguyen et al. 2014).

Moreover, the fact that localised and monocular visual field defects are most pronounced the day after migraine argues against a loss of concentration or fatigue. Rather, a suggested mechanism for these localised and monocular defects is the occurrence of aberrant local retinal vasospastic events, leading to reduced perfusion and temporary, focal losses of sensitivity (McKendrick and Badcock 2004b, McKendrick et al. 2000). The previously noted flicker loss also supports such a possibility (Section 5.1.1.3). The potential for visual field deficits to be directly related to the occurrence of a migraine attack is relevant to glaucoma because of the additional risk of ocular damage, and raises the possibility for cumulative damage

with repeated episodes of migraine. Despite being the most debilitating of all neurological conditions in terms of years lived with disability (Vos et al. 2012), and despite the advent of new and effective therapies over the last two decades, migraine remains undertreated – on average, only 10% of migraine sufferers take anti-migraine medications prescribed by a physician (e.g. triptans), whereas most sufferers primarily use over-the-counter analgesics, if any (Cooke and Becker 2010, MacGregor et al. 2003). The use of effective anti-migraine therapy to minimise the duration of an attack may have future benefit in reducing the possibility for adverse vasospastic effects and visual field loss in susceptible individuals. However, longitudinal data on the long-term significance of visual field deficits in people with migraine is lacking – such a study design would have to occur over decades, given migraine is most common between 18 and 55 years of age (Bigal and Lipton 2009, Smitherman et al. 2013), whereas the prevalence of glaucoma increases with every decade of life (Tham et al. 2014), particularly above the age of 75 (Klein and Klein 2013, Quigley and Broman 2006).

Even if there is no long-term cumulative damage from repeated attacks of migraine, it is important to know whether duration after migraine is likely to affect visual field performance in order to accurately interpret perimetric results. Given significant test-retest variability of visual field sensitivity in normal subjects (Artes et al. 2002), it is challenging for clinicians and researchers who use perimetric methods to determine whether a person's visual field performance represents normal variation or progression of a disease such as glaucoma. Migraine adds a further confound to this challenge. Figure 4 plots baseline sensitivity (measured at least one week after a migraine) against retest sensitivity (measured 1-6 days after a migraine) (Nguyen et al. 2014). People with migraine show worse sensitivity than non-headache controls closer to a migraine (McKendrick and Badcock 2004b, Nguyen et al. 2014). This widening of the range of retest sensitivity may, in part, be due to adverse effects of the migraine attack itself, or reflect an increase in test-retest variability in proximity to a migraine event (see Section 5.1.3). Higher test-retest variability adds noise to the clinical interpretation of visual field results, particularly when evaluating for early signs of visual field progression in glaucoma. The exclusion of people with regular, active migraines from normative perimetric databases (see Section 5.1.1.1) may result

in tightening of test-retest variability and enhance the ability to monitor progression in glaucoma and other disorders that affect visual field sensitivity.

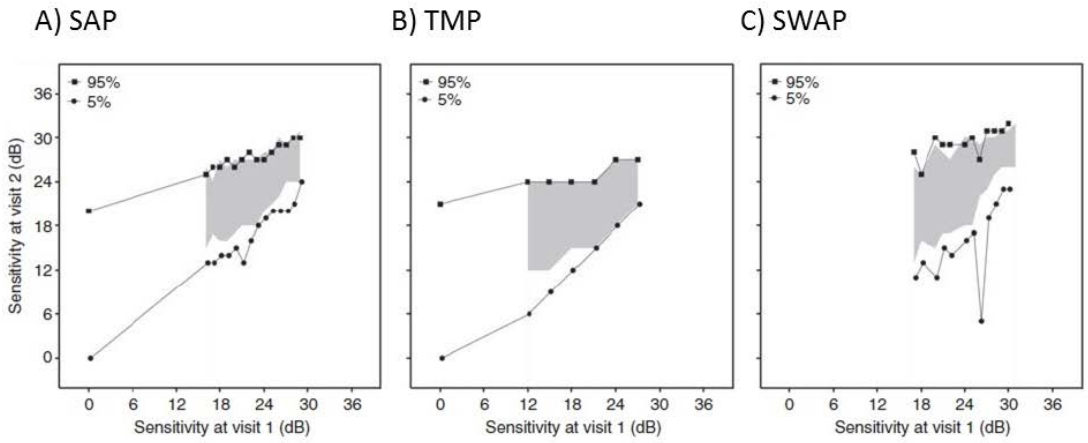

Figure 4. Test-retest variability of visual field sensitivity in people with migraine. Visual field sensitivity at the second visit (1-6 days after a migraine event) is plotted as a function of sensitivity at the first visit (at least one week after a migraine event) for three perimetric tasks: (A) static automated perimetry (SAP) (B) temporal modulation perimetry (TMP) (C) short-wavelength automated perimetry (SWAP). The shaded area is the 90% confidence interval of test-retest sensitivity for the non-headache control group (n = 26). The 5th (circles) and 95th (squares) percentile limits for the migraine group (n = 17) are shown as individual symbols. Modified from: Nguyen, B.N., Vingrys, A.J., and McKendrick, A.M. "The effect of duration post-migraine on visual electrophysiology and visual field performance in people with migraine." *Cephalalgia* 2014; 34: 42-57.

5.2 Visual electrophysiology

Electrophysiological techniques are non-invasive measures that can be used to indirectly assess neuronal activity. In the context of glaucoma, electrophysiological techniques that target the retinal ganglion cell population have been developed (reviewed by Bach and Poloschek 2013) – for example, the pattern electroretinogram (pERG) (Bach and Hoffmann 2008, Porciatti 2015) or the photopic negative response of the flash ERG (Viswanathan et al. 2001). Of these techniques, only the pattern ERG is a standardised clinical measure approved by the International Society for the Clinical Electrophysiology of Vision (ISCEV) (Bach et al. 2013). The simultaneous recording of visual evoked potentials in response to the same patterned stimulus – the standard ISCEV pattern VEP (Odom et al. 2010) – is of benefit when testing migraine

patients as it enables assessment of the retino-cortical pathway, up to and including the visual cortex. The pattern ERG and the pattern VEP have been applied to glaucoma and migraine groups, with different results.

5.2.1 Pattern electrophysiology in people with migraine

5.2.1.1 Standard pattern electoretinography

The standard ISCEV pattern ERG protocol involves recording a 'transient' response to a patterned stimulus that is modulated at temporal frequencies of less than 3 Hz (6 reversals/second). Example transient pattern ERG waveforms are depicted in Figure 5A, consisting of two major deflections: the P50 and N95 components. Although the pattern ERG is a measure of retinal ganglion cell function, not all of the pattern ERG response is generated by the ganglion cells. The N95 component displays spatial tuning and is considered a contrast-related component originating in the retinal ganglion cells (Berninger and Schuurmans 1985, Hess and Baker 1984, Korth 1983, Luo and Frishman 2011, Viswanathan et al. 2000), whereas the P50 is partly derived from ganglion cells but also has an additional luminance component that is believed to arise in the outer retina (Korth 1983, Luo and Frishman 2011, Trick and Wintermeyer 1982). Reduced P50 and/or N95 amplitude and delays in timing of these major components of the transient pattern ERG have been reported in patients with early glaucoma (Hood et al. 2005, Marx et al. 1987, Parisi 2001, Parisi et al. 2006). To investigate whether similar deficits are present in people with migraine, we adopted the ISCEV standard approach to measure the transient pattern ERG (1 Hz, 0.8° checks, 31° field, high contrast > 95%) in a group of 45 migraine sufferers (26 MO, 19 MA) and 30 non-headache controls. The P50 and N95 responses were normal in our migraine sufferers (Figure 5A) (Nguyen et al. 2012), which is consistent with all other studies of pattern ERG in migraine to date, even though prior studies did not explicitly adhere to the ISCEV guidelines (Khalil 1991, Moreira Filho and Dantas 1995, Shibata et al. 1997).

5.2.1.2 Steady-state pattern electroretinography

For the evaluation of glaucoma, the ISCEV guidelines recommend that electrophysiologists consider the additional recording of the 'steady-state' pattern ERG (≥ 4 Hz or 8 reversals/second) (Bach et al. 2013), as glaucoma patients show more pronounced reductions in amplitude with steady-state than transient stimulation

(Bach and Hoffmann 2008). With increasing temporal frequency, the successive transient waveforms begin to overlap and a cyclic, sinusoidal-like waveform is generated (Figures 5B and 5C) that can be deconstructed into its frequency components using discrete Fourier transformation (Figures 5D and 5E) (Bach and Meigen 1999). The component of interest is the second harmonic (2F), which occurs at twice the stimulation frequency and represents the retinal ganglion cell response to contrast-reversal. Our previous work (Nguyen et al. 2012) found normal 2F amplitudes of the steady-state pattern ERG (8 Hz, 0.8° checks, 31° field) in 45 people with migraine, compared to a non-headache control group (Figures 5B and 5D). We used the same stimulus and protocol to record responses from 13 glaucoma patients (aged 58-77, 11 with POAG and 2 with NTG) and 15 age-similar, healthy controls. Importantly, it was ensured that all glaucoma and non-glaucoma participants reported a migraine-free history. Steady-state pattern ERG amplitudes were reduced in the glaucoma group relative to their age-similar controls (Figures 5C and 5E), consistent with previous reports (Bach and Speidel-Fiaux 1989, Bach et al. 1997, Bode et al. 2011, Porciatti et al. 1987, Ventura et al. 2005).

The reduction in steady-state pattern ERG amplitude in glaucoma is not uniform across different spatial frequencies, but occurs mainly in the medium range of spatial frequencies (0.5 to 3 cycles/degree or check sizes ~1°) (Bach and Speidel-Fiaux 1989, Porciatti et al. 1987, Tsaousis et al. 2013) with relative preservation of the response to large stimulus checks (≥8°) (Bach and Speidel-Fiaux 1989, Tsaousis et al. 2013). Inter-observer variability can be reduced by calculating a ratio between large and small check responses (Bach and Hoffmann 2008). This ratio is a useful electrophysiological indicator of earlier stages of glaucoma (Bach and Hoffmann 2008, Tsaousis et al. 2013), yet is normal in people with migraine (Nguyen et al. 2012). Taken together, pattern ERG responses elicited by different-sized checks (small/large) and/or different temporal frequencies of stimulation (transient/steady-state) consistently reveal group differences between glaucoma patients and healthy controls, whereas no such group differences are evident in migraine studies. Given the similarity in visual field deficits found in glaucoma and migraine (see Section 5.1.2), and that pattern ERG changes can be present in some patients with early glaucoma before visual dysfunction becomes evident on perimetric testing (Bach et al. 1997, Bode et al. 2011), electrophysiological techniques may prove a useful adjunct to help

differentiate between these two conditions. However, it must be noted that a significant proportion of patients with clearly documented glaucomatous damage (more than 25% of eyes) will not be identified as abnormal based on pattern ERG measures (Hood et al. 2005), because of the wide range of pattern ERG amplitudes seen in a normal population and because the pattern ERG amplitude does not necessarily reduce to zero (or noise level) in glaucoma (Figure 6B).

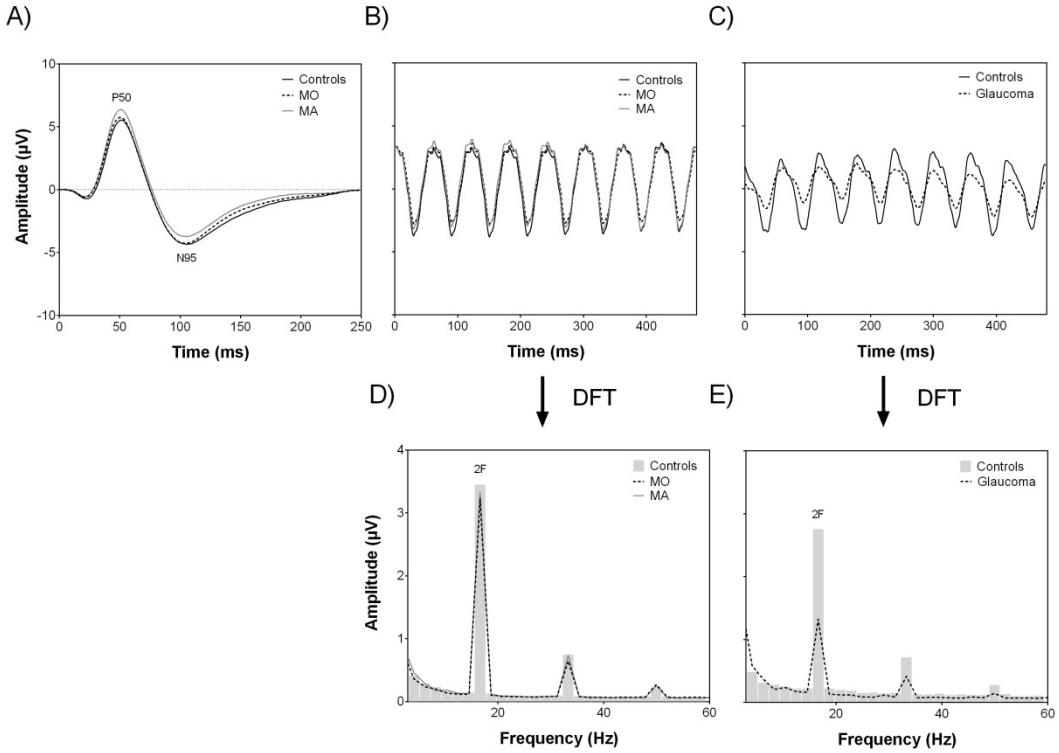

Figure 5. The pattern electroretinogram in migraine and glaucoma patients. (A) Group average transient pattern ERG waveforms (1 Hz, 0.8° checks, 31° field, 97% contrast) of 45 migraine (26 MO aged 20-41, 19 MA aged 19-43) and 30 non-headache control participants (aged 19-46). (B) Group average steady-state pattern ERG waveforms (8 Hz, 0.8° checks, 31° field, 97% contrast) obtained from the same migraine and non-headache control participants as in Panel A. (C) Group average steady-state pattern ERG waveforms (8 Hz, 0.8° checks, 31° field, 97% contrast) of 13 glaucoma patients (11 POAG, 2 NTG, aged 58-77) and 15 non-glaucoma age-similar participants (aged 49-76). Panels (D) and (E) show the corresponding group average amplitude spectra of the steady-state pattern ERG waveforms in the frequency domain following discrete Fourier transformation (DFT). The components of interest are indicated: transient P50 and N95 (Panel A) and steady-state 2F (second harmonic, Panels D and E). Migraine participants were tested during the interictal period at least one week after a migraine event.

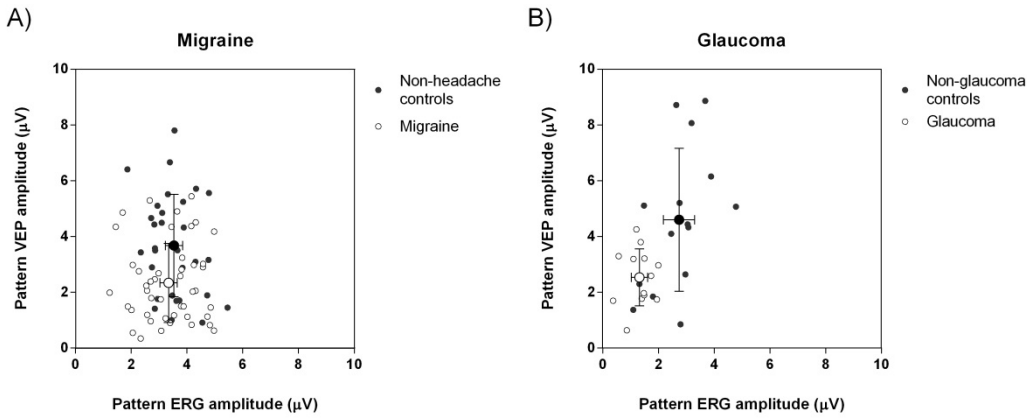

Figure 6. The simultaneously recorded pattern electoretinogram and visual evoked potential in migraine and glaucoma patients. Steady-state pattern VEP amplitudes are plotted as a function of pattern ERG amplitude (8 Hz, 0.8° checks, 97% contrast) from (A) 45 people with migraine (aged 19-43, 26 MO, 19 MA) and 30 non-headache controls (aged 19-46). (B) 13 glaucoma patients (aged 58-77, 11 POAG, 2 NTG) and 15 non-glaucoma controls (aged 49-76). Note the age difference between the groups depicted in Panels A and B. Individual and group mean data are plotted. Error bars locate the 95% confidence intervals of the mean. Relative to their non-headache control group, the migraine group shows reduced pattern VEP amplitude but normal ERG amplitudes (Panel A). On the other hand, compared to their non-glaucoma (older) control group, the glaucoma patients show a reduction in both pattern VEP and ERG amplitude (Panel B). Migraine participants were tested during the interictal period at least one week after a migraine event.

5.2.1.3 Simultaneous pattern visual evoked potentials

Retinal ganglion cell dysfunction or death in glaucoma can be associated with post-retinal neurodegenerative changes, such as at the lateral geniculate nucleus (Gupta et al. 2006, Weber et al. 2000, Yucel et al. 2003) and visual cortex (Gupta et al. 2006). Simultaneous pattern ERG and VEP recording is therefore useful to investigate both cortical and retinal dysfunction (Bach et al. 2013), given that an abnormal VEP result can be a result of pre-cortical and/or cortical changes.

Despite the pattern ERG being normal in migraine (Khalil 1991, Moreira Filho and Dantas 1995, Nguyen et al. 2012, Nguyen et al. 2014, Shibata et al. 1997), the simultaneously recorded pattern VEP is abnormal (Nguyen et al. 2012, Nguyen et al. 2014, Shibata et al. 1997). However, the nature of the VEP abnormality in migraine is inconsistent, with studies yielding heterogeneous results (reviewed by Ambrosini et al. 2003, Magis et al. 2007). When electrophysiological studies have investigated the

pattern VEP in isolation in people with migraine, the findings have been for: increased amplitude (e.g. Diener et al. 1989), reduced amplitude (e.g. Boylu et al. 2010), increased amplitude with repeated stimulation (also referred to as deficient 'habituation', reviewed by Coppola et al. 2009), increased asymmetry between the right and left hemispheres (e.g. Tagliati et al. 1995), timing delays (e.g. Mariani et al. 1990) and advances (e.g. Spreafico et al. 2004), as well as normal responses. Regardless of the nature of the VEP abnormality, the common finding from the few studies that have measured pattern ERG and VEP responses simultaneously is that they do not find an abnormality in the ERG. This provides a key point of contrast to the pattern of results typically obtained in glaucoma, where the pattern VEP is reduced in amplitude (Parisi et al. 2006, Tsaousis et al. 2013) and/or delayed in timing (Price et al. 1988) with retinal deficits of a similar nature (Parisi 2001, Parisi et al. 2001, Parisi et al. 2006, Tsaousis et al. 2013). Figure 6 incorporates data from an earlier publication where pattern ERG and VEP responses were simultaneously recorded in people with migraine at least 7 days after a migraine (Nguyen et al. 2012). The effect size of the reduction in steady-state pattern VEP amplitude in the people with migraine is large (Figure 6A, Cohen's d = -0.82), with no group difference in pattern ERG amplitude. In contrast, in patients with glaucoma and no history of migraine (Figure 6B), the reduction in both pattern ERG and VEP amplitude in the glaucoma group relative to the age-similar control group is large, with effect sizes of d = -1.80 and d = -1.06, respectively.

A confound for glaucoma evaluation using pattern electrophysiology is that both patients with glaucoma (Parisi et al. 2006, Tsaousis et al. 2013) and people with migraine (Boylu et al. 2010, Khalil 1991, Khalil et al. 2000, Nguyen et al. 2012, Nguyen et al. 2014) can show reduced pattern VEP amplitude. The mechanism behind the reduction in pattern VEP response in migraine is still a matter of conjecture. Reduced pattern VEP amplitudes could be due to more generalised mechanisms involving the brain that are not specifically visual in nature, such as differences in cognitive function, attention, aversion (Coleston and Kennard 1993, Huang et al. 2003, Karanovic et al. 2011, Khalil 1991, Marcus and Soso 1989, Shepherd 2000, Thabet et al. 2013, Wilkinson et al. 2008) or cortical inhibitory/excitatory imbalance (Vecchia and Pietrobon 2012). Nevertheless, the presence of normal pattern ERG yet abnormal pattern VEP in migraine may be

helpful in clinically distinguishing the cause for visual dysfunction with respect to migraine or glaucoma.

5.2.2 Spatial characteristics of electrophysiological defects in people with migraine

Unlike visual field testing, the pattern ERG and VEP is performed using a large target (e.g. 31° diameter, Nguyen et al. 2014) and is not designed to find small, localised losses or investigate the spatial extent of visual dysfunction. A potential tool in electrophysiology for spatial localisation is the use of a multifocal technique that localises visual stimuli to discrete regions of the visual field. For example, for the ISCEV multifocal pattern ERG (Hood et al. 2012), the stimulus field (40-50° diameter) is divided into an array of smaller elements (61 or 103 hexagons) scaled for retinal eccentricity, such that any given element may range from approximately 2° to 6° in size (Harrison et al. 2006). The resolution of this sampling array cannot be significantly increased because of the signal-to-noise required to obtain a response of sufficient amplitude from each location (reviewed by Hood and Greenstein 2003). To date, there are no published studies using multifocal electrophysiological techniques to measure evoked responses in people with migraine. However, it must be noted that current multifocal techniques do not afford the same spatial resolution as does visual field testing (0.43° targets for Goldman size III stimuli), and abnormalities in the multifocal pattern ERG response do not necessarily correspond to locations of visual field loss in people with glaucoma (Klistorner et al. 2000, Harrison et al. 2006).

5.2.3 Changes in electrophysiological responses in people with migraine over time

The pattern ERG is indistinguishable between migraine and non-headache control groups during the interictal period (Figure 5). To our knowledge, only one study has recorded the pattern ERG at more than one visit to determine the effect of time post-migraine on retinal evoked responses (Nguyen et al. 2014). That study found that the pattern ERG remained normal at the second visit 1-6 days after a migraine, despite the presence of worse monocular, localised losses in visual field sensitivity (Nguyen et al. 2014). On the other hand, the pattern VEP is abnormal after migraine (Judit et al. 2000, Nguyen et al. 2014, Sand and Vingen 2000, Sand et al. 2009), but normalises 12 to 24 hours prior to migraine onset (Judit et al. 2000, Sand and Vingen 2000, Sand et al. 2009, Shibata et al. 1998). This fluctuation in cortical activity may be due to the

episodic and ‘cyclic’ nature of migraine, and highlights the importance of considering the time of testing relative to a migraine. However, using the pattern VEP on its own to help differentiate glaucoma and migraine has limitations – the nature of the VEP abnormality after migraine is inconsistent (see Section 5.2.1.3) – whereas simultaneous recording of the pattern ERG and VEP is useful for cases where the distinction between glaucoma and migraine is needed, because the pattern ERG is consistently normal in people with migraine regardless of proximity to a migraine event.

5.3 Ocular imaging

Characteristic pathological findings in early glaucoma are narrowing of the neuroretinal rim of the optic nerve and thinning of the retinal nerve fibre layer (reviewed by Weinreb et al. 2014). These structural changes can be assessed by examining the optic nerve head and peripapillary retinal nerve fibre layer using direct and indirect ophthalmoscopy. However, recent advances in clinical ocular imaging have enhanced the ability to detect and quantify changes in retinal structure in vivo, with high sensitivity and specificity for glaucoma diagnosis (Bussel et al. 2014) and progression (Bussel et al. 2014, Mansouri et al. 2011). Given the possible association between migraine and glaucoma, a host of recent studies have emerged where ocular imaging modalities used to evaluate glaucoma have been applied to study differences between migraine and non-migraine groups.

5.3.1 Optic nerve head imaging in people with migraine

5.3.1.1 Optic nerve head morphology

The potential for optic nerve head morphological changes in people with migraine has been investigated using the confocal scanning laser ophthalmoscope, the Heidelberg Retinal Tomograph (HRT, Heidelberg Engineering GmBH, Heidelberg, Germany). Global HRT stereometric parameters that describe optic nerve head morphology, such as rim area and rim volume are, on average, normal in migraine groups (Moehnke et al. 2008, Nguyen et al. 2014). On the other hand, the capacity for the HRT to detect glaucomatous damage to the optic nerve head is greatest for these same stereometric parameters (area under the receiver operating characteristic curve > 0.75) (Iester et al. 1997b). This normal structural outcome in people with migraine concurs with the normal pattern ERG results discussed earlier (see Section 5.2, Figure 5).

Of the range of stereometric parameters returned by the HRT, global rim area has been identified as the most important predictor of Pattern Standard Deviation (index of localised visual field loss) in patients with glaucoma (Iester et al. 1997a). Additionally, several disc parameters (namely global rim volume, global rim area, and cup shape measure) correlate well with generalised visual field loss, as described by the Mean Defect on the Humphrey perimeter (Iester et al. 1997a). Accordingly, we have investigated whether a similar relationship exists between these measures of optic nerve head morphology and global indices of visual field loss in people with migraine. Our 17 migraine participants (11 MO, 6 MA) and 26 non-headache control observers completed both HRT and SAP visual field tests (Medmont perimeter) on the same day during the interictal period. These participants appear in our previously published study (Nguyen et al. 2014). None of the HRT stereometric parameters, which have previously been shown to be useful for the diagnosis of glaucoma (Iester et al. 1997a), were related to generalised visual field loss in people with migraine (Pearson correlations, $p > 0.05$). Furthermore, unlike in glaucoma patients (Iester et al. 1997a), Figure 7 shows there is no correlation between global rim area and localised visual field loss, despite an increase in Pattern Defect in a significant proportion of individuals with migraine.

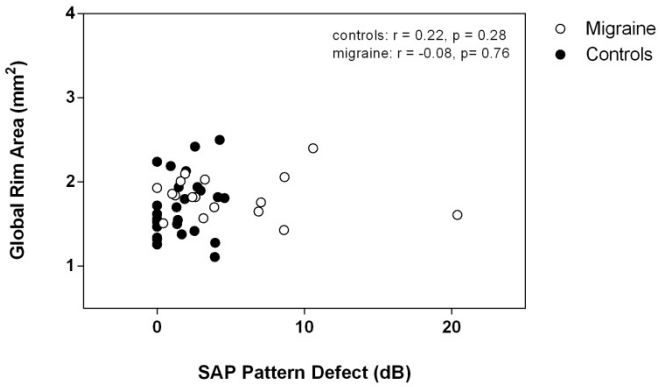

Figure 7. Relationship between localised visual field loss and optic nerve head global rim area in people with migraine. Global rim area measurements from the Heidelberg Retinal Tomograph (HRT) confocal scanning laser ophthalmoscope are plotted against the Pattern Defect measured using standard automated perimetry (SAP) on the Medmont M700 perimeter. Seventeen people with migraine (11 MO, 6 MA) and 26 non-headache controls completed imaging and visual field tests on the same day. Migraine participants were tested during the interictal period at least one week after a migraine event. The results of Pearson correlation analysis between global rim area and SAP Pattern Defect for the control and migraine groups are given separately and are not significant.

5.3.1.2 Peripapillary retinal nerve fibre layer

There are several reports of thinner circumpapillary retinal nerve fibre layer in people with migraine, as measured using optical coherence tomography (OCT) (Demirci et al. 2015, Ekinci et al. 2014, Gipponi et al. 2013, Martinez et al. 2008, Sorkhabi et al. 2013, Yulek et al. 2015) and scanning laser polarimetry (Martinez et al. 2009). The reduction in global retinal nerve fibre layer thickness is subtle – on average, the difference is 5-7 μm between migraine and non-migraine groups on OCT (Demirci et al. 2015, Ekinci et al. 2014, Gipponi et al. 2013, Martinez et al. 2008, Sorkhabi et al. 2013, Yulek et al. 2015). However, this finding of reduced peripapillary retinal nerve fibre layer thickness is not universal (Salman et al. 2015, Simsek et al. 2015). The inconsistencies in the literature may arise because of factors other than neural loss that can influence OCT measures of retinal thickness, such as interference from blood vessels (Hood et al. 2008). Lending support to the idea that migraine involves vascular dysregulation outside of the brain is the recent finding that migraine patients who are current smokers show a reduction in average retinal nerve fibre layer thickness (Demirci et al. 2015). The authors suggest that smoking and nicotine, which can alter retinal blood flow and autoregulatory capacity (Steigerwalt et al. 2000), is an additional risk factor for retinal structural changes in people with migraine who may already have compromised vasculature. Furthermore, retinal vascular changes are likely to be dynamic processes that are not always captured by cross-sectional imaging. Whether the changes in retinal nerve fibre layer thickness in people with migraine vary with time after headache or fall outside test-retest variability has not yet been considered.

5.3.2 Macula imaging in people with migraine

Until more recently, the possibility for early glaucomatous damage involving the macular region has largely been ignored but is now widely accepted as being common in glaucoma (Hood et al. 2013). In addition to measuring total macular thickness, recent advances in spectral-domain OCT have enabled identification of the innermost retinal layers that are most pertinent to glaucoma – the macular layers where ganglion cell axons (retinal nerve fibre layer), cell bodies (ganglion cell layer), and dendrites (inner plexiform layer) are located. In-built segmentation algorithms (Ishikawa et al.

2005, Tan et al. 2008) currently have the capacity to segment thickness measures into the following parameters: the macular retinal nerve fibre layer (mRNFL), the ganglion cell layer with inner plexiform layer (GCIPL) and the ganglion cell complex (mRNFL + GCIPL), all of which have been useful in tracking longitudinal retinal structural changes in human glaucoma subjects (Bussel et al. 2014). Currently, the results of interictal macula imaging studies in migraine sufferers are inconclusive, with conflicting results of normal (Yulek et al. 2015) or reduced ganglion cell complex measures in people with migraine (Ekinci et al. 2014). Given that the functional data collected with perimetry can show improvement with time after a migraine (see Section 5.1.3), this predicts that the neural structure could be expected to remain normal with a gradual reduction in dysfunction after the headache. It is possible that cumulative damage might be found with long term migraine sufferers, or that differences in macular thickness may vary with time post-migraine.

5.3.3 Choroidal imaging in people with migraine

Unlike the retinal vasculature with its efficient autoregulatory capacity, the choroidal circulation is mainly controlled by sympathetic innervation (Delaey and Van De Voorde 2000). Part of the blood supply to the optic nerve head comes from this choroidal-derived vasculature, which perfuses the pre-laminar area of the optic nerve head (Hayreh 1969). Accordingly, there has been growing interest in imaging the choroid of glaucoma patients using spectral-domain OCT (reviewed by Banitt 2013), and this interest has extended to studies of people with migraine because of the posited vascular mechanism and the potential link to glaucoma. Cross-sectional studies during the interictal period find reduced choroidal thickness in migraine sufferers in general (Zengin et al. 2015), or in MA but not MO sufferers (Ekinci et al. 2014). The mechanism for the reduction in choroidal thickness is unclear, but it is presumed that the differences are vascular in origin.

A challenge for interpreting the results of choroidal imaging studies to date as a whole is that both decreased and increased choroidal thickness have been reported in people with migraine. The apparent conflict in findings appears to be related to the time of testing. A cross-sectional study imaged migraine participants during a migraine attack and reported an increase in choroidal thickness relative to a group of non-headache controls (Karalezli et al. 2014). Dadaci et al. (2014) shed further light on this result, by comparing choroidal thickness across two test visits in the same migraine

observers (one at baseline, the other during an attack). Choroidal thickness was increased during a migraine attack compared to the baseline interictal visit (Dadaci et al. 2014). A plausible explanation put forth by the authors to account for the increase in choroidal thickness during the attack phase is choroidal vasodilation and perivascular inflammation, as a result of autonomic nervous system dysfunction associated with acute migraine symptoms. However, because a control group was lacking in this study, it is not known whether the changes in choroidal thickness within the migraine cohort fall outside expected test-retest variability.

At present, the consensus of data from HRT measurements of optic nerve head morphology would suggest normal outcomes in people with migraine, although the use of spectral-domain OCT has largely superseded the HRT in clinical and research settings. However, the results of peripapillary retinal nerve fibre layer and macular thickness measurements in people with migraine using the OCT show differing outcomes, from which no firm conclusions can be drawn at this stage. There is some compelling evidence that measures of choroidal thickness can vary depending on the time of testing relative to a migraine (ictal versus interictal period). Although fluctuations in choroidal thickness may not be mechanistic in terms of the cause of vision loss in migraine (see Sections 5.1 and 5.2), it may reflect a vascular dysregulation in migraine that could explain why the retina is susceptible to glaucoma development in some migraine sufferers.

6 Conclusions and future directions

Migraine is a common neurological disease with a potential association with glaucoma. There is a growing body of evidence that clinical tests regularly used as part of glaucoma assessment can be abnormal in-between migraine attacks, namely visual fields, electrophysiology and ocular imaging. Migraine poses a significant challenge for clinicians and researchers because it can mimic changes seen in early glaucoma. Moreover, the episodic nature of migraine and the fluctuation in clinical test results in migraine observers makes it difficult to track progression of glaucoma in patients with a history of migraine. It is evident from visual field and imaging studies and, to a lesser extent, visual electrophysiological studies, that the timing of the testing relative to a migraine (ictal, interictal, duration post-migraine) can influence the results of clinical tests in people with migraine.

Clinicians and researchers should be aware of the possibility for abnormal clinical test results in apparently healthy young individuals with no other co-morbid condition besides migraine, and likewise for older adults who report a lifetime of migraine events. As a result of this review, practical clinical suggestions for the interpretation of test results and management of glaucoma in patients with migraine have been identified and are summarised in Table 4 for consideration by researchers and clinicians alike. A number of questions remain unanswered, some of which we have identified below and which can provide a basis for future research.

Table 4. Recommendations to consider for the assessment and management of patients with migraine

- Specifically enquire and make note of migraine history in all patients presenting for eye-care. A simple three-question tool 'ID Migraine' (Table 3) can be used to aid in screening for migraine.
- Collect baseline visual field results for future reference in all patients with migraine, even if there is no other indication for visual field testing.
- Note time of visual field testing relative to a migraine (days or weeks after last migraine event).
- Note if any migraine medications were taken at the time of visual field testing.
- Given visual field test results may fluctuate and can be abnormal in patients with migraine, clinicians may need to rely more on optic nerve head assessment using imaging for diagnosis and management of glaucoma.
- Supplement visual field testing with the results of ISCEV pattern ERG and simultaneous recording of pattern VEP to help differentiate glaucoma from migraine.
- Avoid including regular, active migraine sufferers in normative databases.

6.1 Does migraine increase susceptibility to glaucoma and visual dysfunction?

An important question is whether abnormal clinical test results are due to underlying differences in visual performance in people susceptible to migraine, or reflect residual damage from the attack itself. There may be underlying vascular, metabolic, or neurologic differences in some individuals with migraine that render them more susceptible to both migraine and glaucoma. For example, future work could investigate the dynamics of regional blood flow surrounding the optic nerve head or the choroidal blood flow in healthy, young migraine sufferers to consider the prospect for vascular dysregulation predisposing to glaucoma.

Our review identifies that migraine attacks can affect visual function directly, particularly considering the potential for vascular dysregulation associated with migraine. Longitudinal studies and long-term follow-up would therefore be useful to

investigate the relationship, if any, between interictal visual abnormalities in healthy, young migraine sufferers and the risk of developing glaucoma later in life. If abnormal findings in people with migraine are predictive of future eye disease, further investigations need to consider whether visual abnormalities are associated with cumulative migraine frequency or some other feature of migraine. If so, it may be possible to minimise ocular damage by timely use of effective migraine therapy. Prophylactic treatment of migraine for the sole purpose of reducing the risk of ocular damage is unlikely to outweigh the potential adverse risks and side-effects of the medications. However, migraine is the most debilitating neurological condition in terms of years lived with disability (Leonardi and Raggi 2013) and a substantial proportion (~40%) of migraine sufferers who might benefit from therapy do not receive it (Lipton et al. 2007). Adequate migraine therapy decreases disability and increases the productivity and quality of life of migraine sufferers (Buse et al. 2009, Lipton et al. 2005, Silberstein 2000), and may have an additional beneficial side-effect of reducing the risk of visual field loss in susceptible patients.

6.2 Do migraine medications affect clinical test results?

It is not known whether the use of anti-migraine medications for acute attacks, or prophylactic medications for migraine can influence clinical test results. Most of the studies discussed in this review occurred during the interictal period, and it is assumed that, in doing so, they avoided testing patients whilst feeling unwell and the possible confound of migraine medication effects. Some studies have explicitly excluded chronic migraine patients, defined as suffering more than 15 days of migraine per month for more than 3 months (International Headache Society 2013), or have tested people during the interictal period with at least 24 hours of medication washout (Dadaci et al. 2014, McKendrick and Badcock 2004a, McKendrick and Badcock 2004b, McKendrick and Badcock 2004c, McKendrick et al. 2002, McKendrick et al. 2000, Nguyen et al. 2012, Nguyen et al. 2014, Shibata et al. 1997) to avoid these confounds. However, other studies report the inclusion of patients on medications for migraine prophylaxis (e.g. Moehnke et al. 2008, Yucel et al. 2005) or simply do not comment on the use of medications in their patient cohort (e.g. Martinez et al. 2008, Sorkhabi et al. 2013). Future work needs to be carefully controlled to ensure that medication use is properly documented.

6.3 Are visual abnormalities related to specific migraine characteristics?

A better understanding of which migraine characteristics might be associated with visual dysfunction in migraine can help flag which individuals may need to be monitored more closely by clinicians. It is clear from perimetric studies that some people with migraine can show monocular and localised visual field defects during the interictal period. Several of these studies have additionally identified significant correlations between visual field loss and certain migraine features such as migraine frequency (De Natale et al. 1993, McKendrick and Badcock 2004a, Nizankowska et al. 1997, Yenice et al. 2006), cumulative migraine history (McKendrick and Badcock 2004a), and duration of worst headache (Harle and Evans 2005), even if group differences in visual field performance were not found (Harle and Evans 2005). Similarly, while there are no compelling group differences in structural retinal measures using the OCT, significant inverse relationships have been reported between retinal nerve fibre layer thickness and frequency of attacks (Martinez et al. 2009), duration of migraine history (Yulek et al. 2015), and severity of migraine (Martinez et al. 2009) as estimated by the Migraine Disability Assessment (MIDAS) questionnaire score (Lipton et al. 2001b, Stewart et al. 2001). These significant correlations raise the possibility that migraine may be associated with cumulative damage over time.

Nevertheless, correlations with migraine characteristics should be interpreted with caution, because migraine is a heterogeneous condition and the results could reflect the characteristics of the specific migraine cohort tested. In general, studies have tested relatively small cohorts (<50 in each migraine group), whereas larger sample sizes would be required to yield a high statistical power for identifying relationships with migraine characteristics. In addition, the difficulties with retrospective reporting of migraine are well-recognised, as has been discussed by several authors (Coppola et al. 2007, Russell et al. 1994, Wilkinson and Crotogino 2000). Self-reporting relies on retrospection over many years of migraine. Therefore, accurate estimates are limited or might be biased towards the most recent, most severe, or most interesting events that are not representative of a person's typical migraine history.

A further complexity of retrospective reporting is that particular characteristics such as migraine attack frequency can fluctuate over a lifetime (Bigal and Lipton 2009, Stewart et al. 1994, Stovner et al. 2007). One approach to address this challenge is to provide migraine patients with a headache diary to complete in-between visits

(McKendrick and Badcock 2004b, Nguyen et al. 2014). The diary or series of questions could be incorporated online (Moloney et al. 2009) or into an application that is accessible via portable devices (Turpin et al. 2014) to enable date- and time-stamping and more 'real-time' tracking of changes in an individual's migraine history over time. Given inter-individual variability in migraine features, as well as known fluctuations in the results of clinical tests of vision in migraine sufferers, it is not always useful to simply look for group differences. Rather, the risk of adverse effects of migraine may need to be considered for each individual, so that treatment regimens can be implemented and patients can be monitored on a case-by-case basis.

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