ABSTRACTS

Neuro-Ophthalmic Literature Review

Carmen Chan, Evan Price, John H. Pula, Matthieu Robert, Michael Vaphiades,
An-Guor Wang, and Sui Wong

HIV NEURORETINAL DISORDER

Jabs DA, Drye L, Van Natta ML, Thorne JE, Holland GN; Studies of the Ocular Complications of AIDS Research Group. Incidence and long-term outcomes of the human immunodeficiency virus neuroretinal disorder in patients with AIDS. *Ophthalmology* 2015;122:760–768.

Patients with acquired immunodeficiency syndrome (AIDS) can have subtle abnormalities of vision (e.g. decreased contrast sensitivity, abnormal colour vision, visual field loss, abnormal results on other psychophysical tests) in the absence of ocular infection or media opacity. This is presumed to be caused by an “HIV neuroretinal disorder”. A neuroretinal origin of the visual loss is supported by decreased retinal nerve fibre layer thickness on optical coherence tomography (OCT) and autopsy results of AIDS patients showing loss of optic nerve axons. In this paper, the authors used decreased contrast sensitivity as a marker for human immunodeficiency virus (HIV) neuroretinal disorder and analysed the contrast sensitivity data of the Longitudinal Study of the Ocular Complications of AIDS (LSOCA). LSOCA is a prospective, multi-centred observational cohort study of patients with AIDS, which recruited patients from 19 US centres. Out of the 1822 patients available for analysis, 294 (16%) had the HIV neuroretinal disorder at enrolment. HIV neuroretinal disorder was more common in women and African Americans, and it was associated with hepatitis C infection, low CD4 count, and detectable HIV RNA in the blood. Patients with HIV neuroretinal disorder tended to have a mildly but significantly reduced visual acuity and Humphrey visual field mean deviation at baseline; and the presence of HIV neuroretinal disorder was associated with a significantly higher risk of bilateral visual impairment and mortality during follow-up. The authors estimated that the cumulative incidence of HIV neuroretinal disorder was up to 50% 20 years after AIDS diagnosis. Therefore, HIV neuroretinal disorder is an important differential diagnosis of “visual loss of unknown cause” in AIDS patients.

Carmen Chan

LAMINA CRIBROSA QUALITIES ON EDI FOUND TO BE DETERMINANTS OF RNFL THICKNESS

Lee EJ, Kim TW, Kim M, Kim H. Influence of lamina cribrosa thickness and depth on the rate of progressive retinal nerve fiber layer thinning. *Ophthalmology* 2015;122:721–729.

In this prospective, observational study, the authors investigate the association of lamina cribrosa thickness (LCT) and lamina cribrosa depth (LCD) with rate of thinning of the retinal nerve fibre layer (RNFL) as measured by spectral-domain (SD) optical coherence tomography (OCT). One hundred ten eyes with primary open-angle glaucoma (POAG) were followed by SD OCT for at least 2.5 years. LCD and LCT were assessed by enhanced depth imaging (EDI) SD OCT. In prior experimental studies, posterior displacement (increased LCD) and thinning of the lamina cribrosa have been shown to precede RNFL loss. Increased LCD and decreased LCT have been demonstrated histologically in glaucomatous eyes. However, this is the first known report to demonstrate that increased LCD and decreased LCT precede thinning of the RNFL on SD OCT and contribute to an increased rate of RNFL thinning. Notably, the authors also identified an LCD breakpoint (489.7 µm) when Davies’ test was

employed, implying that LCD became a statistically significant determinant of RNFL thickness specifically when it was greater than this value. The authors note that it would be interesting to investigate whether increasing LCD has biomechanical implications in addition to its serving as a marker of lamina cribrosa displacement. They also posit that decreased LCT may impart a biomechanical disadvantage, possibly through pinching of axons and relative blockade of axoplasmic flow or through compression of laminar capillaries. They also note that pseudoexfoliation glaucoma patients with the same disease severity have a thinner LCT than their POAG counterparts, as well as a worse prognosis.

Evan Price

VISION IS PAINTED BY EMOTION

Vuilleumier P. Affective and motivational control of vision. *Curr Opin Neurol* 2015;28:29–35.

The ways that we perceive our surroundings are influenced directly by our emotions. In this review, the author shows exactly how directly affective inputs can modulate our experience of the visual world. Through thorough citing of recent research, it is shown that visual targets with emotional meaning (such as faces expressing fear and violent scenes) are found faster in visual search tasks and serve as better distractors. They are judged as sharper and more vivid when compared with images with equal luminance and contrast. Eye tracking studies reveal that they attract more total fixations and first fixations than details related to brightness or contrast. In addition, emotional face and body gestures incite increased activity in extrastriate cortex on functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Interestingly, they also bring about more activity in areas of earlier visual processing (V1), which the author argues accounts for the perceptual advantage of these types of stimuli. The amygdala, which is known to be central to emotional learning and assessment, has been found to project to V1. In patients with amygdalar damage, visual cortex sees less of an incremental boost in signal on fMRI and EEG from emotional stimuli than it does in controls. It is also noted that the amygdala exhibits spatial correspondence, with a greater response seen to emotional stimuli in the contralateral hemifield. It is possible that this has implications in attentional orientation. Although most of these findings can be replicated with reward stimuli, the functional anatomy of the reward system's contribution to vision is less well known. It is suspected to involve the basal ganglia, dopaminergic projections from the midbrain, and possibly the amygdala as well. The author also notes that these findings have possible applications in rehabilitation of visual disorders. For example, in patients with hemispatial neglect, visual stimuli that are consistently presented with loud white noise in a Pavlovian manner are better detected in neglected space on later testing than are non-conditioned visual stimuli. In addition, when patients with neglect are rewarded for finding certain visual targets in their neglected field, they preferentially shift their search strategy to that field. Interestingly, the subset of these patients with basal ganglia damage showed less shift in their search bias. The author concludes that our understanding of affective and motivational modulation of vision is in its nascent stages and that therapeutic application of our understanding should be further investigated.

Evan Price

HOW DO ER DOCTORS EVALUATE PAEDIATRIC HORNER?

Cahill JA, Ross J. Eye on children: acute work-up for pediatric Horner's syndrome. Case presentation and review of the literature. *J Emerg Med* 2015;48:58–62.

This paper takes a specific scenario—a child with Horner syndrome—and presents it from the perspective of an emergency room (ER) physician. It behoves us to be aware of what non-neuro-ophthalmologists know about the diseases we treat and what their literature reports to them. In this case, the authors first give a brief review of the anatomy and differential diagnosis of ptosis and anisocoria in both adults and children, then focusing on the specific topic of how paediatric Horner is evaluated. They acknowledge that there is little consensus, and without stating it specifically, imply correctly that there are no high-level studies to guide us. Although there are several papers that recommend no evaluation beyond physical examination for paediatric Horner, this paper does not focus on *if* to evaluate, rather *how* and *what* to evaluate. The authors acknowledge that it may not be necessary to work up paediatric Horner in the emergency room, per se (carotid dissection is not expected in paediatrics as it is in adults), but if evaluation is initiated, a flow chart of recommendations is offered for guidance. The role of

diagnostic eye drops (hydroxyamphetamine, cocaine) is essentially disregarded, and there is no mention of the limitations of urine catecholamine testing. The authors admit to lack of guidance regarding modality of imaging (computed tomography [CT] versus magnetic resonance imaging [MRI]) and ultimately, how and what to image is left to the specific resources of the ER physician. In general, though, this report should be essential reading for emergency room physicians. It's too bad the authors didn't recommend involvement of a neuro-ophthalmologist early to help guide the workup.

John H. Pula

GANGLION CELL AND INNER PLEXIFORM LAYER THICKNESS IN OPTIC PATHWAYS LESIONS

Moon H, Yoon JY, Lim HT, Sung KR. Ganglion cell and inner plexiform layer thickness determined by spectral domain optical coherence tomography in patients with brain lesions. *Br J Ophthalmol* 2015;99:329–335.

The authors retrospectively studied the visual fields (VF); the ganglion cell and inner plexiform layer (GCIPL) thickness; and the peripapillary retinal nerve fibre layer (pRNFL) thickness in 98 patients with brain lesions and 58 healthy controls. Their results showed good correlations between VF deficits, GCIPL thickness maps, and pRNFL thickness profiles, suggesting the interest of studying GCIPL thickness map modifications in patients with optic pathways lesions.

Matthieu Robert

KNOBLOCH SYNDROME AND THE ROLE OF COL18A1 IN HUMAN CORTICAL DEVELOPMENT

Caglayan AO, Baranoski JF, Aktar F, Han W, Tuysuz B, Guzel A, Guclu B, Kaymakcalan H, Aktekin B, Akgumus GT, Murray PB, Erson-Omay EZ, Caglar C, Bakircioglu M, Sakalar YB, Guzel E, Demir N, Tuncer O, Senturk S, Ekici B, Minja FJ, Sestan N, Yasuno K, Bilguvar K, Caksen H, Gunel M. Brain malformations associated with Knobloch syndrome—review of literature, expanding clinical spectrum, and identification of novel mutations. *Pediatr Neurol* 2014;51:806–813.

Four cases of Knobloch syndrome from four distinct consanguineous families are described. Their phenotype was characterised by severe structural brain malformation, but without encephalocele-polymicrogyria in three cases, cerebellar vermis atrophy in the remaining case, which led to whole-exome genotyping, whole-exome sequencing, and confirmatory Sanger sequencing. Mutations in the *COL18A1* gene were found. The ocular phenotype was variable—only one of them exhibited both high myopia and vitreoretinal degeneration, another one congenital aphakia, another one lens subluxation, and the last one bilateral retinal detachment. Using immunohistochemical analysis, the authors also studied the protein expression of *COL18A1* in foetal and adult cerebral cortex and during human cortical development. Their data support an important role for *COL18A1* in brain development.

Matthieu Robert

OUTER RETINAL THINNING IN PATIENTS WITH UNILATERAL OPTIC NERVE HYPOPLASIA

Abbasian J, Blair N, Shahidi M, Ying GS, Huang J, Kaufman L, Blair M. Macular optical coherence tomography in patients with unilateral optic nerve hypoplasia. *JAAPOS* 2015;19:57–61.

The authors retrospectively analysed the macular SD-OCT findings in five patients with unilateral optic nerve hypoplasia. In addition to the unsurprising thinning of the ganglion cell layer, thinning of the inner retinal layer but also of the outer retinal layer was found. This new finding does not cast light on the still unknown pathophysiology of the condition, but instead brings up new exciting questions.

Matthieu Robert

NMO AFTER BONE MARROW TRANSPLANTATION

Baumer FM, Kamihara J, Gorman MP. Neuromyelitis optica in an adolescent after bone marrow transplantation. *Pediatr Neurol* 2015;52:119–124.

The authors report the case of a 17-year-old boy with seronegative neuromyelitis optica (NMO) having started 2 months after a bone marrow transplant for acute myeloid leukemia. In addition to intravenous (IV) methylprednisolone, he received five sessions of plasma exchange over 2 weeks. Mycophenolate mofetil and then intravenous immune globulin (IVIG) were subsequently used for prophylaxis. By 19 months post-transplant, his condition was stable, with partial recovery and no relapse. The authors were able to find two similar cases in the literature, although such cases are usually susceptible to be given a diagnosis of presumed autoimmune myelopathy. They urge not to give a diagnosis of graft-versus-host disease (GVHD) in such conditions unless there is requisite supporting evidence for it. They also insist on the low sensitivity of NMO antibodies in these situations, due to the use of immunosuppressants, and the need to repeat testing at regular intervals.

Matthieu Robert

COLOUR SYNAESTHESIA

Safran AB, Sanda N. Color synesthesia. Insight into perception, emotion, and consciousness. *Curr Opin Neurol* 2015;28:36–44.

The authors review the phenomena of synaesthesia, a disorder in which individuals experience unusual percepts elicited by the activation of an unrelated sensory modality or by a cognitive process. Emotional reactions are commonly associated. Like prosopagnosia, synaesthesia is classified as developmental and acquired. Structural and functional imaging has demonstrated distinct patterns in cortical activation and brain connectivity.

Michael Vaphiades

HIDING IN PLAIN SIGHT

Beh SC, Muthusamy B, Calabresi P, Hart J, Zee D, Patel V5, Frohman E. Hiding in plain sight: a closer look at posterior cortical atrophy. *Pract Neurol* 2015;15:5–13.

The authors review the clinical features posterior cortical atrophy, a neurodegenerative syndrome dominated by deterioration visuospatial and visuoperceptual function. It is most commonly due to Alzheimer disease, but may also be caused by Lewy body dementia, corticobasal degeneration, or Creutzfeldt-Jakob disease.

Michael Vaphiades

NAION: A MISNOMER

Parsa CF, Hoyt WF. Nonarteritic anterior ischemic optic neuropathy (NAION): a misnomer. Rearranging pieces of a puzzle to reveal a nonischemic papillopathy caused by vitreous separation. *Ophthalmology* 2015;122:439–442.

This editorial explores the topic of nonarteritic anterior ischaemic optic neuropathy (NAION) and questions the underlying presumption of ischaemia as an aetiology for NAION. The authors propose that traction and separation of the vitreous from the optic disc alters its structure and perhaps NAION is not primarily an ischaemic optic neuropathy and thus needs to be renamed as a papillary vitreous detachment.

Michael Vaphiades

NEURO-OPHTHALMOLOGIC SYMPTOMS AFTER PTERIONAL CRANIOTOMY

Desai SJ, Lawton MT, McDermott MW, Horton JC. Vertical diplopia and ptosis from removal of the orbital roof in pterional craniotomy. *Ophthalmology* 2015;122:631–638.

The authors report a case series of eight patients with neuro-ophthalmic symptoms after pterional craniotomy and described a newly recognised clinical syndrome consisting of ptosis, diplopia, vertical gaze limitation, and abduction weakness that can occur in 1% of patients after orbital roof removal during this surgery. The diplopia occurs from tethering of the superior rectus-levator palpebrae superioris complex to the surgical defect in the orbital roof. Lateral rectus function sometimes is compromised by muscle attachment to the lateral orbital osteotomy.

Michael Vaphiades

NATALIZUMAB AND QOL IN MULTIPLE SCLEROSIS

Chahin S, Balcer LJ, Miller DM, Zhang A, Galetta SL. Vision in a phase 3 trial of natalizumab for multiple sclerosis: relation to disability and quality of life. *J Neuroophthalmol* 2015;35:6–11.

In post-trial analyses, the authors studied the relation of visual function to quality of life (QOL), magnetic resonance imaging (MRI), and Expanded Disability Status Scale (EDSS) scores. Low-contrast visual acuity (LCVA) demonstrated treatment effects as a secondary outcome measure in the Phase 3 trial of natalizumab, AFFIRM. They concluded that loss of visual function, particularly as measured by LCVA, was common in AFFIRM, occurring in >20% of patients. Also, vision represented a key dimension of outcome assessment for MS and adds valuable information on disability and QOL measures.

Michael Vaphiades

PDE-5 INHIBITORS AND NAION

Nathoo NA, Etminan M, Mikelberg FS. Association between phosphodiesterase-5 inhibitors and nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol* 2015;35:12–15.

A pharmacoepidemiological nested case-control study was used to examine the association in a health claims database of physician diagnoses and prescription medication dispensing of phosphodiesterase-5 inhibitors and nonarteritic anterior ischaemic optic neuropathy (NAION) in 1,109 cases of NAION matched to 1,237,290 controls identified within the database. They found that cases were more likely to have hyperlipidaemia, diabetes, hypertension, myocardial infarction, and cerebrovascular accident in the year preceding their NAION, but their data did not suggest any association between having a prescription filled for PDE-5 inhibitor medication and receiving a diagnosis code for NAION.

Michael Vaphiades

EYE MOVEMENTS IN SCA

Moscovich M, Okun MS, Favilla C, Figueroa KP, Pulst SM, Perlman S, Wilmot G, Gomez C, Schmahmann J, Paulson H, Shakkottai V, Ying S, Zesiewicz T, Kuo SH, Mazzoni P, Bushara K, Xia G, Ashizawa T, Subramony SH. Clinical evaluation of eye movements in spinocerebellar ataxias: a prospective multicenter study. *J Neuroophthalmol* 2015;35:16–21.

The authors analysed eye movement abnormalities detected prospectively in 301 patients at the baseline visit during a large multi-centre natural history study of spinocerebellar ataxias (SCAs) 1, 2, 3, and 6. No specific ocular motor abnormality was pathognomonic to any SCA; significant differences were noted in their occurrence among different disorders. SCA 6 was characterised by frequent occurrence of nystagmus and abnormal pursuit and rarity of slow saccades and ophthalmoparesis and SCA 2 by the frequent occurrence of slow saccades and

infrequent nystagmus and dysmetric saccades. SCA 1 and SCA 3 subjects had a more even distribution of eye movement abnormalities.

Michael Vaphiades

CLINICAL CHANGES AFTER CSF SHUNTING IN PSEUDOTUMOR CEREBRI

Rizzo JL, Lam KV, Wall M, Wilson MD, Keltner JL. Perimetry, retinal nerve fiber layer thickness and papilledema grade after cerebrospinal fluid shunting in patients with idiopathic intracranial hypertension. *J Neuroophthalmol* 2015;35:22–25.

The authors retrospectively reviewed all cases of idiopathic intracranial hypertension (IIH) with cerebrospinal fluid (CSF) shunting at their institution between 2004 and 2011. Perimetry was performed before and after surgery in 15 patients, and the mean deviation was compared before and after surgery to assess the effect of the intervention. The results suggested that CSF shunting results in improvement in perimetry, retinal nerve fibre layer swelling, and papilloedema grade in patients with IIH.

Michael Vaphiades

MILD COGNITIVE IMPAIRMENT IN PSEUDOTUMOR CEREBRI

Zur D, Naftaliev E, Kesler A. Evidence of multidomain mild cognitive impairment in idiopathic intracranial hypertension. *J Neuroophthalmol* 2015;35:26–30.

Thirty consecutive idiopathic intracranial hypertension (IIH) patients completed a cognitive test battery including non-verbal memory, executive function, visual spatial processing, attention, motor skills, problem solving, and information processing. All domain index scores were below average for age and education. The global cognitive score, attention, and visual spatial indices had the lowest scores indicating that patients with IIH have mild multi-domain cognitive impairment. The relationship between cognitive impairment and chronically elevated intracranial pressures and its role in contributing to patient morbidity requires further study.

Michael Vaphiades

B CELLS INITIATE DEMYELINATION IN OPTIC NEURITIS

Feldman A, Gurevich M, Huna-Baron R, Achiron A. The role of B cells in the early onset of the first demyelinating event of acute optic neuritis. *Invest Ophthalmol Vis Sci* 2015;56:1349–1356.

The initial phase of the immune response plays an important role in the pathogenesis of demyelinating optic neuritis. The authors evaluated the gene expression profiles of peripheral blood mononuclear cells using high throughput Affymetrix technology. They found that there is significantly differentiating gene expression in the CD19-positive B cells, with less expressional change in macrophage and T cells, in the early stage of acute optic neuritis (ON). This differentiating gene expression has been verified by quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) and Western blot. The authors conclude that CD19-positive B cells have a significant role in the pathogenesis of the first demyelinating event in acute ON and suggest their role as a possible target for immunomodulation.

An-Guor Wang

ACQUIRED PROSOPAGNOSIA

Schmidt D. Neuro-ophthalmological findings in patients with acquired prosopagnosia. *Graefes Arch Clin Exp Ophthalmol* 2015;253:333–334.

The author compiled the clinical data of 147 patients with acquired prosopagnosia from the international literature and summarised the laterality, aetiology, visual field defect, and associated neuro-ophthalmic disturbances.

An-Guor Wang

IS MS A MITOCHONDRIAL DISEASE?

Matthews L, Enzinger C, Fazekas F, Rovira A, Ciccarelli O, Dotti MT, Filippi M, Frederiksen JL, Giorgio A, Küker W, Lukas C, Rocca MA, De Stefano N, Toosy A, Yousry T, Palace J, On behalf of the MAGNIMS network. MRI in Leber's hereditary optic neuropathy: the relationship to multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2015;86:537–542.

The association between Leber's hereditary optic neuropathy (LHON) and multiple sclerosis (MS) has been shown to occur up to 50 times more often than expected by chance. This research group compared magnetic resonance imaging (MRI) features of patients with MS ($n=30$); patients with MS and LHON mutation ("LMS"; $n=11$); and patients with LHON (only), *i.e.* with no diagnosis of MS ($n=31$). The objective was to assess whether the MRI appearances of patients with LMS differed from those with relapsing remitting MS, to characterise cerebral MRI findings in LHON, and to determine whether female patients with LHON are more likely to have brain MS-like lesions than male patients. Three neuroradiologists did blinded assessments of MRIs.

The results showed that the MRI features of MS and LMS were indistinguishable, whereas LHON (only) had either a normal MRI or non-specific white matter lesions. More female patients with LHON had LMS compared with the male patients, suggesting that female patients who develop LHON clinically have a high risk of clinical or radiological MS.

In the discussion section, the authors nicely summarised the previous papers reporting this association and the possible hypotheses for why LHON may be a risk factor for MS—*e.g.* mitochondrial defects trigger the autoimmune process; the final common pathway of neural damage from mitochondrial dysfunction.

This is the first blinded observational study of MRI features of LHON and LMS. The paper is interesting in confirming what has been observed clinically by some neuro-ophthalmologists. This study puts further weight on the importance of mitochondrial dysfunction in the pathogenesis of MS, although much is still not understood. Unfortunately, as this was a paper focusing on the MRI changes, detailed clinical information was limited, *e.g.* whether the clinical picture was typical for LHON (subacute onset) or a progressive optic neuropathy, and whether MS onset occurred before LHON or vice versa.

Sui Wong

IIH: A GLOBAL PROBLEM!

Almarzouqi SJ, Morgan ML, Lee AG. Idiopathic intracranial hypertension in the Middle East: a growing concern. *Saudi J Ophthalmol* 2015;29:26–31.

The authors highlight the importance of idiopathic intracranial hypertension (IIH) in the Middle East, by reviewing published work on the epidemiology in this region. The incidence of IIH is estimated at 2.02–2.2/100,000, *i.e.* higher than what was estimated in the USA (0.9–1/100,000). This is linked with the epidemic of obesity in the region. Comment in the paper was made about the higher risk of visual loss in patients of African heritage, men, older patients, those with uraemia, and hypertension—although strictly speaking perhaps there may be some mix of pseudotumor cerebri from other causes rather than "idiopathic" intracranial hypertension as such. This paper highlights an important issue, on the problem of the obesity epidemic, even seen outside the "western" hemisphere, and its significant contribution to visual loss.

Sui Wong