ABSTRACTS

Neuro-Ophthalmic Literature Review

Axel Petzold, Michael Vaphiades, An-Guor Wang, and Sui Wong

THE NEW ENGLAND HAT-TRICK

- [1] Sukhija J, Kaur S. Morgagnian cataract. *N Engl J Med* 2014;370:2326.
[2] Mahroo OA, Graham EH. Roth spots in infective endocarditis. *N Engl J Med* 2014;370:e38.
[3] Fante RJ, Trobe JD. Bilateral corneal abrasions from airbag deployment. *N Engl J Med* 2014;370:e36.
[4] Lazar JD, Willis LK. A Blinking knee. *N Engl J Med* 2014;370:e36.

We had to have a *hat-trick* in honor of the 2014 Football World Cup, correct? Three consecutive issues of the *New England Journal of Medicine* (NEJM) presented problems of interest to the neuro-ophthalmologist. The first *goal* was scored by Lazar and Willis in the June 12, 2014, issue presenting a case of gradual loss of vision down to hand movements in a 48-year-old man caused by a Morgagnian cataract. Vision improved to 20/30 after surgery.¹ The second *goal* came by Mahroo and Graham in the June 19, 2014, issue from a case of reduced vision due to transient Roth spots in the macular area on basis of an infectious endocarditis that improved with intravenous antibiotics to 20/20.² The third *goal* was a contribution by Fante and Trobe in the June 26, 2014, issue of a young woman with visual loss and pain due to an airbag nylon mesh imprint on her cornea that resolved within 24 hours after treatment with erythromycin ointment.³ And in case we needed more ophthalmology reports from the NEJM, in these same issues we also learned of a patient who had a “blinking knee.”⁴

Axel Petzold

HYPER-REFLECTIVE DOTS IN OCT: CLASSIFICATION AND DISEASE SPECTRUM

Scoles D, Higgins BP, Cooper RF, Dubis AM, Summerfelt P, Weinberg DV, Kim JE, Stephien KE, Carroll J, Dubra A. Microscopic inner retinal hyper-reflective phenotypes in retinal and neurologic disease. *Invest Ophthalmol Vis Sci* 2014;55:4015–4029.

The presence of scattered hyper-reflective spots on OCT images has, as the authors correctly point out, been observed for some time but not been studied systematically. Here the authors for the first time used adaptive optics to systematically study the presence and distribution of hyper-reflective dots in the retina in a large disease spectrum (101 patients, 38 diseases, 11 unknown aetiologies). A classification scheme of seven categories was proposed: (i) punctate reflectivity, (ii) nummular (disc-shaped) reflectivity, (iii) granular membrane, (iv) waxy membrane, (v) vessel-associated membrane, (vi) microcysts, and (vii) striate reflectivity. The authors were careful to include longitudinal data and apply their proposed classification to each disease. This led to the conclusion that the finding was not disease specific, but may merit further investigation as a candidate biomarker. As a major limitation, the authors discussed the small number of subjects per disease category, opening avenues for future studies to apply the proposed classification to larger, clinically well-categorized cohorts.

Axel Petzold

CLOSING IN ON RETROGRADE TRANS-SYNAPTIC AXONAL DEGENERATION

Klistorner A, Sriram P, Vootakuru N, Wang C, Barnett MH, Garrick R, Parratt J, Levin N, Raz N, Van Der Walt A, Masters L, Graham SL, Yiannikas C. Axonal loss of retinal neurons in multiple sclerosis associated with optic radiation lesions. *Neurology* 2014;82:2165–2172.

This cross-sectional study elegantly describes how multiple sclerosis (MS) lesions in the optic radiations might be responsible for retrograde trans-synaptic axonal degeneration leading to loss of retinal nerve fibre layer (RNFL) and retinal ganglion cells. The authors built their hypothesis on an earlier observation of RNFL thinning in patients with MS who never suffered from a clinical episode of MS optic neuritis (MSON), yet had latency delay on multifocal visual evoked potentials (VEP). How could this be explained other than by demyelination of the posterior visual pathways? The present study closed in on this hypothesis by combining magnetic resonance imaging (MRI) tractography with structural and quantitative MRI data. There were no MS lesions in the optic tract. There was a linear relationship between the MS lesion volume in the optic radiations, as identified by tractography, and thinning of the temporal RNFL (Pearson $r=0.64$, $p<0.001$; $N=38$). Likewise diffusion tensor imaging indices were significantly correlated to temporal RNFL thinning. We do not know yet about possible correlations with the retinal ganglion cell layer, but the inner nuclear layer (INL) stands as a firm barrier (37.1 μm in controls and 37.7 μm in MS patients).

Axel Petzold

ENLARGEMENT OF THE INFRAORBITAL NERVE

Hardy TG, McNab AA, Rose GE. Enlargement of the infraorbital nerve: an important sign associated with orbital reactive lymphoid hyperplasia or IgG4-related disease. *Ophthalmology* 2014;121:1297–1303.

The authors performed a retrospective, noncomparative review of 14 patients with proptosis and periocular pain. All patients had some extraocular muscle enlargement. The infraorbital canal was enlarged in 20 of the 28 orbits. When tested, serum immunoglobulin G4 (IgG4) was elevated in 6 of 7 patients and reactive lymphoid hyperplasia in 7 patients. The authors concluded that enlargement of the infraorbital nerve and canal is rare and strongly suggests a diagnosis of reactive lymphoid hyperplasia or IgG4-related disease, especially in the presence of ipsilateral extraocular muscle enlargement, sinus disease, or orbital disease.

Michael Vaphiades

PAPILLOEDEMA AS THE INITIAL PRESENTATION OF CASTLEMAN DISEASE

Tian G, Jing Y, Jiang H, Wang J, Zhang X. Papilledema as the initial presentation of Castleman disease. *J Neuroophthalmol* 2014;34:169–172.

The authors report a patient with papilloedema from Castleman disease, which is a rare lymphoproliferative disorder that has many presentations ranging from unifocal or multifocal mass lesions to a monoclonal gammopathy. It can also rarely present with increased intracranial pressure as in this case.

Michael Vaphiades

CONGENITAL FIXED DILATED PUPILS

Roulez FM, Faes F, Delbeke P, Van Bogaert P, Rodesch G, De Zaeytijd J, Depasse F, Coucke PJ, Meire FM. Congenital fixed dilated pupils due to ACTA2- multisystemic smooth muscle dysfunction syndrome. *J Neuroophthalmol* 2014;34:137–143.

The authors report 3 patients with congenital fixed dilated pupils all carrying the p.R179H heterozygous mutation in the ACTA2 gene. Congenital fixed dilated pupils is a rare condition and should alert ophthalmologists to the

possibility of the coexistence of systemic life-threatening disorders such as thoracic aortic aneurysms and dissections, early coronary artery disease, and strokes.

Michael Vaphiades

TOPOLOGY OF BRAINSTEM LESIONS ASSOCIATED WITH SUBJECTIVE VISUAL VERTICAL TILT

Yang TH, Oh SY, Kwak K, Lee JM, Shin BS, Jeong SK. Topology of brainstem lesions associated with subjective visual vertical tilt. *Neurology* 2014;82:1968–1975.

The authors measured the subjective visual vertical (SVV) in 82 patients with acute unilateral infarction of the brainstem. The topology of the brainstem lesions were mapped using MRI. Fifty percent of patients with acute unilateral brainstem infarcts had abnormal SVV tilt, of which 76% had ipsiversive tilt and 24% had contraversive tilt and these infarcts were mapped to various nuclei and fasciculi in the brain. The authors concluded that their findings provide evidence of a pathway transmitting ipsiversive otolithic signals that bypass the oculomotor system at the medial side of the medial lemniscus, called the ipsilateral vestibulothalamic tract.

Michael Vaphiades

RETINAL ARCHITECTURE AND MF-ERG

Schnurman ZS, Frohman TC, Beh SC, Conger D, Conger A, Saidha S, Galetta S, Calabresi PA, Green AJ, Balcer LJ, Frohman EM. Retinal architecture and mfERG: optic nerve head component response characteristics in MS. *Neurology* 2014;82:1888–1896.

The authors studied the relationship between optic nerve head component (ONHC) response abnormalities and performance using a variety of different parameters including multifocal ERG (mfERG) in 18 in patients with multiple sclerosis (MS), 18 controls, and 3 glaucoma patients. They found that MS patients exhibited an increased number of abnormal or absent ONHC responses on mfERG. They concluded that further characterization of ONHC abnormalities may contribute to the development of novel neurotherapeutics in MS.

Michael Vaphiades

VITAMIN D AND OTHER FACTORS INFLUENCING OPTIC NEURITIS

Malik MT, Healy BC, Benson LA, Kivisakk P, Musallam A, Weiner HL, Chitnis T. Factors associated with recovery from acute optic neuritis in patients with multiple sclerosis. *Neurology* 2014;82:2173–2179.

The authors evaluated 253 adult and 38 paediatric patients with acute optic neuritis (AON). Demographic and clinical features associated with attack severity and recovery were identified. For another group of patients, blood samples were available within 6 months of an AON attack. In this group, the impact of vitamin D level on the severity/recovery was also assessed. The authors concluded that vitamin D levels affect AON severity, whereas younger age, attack severity, and male sex affect recovery.

Michael Vaphiades

A PAIN IN THE EYE

Armbrust KR, Kosmorsky GS, Lee MS, Friedman DI. A pain in the eye. *Surv Ophthalmol* 2014;59:474–477.

The authors discuss the differential diagnosis and work-up of a 38-year-old woman who presented with chronic left retro-orbital pain and photophobia. The diagnosis of cervicogenic headache was

confirmed by symptom resolution following left greater occipital nerve blockade. Referred retro-orbital pain is discussed.

Michael Vaphiades

HIV AND CANNOT SEE

Prospero Ponce CM, Al Zubidi N, Beaver HA, Lee AG, Huey DA, Chavis PS. HIV and cannot see. *Surv Ophthalmol* 2014;59:468–473.

A 55-year-old human immunodeficiency virus (HIV)-positive man presented with acute vision loss in the right eye and altered mental status. Ophthalmic evaluation revealed light perception vision OD with a right relative afferent pupillary defect, conjunctival chemosis, large mutton-fat keratic precipitates, and diffuse cream-coloured vitreous cells. Magnetic resonance imaging of the brain and orbit with and without contrast with fat saturation showed choroidal thickening OD, multifocal deep periventricular and deep ganglionic enhancing lesions, and a suprasellar mass. Brain biopsy showed diffuse large B-cell lymphoma. The authors review the case as an unknown and generate comments and a differential diagnosis at various steps of the evaluation.

Michael Vaphiades

PARAINFECTIOUS OPTIC NEURITIS: CHILDREN VERSUS ADULTS

Rappoport D, Goldenberg-Cohen N, Luckman J, Leiba H. Parainfectious optic neuritis: manifestations in children vs adults. *J Neuroophthalmol* 2014;34:122–129.

Ten children (50% female) and 8 adults (50% female) diagnosed with parainfectious optic neuritis were evaluated by two neuro-ophthalmology services between 2005 and 2012, with a mean follow-up was 29.4 months in the paediatric group and 14.2 months in the adults. The main inclusion criterion was acute optic neuritis within 1 month after an infection. The patients had a standard work-up, including neuroimaging and cerebrospinal fluid (CSF) analysis. The authors concluded that parainfectious optic neuritis is associated with a favourable visual prognosis regardless of age. Children tend to manifest visual symptoms sooner after the antecedent infectious illness and more often bilaterally and in conjunction with acute disseminated encephalomyelitis (ADEM). The causative agent is isolated less frequently in children compared with adults.

Michael Vaphiades

OCT SHAPE ANALYSIS OF THE PERIPAPILLARY RPE LAYER IN PRESUMED OPTIC NERVE SHEATH MENINGIOMA

Sibony P, Strachovsky M, Honkanen R, Kupersmith MJ. Optical coherence tomography shape analysis of the peripapillary retinal pigment epithelium layer in presumed optic nerve sheath meningiomas. *J Neuroophthalmol* 2014;34:130–136.

Geometric morphometrics (GM) was used to compare the shape of the peripapillary retinal pigment epithelium–Bruch's membrane (ppRPE) layer imaged on spectral domain optical coherence tomography (SD-OCT) of 10 patients (11 eyes) with presumed optic nerve sheath meningiomas (pONSM) and 30 controls. The shape of the RPE layer in pONSM was characterized by an inverted-U shape or indentation that differs significantly from normal and is indistinguishable from the shape previously reported in papilloedema and is not caused by disc oedema. The mechanism is unknown.

Michael Vaphiades

INTERMITTENT HORNER SYNDROME IN A PAEDIATRIC PATIENT

Gupta M, Leskov I, Kruger JM, Cestari DM. Intermittent Horner syndrome in a pediatric patient. *J Neuroophthalmol* 2014;34:149–150.

In this photo essay, the authors describe a paediatric patient with an intermittent Horner syndrome in a patient with a syrinx at C7. They discuss potential aetiologies of the Horners.

Michael Vaphiades

FRIEDREICH ATAXIA AND OCT

Dağ E, Ornek N, Ornek K, Erbahçeci-Timur IE. Optical coherence tomography and visual field findings in patients with Friedreich ataxia. *J Neuroophthalmol* 2014;34:118–121.

The authors evaluated 10 patients with genetically confirmed Friedreich ataxia (FRDA), and 22 age- and gender-matched controls. All eyes were examined with spectral domain OCT and Humphrey Field analyzer. The authors concluded that FRDA patients may have a measurable degree of retinal thinning on OCT and generalized reduction of sensitivity in visual field testing. Combining these parameters may be useful in the follow-up of patients with FRDA.

Michael Vaphiades

RETINAL MICROSTRUCTURAL CHANGES IN EYES WITH RESOLVED BRANCH RETINAL VEIN OCCLUSION

Akagi-Kurashige Y, Tsujikawa A, Ooto S, Makiyama Y, Muraoka Y, Kumagai K, Uji A, Arichika S, Murakami T, Miyamoto K, Yoshimura N. Retinal microstructural changes in eyes with resolved branch retinal vein occlusion: an adaptive optics scanning laser ophthalmoscopy study. *Am J Ophthalmol* 2014;157:1239–1249.

The authors performed a prospective observational cross-sectional case series of 21 eyes (21 patients) with branch retinal vein occlusion (BRVO). Each patient underwent full ophthalmologic examination and imaging with optical coherence tomography (OCT) and a prototype adaptive optics scanning laser ophthalmoscopy (AO-SLO). After complete resolution of macular oedema and retinal haemorrhage, cone mosaic patterns were disorganized and parafoveal cone density was significantly decreased, retinal capillaries were dilated, no longer had a uniform caliber, and had less direct paths through the retina. Interestingly, these cone changes were seen in the parafoveal regions in the unaffected side.

Michael Vaphiades

MULTIFOCAL VISUAL EVOKED POTENTIALS AND OPTIC RADIATION LESIONS

Alshowaier D, Yiannikas C, Garrick R, Parratt J, Barnett MH, Graham SL, Klistorner A. Latency of multifocal visual evoked potentials in nonoptic neuritis eyes of multiple sclerosis patients associated with optic radiation lesions. *Invest Ophthalmol Vis Sci* 2014;55:3758–3764.

Multiple sclerosis (MS) may affect the entire visual pathway. However, most of the visual complaints in MS patients are attributed to the anterior portion of the visual pathway. The authors conducted an electrophysiologic study to evaluate retrochiasmal demyelinating lesions in non-optic neuritis eye of MS patients. They found a significant delay in multifocal visual evoked potential (mfVEP) latency for the MS cohort compared with controls. This latency delay in mfVEP was significantly correlated with the optic radiation (OR) lesion load. The findings in

this study support the hypothesis that latency delay of the mfVEP in eyes of MS patients without previous optic neuritis (ON) is related to retrogenicular demyelinating lesions. Additionally, mfVEP shows its potential in the evaluation of retrochiasmal white matter lesions.

An-Guor Wang

OCT IN MILD PAPILLOEDEMA AND PSEUDOPAPILLOEDEMA

Fard MA, Fakhree S, Abdi P, Hassanpoor N, Subramanian PS. Quantification of peripapillary total retinal volume in pseudopapilledema and mild papilledema using spectral-domain optical coherence tomography. *Am J Ophthalmol* 2014;158:136–143.

Traditionally we use the direct exam to detect disc oedema. Many ophthalmoscopic clues help us differentiate pseudopapilloedema from true papilloedema. Nevertheless, mild or moderate grades of papilloedema at times cannot be distinguished reliably from pseudopapilloedema by ophthalmoscopy. In a cohort study, the authors use spectral-domain optical coherence tomography (SD-OCT) to study eyes with mild papilloedema, pseudopapilloedema (congenitally elevated optic discs), and normal eyes. They found that the peripapillary total retinal outer circle volume (between diameter of 2.22 mm and 3.45 mm) was significantly larger in papilloedema group ($2.68 \pm 0.49 \text{ mm}^3$) compared with the pseudopapilloedema group ($2.03 \pm 0.24 \text{ mm}^3$). The authors conclude that outer peripapillary total retinal ring volumes might be useful in differentiating papilloedema from pseudopapilloedema.

An-Guor Wang

RETROBULBAR HAEMODYNAMICS IN N-AION

Zhu W, Cui M, Yao F, Liao R, Liu L. Retrobulbar and common carotid artery haemodynamics and carotid wall thickness in patients with non-arteritic anterior ischaemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2014;252:1141–1146.

Investigating retrobulbar haemodynamics may help delineating the pathogenesis of nonarteritic anterior ischaemic optic neuropathy (N-AION). The authors recruited 22 N-AION patients and 28 age- and sex-matched controls in this prospective study. The retrobulbar and common carotid artery (CCA) haemodynamics and CCA wall thickness were evaluated by colour Doppler imaging. They found that blood flow velocities in the central retinal artery (CRA) were significantly decreased on the affected side of N-AION patients as compared with normal controls. In addition the intima-media thickness of the CCA was greater on the affected side of N-AION patients compared with normal controls. Thus, decreased blood velocities in the CCA and increased carotid wall thickness were found on the affected side of acute N-AION compared with normal controls.

An-Guor Wang

IGG4-RELATED HYPERTROPHIC PACHYMENINGITIS

Lu L, Della-Torre E, Stone JH, Clark SW. IgG4-related hypertrophic pachymeningitis: clinical features, diagnostic criteria and treatment. *JAMA Neurol* 2014;71:785–793.

Are you worried about inflammatory meningeal diseases such as sarcoidosis or granulomatosis with polyangiitis, but although biopsy excluded infection and malignancy, results were otherwise inconclusive? Consider if your histopathologist has tested for IgG4 disease.

IgG4-related disease (IgG4-RD) was first described in 2001 but only recently recognized to present with hypophysitis and hypertrophic pachymeningitis. The authors reviewed all published reports of IgG4-related hypertrophic pachymeningitis to date: 33 patients. There was a predominance of men (64%), middle-aged or older, presenting with headache (67%), cranial nerve palsies (33%), and visual problems (21%), including diplopia or reduced acuity. Presentation typically reflected mechanical compression of vascular or nerve structures. The majority (70–90%) of IgG4-RD patients had elevated serum IgG4 levels, although this test lacked sufficient

sensitivity and specificity for the purposes of diagnosis—serum IgG4 may remain normal particularly if the meninges were the only site of disease. Cerebrospinal fluid (CSF) was frequently normal, but may show elevated protein, lymphocytosis, and oligoclonal bands; one study reported CSF IgG4 levels to be highly sensitive and specific. Systemic involvement and degree of active inflammation within the meninges can be detected by positron emission tomography scans with fludeoxyglucose F18.

Biopsy is the gold standard for diagnosis: characteristic features include dense lymphoplasmacytic infiltrate, fibrosis with storiform features, and obliterative phlebitis. Elevated IgG4 to IgG plasma cell ratio (>40%) on immunohistochemistry is commonly seen. There is currently no consensus on treatment for IgG4-related hypertrophic pachymeningitis, but most report using glucocorticoids as first-line treatment followed by the addition of other immunosuppressive agents in the event of recurrence, and the authors predict future treatment studies will focus on B-cell depletion.

Sui Wong