ABSTRACTS

Neuro-Ophthalmic Literature Review

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Macular OCT changes detectable before visual loss in Leber's hereditary optic neuropathy

Balducci N, Savini G, Cascavilla ML, La Morgia C, Triolo G, Giglio R, Carbonelli M, Parisi V, Sadun AA, Bandello F, Carelli V, Barboni P. Macular nerve fibre and ganglion cell layer changes in acute Leber's hereditary optic neuropathy. *Br J Ophthalmol* 2016;100:1232–1237.

In acute Leber's hereditary optic neuropathy (LHON), there is initial mild disc swelling, followed by optic atrophy of gradual onset. This is reflected in the peripapillary retinal nerve fibre layer (pRNFL) thickness, with early thickening and late thinning. Increasingly macular ganglion cell inner plexiform layer (GC-IPL) and macular RNFL (mRNFL) measurements are being used in neuro-ophthalmology, particularly in the setting of optic disc swelling. In this prospective observational case series, the authors measured the GC-IPL and mRNFL thickness in six eyes of four patients with LHON at 1, 3, 6, and 12 months after visual loss. In particular, two eyes were examined before the onset of visual loss. As expected, there was gradual GC-IPL and mRNFL thinning, which plateaued at 6 months. More interestingly, in the two pre-symptomatic eyes, GC-IPL and mRNFL thinning was detectable before onset of visual loss: the reduction followed a centrifugal and spiral pattern resembling the anatomical distribution of the papillomacular bundle fibres. This change might allow us to identify LHON carriers who are about to lose vision and for us to test potential therapeutic agents during this crucial early stage.

Carmen Chan

Enlarged infraorbital nerve is a prognostic feature in idiopathic orbital inflammatory disease

Lee KH, Han SH, Yoon JS. Implications of enlarged infraorbital nerve in idiopathic orbital inflammatory disease. *Br J Ophthalmol* 2016;100:1295–1300.

Enlargement of the infraorbital nerve (ION) has been associated with IgG4-related orbital inflammation. In this retrospective comparative case series, the authors identified 89 consecutive patients diagnosed with idiopathic orbital inflammatory disease (IOID), divided them into two groups—those with ION enlargement ($n = 12$, 13.5%) and those without ($n = 77$) and compared the clinical features of the two groups. It was found that in the group with ION enlargement, the patients had significantly more proptosis, eyeball pain, alteration of sensation/pain of cheek, and sclerosing disease. They were also more likely to have recurrences and to need second-line immunosuppressants/radiation therapy. Interestingly, the ratio of IgG4-related disease was not significantly different between the two groups (due to small sample size?). Therefore, enlarged ION can be used as a prognostic feature in IOID—those patients who have it need to be followed up more closely to monitor for recurrences.

Carmen Chan

Wolfram syndrome gene mutations in optic atrophy

Grenier J, Meunier I, Daien V, Baudoin C, Halloy F, Bocquet B, Blanchet C, Delettre C, Esmenjaud

E, Roubertie A, Lenaers G, Hamel CP. WFS1 in optic neuropathies: mutation findings in nonsyndromic optic atrophy and assessment of clinical severity. *Ophthalmology* 2016;123:1989–1998.

The authors performed a retrospective molecular genetic study evaluating for *WFS1* mutations in patients with optic atrophy. *WFS1* mutation is known to cause Wolfram syndrome, an autosomal condition associated with early-onset diabetes and optic atrophy, and later hearing loss, neurologic impairment, and psychiatric illnesses. Grenier et al. evaluated a cohort of patients with autosomal recessive non-syndromic optic atrophy and found that 3 of 24 (15%) had a biallelic mutation in *WFS1*. Four of 20 (20%) of patients with autosomal dominant optic atrophy had a heterozygous mutation in *WFS1* resulting in autosomal dominant Wolfram-like syndrome with associated hearing loss. Patients with autosomal recessive syndromic Wolfram syndrome had worse visual acuities than patients with non-syndromic optic atrophy associated with *WFS1* or autosomal dominant Wolfram-like syndrome.

This study highlights the variable nature of *WFS1* mutations, which can cause syndromic autosomal recessive Wolfram syndrome, dominant Wolfram-like syndrome, and non-syndromic optic atrophy. Based on this study, one can consider screening for *WFS1* mutation in *OPA1*-negative cases of non-syndromic optic atrophy. In addition, a mutation in *WFS1* does not necessarily mean a patient is destined to develop neurologic decline or other systemic symptoms of Wolfram syndrome.

John Chen

Dichoptic reaction times open a new window on functional vision loss

Frisen L. Dichoptic reaction times open a new window on functional loss of vision. *Ophthalmology* 2016;123:1834–1835.

Frisen demonstrated that dichoptic measurements of reaction times did well in identifying patients with functional vision loss. He compared 12 patients with functional vision loss with 15 normal patients and 15 patients with organic vision loss. He used commercial digital video eyewear to randomly flash a light to the left or right eye, with the patient given the task of

clicking when the light was seen. Reaction times were significantly delayed in patients with functional vision loss, which was not seen in patients with organic vision loss. Surprisingly, reaction times on automated perimetry were not delayed in patients with functional vision loss. Frisen speculated on the causes of the delayed reaction time with dichoptic measurements, including the possibility that functional vision loss relates to disordered disambiguation and problems with multi-stable perceptions.

Dichoptic measurements of reaction time could be a helpful adjunct to our current armamentarium for functional vision loss. It will not be helpful in patients claiming to be “no light perception” as was seen in one patient in this study, but these are easily disproved with other techniques.

John Chen

The pharmacotherapy of cerebellar and central vestibular disorders

Kalla R, Teufel J, Feil K, Muth C, Strupp M. Update on the pharmacotherapy of cerebellar and central vestibular disorders. *J Neurol* 2016;263 (Suppl 1):S24–S29.

The authors provide an overview of current pharmacotherapy for central vestibular vertigo, cerebellar disorders, and the most common forms of central nystagmus. Recently, treatment of these disorders with aminopyridines has been developed. Downbeat nystagmus has been treated with γ -aminobutyric acid (GABA)ergic substances with moderate success, but 3,4-diaminopyridine and 4-aminopyridine (4-AP) have been effective with few side effects. Chlorzoxazone is a new agent that has undergone preliminary studies in downbeat nystagmus, but requires a randomised, placebo controlled study. Upbeat nystagmus has also been successfully treated with 4-AP, but often resolves spontaneously and may not need long-term treatment. Periodic alternating nystagmus is successfully treated with baclofen, but other treatments include memantine. Various cerebellar disorders may also be successfully treated with 4-AP, such as cerebellar gait disorder and episodic ataxia type 2. Although preliminary studies show good efficacy with these medications, further study with randomised controlled trials is needed.

Peter MacIntosh

Optic pathway structure and function with compression of the optic chiasm

Phal M, Steward C, Nichols AD, Kokkinos C, Desmond PM, Danesh-Meyer H, Sufaro YZ, Kaye AH, Moffat BA. Assessment of optic pathway structure and function in patients with compression of the optic chiasm: a correlation with optical coherence tomography. *Invest Ophthalmol Vis Sci* 2016;57:3884–3890.

The authors investigate the correlation between retinal nerve fibre thickness by optical coherence tomography (OCT) and anterograde functional and structural differences in the optic pathway of patients with compression of the optic chiasm using functional magnetic resonance imaging (MRI). Surgically irreversible visual field defects and reduced retinal nerve fibre layer thickness were significantly associated with lower functional MRI activation in the visual cortex, suggesting trans-synaptic degeneration in the visual pathway. These factors may be important potential imaging biomarkers for predicting visual recovery after surgical decompression.

Peter MacIntosh

Retinal thinning and epilepsy drug resistance

Balestrini S, Clayton LM, Bartmann AP, Chinthapalli K, Novy J, Coppola A, Wandschneider B, Stern WM, Acheson J, Bell GS, Sander JW, Sisodiya SM. Retinal nerve fibre layer thinning is associated with drug resistance in epilepsy. *Neurol Neurosurg Psychiatry* 2016;87:396–401.

This large ($n = 300$ included optical coherence tomography [OCT] scans), prospective, longitudinal study in epilepsy makes a compelling case for neurodegeneration affecting the peripapillary retinal nerve fibre layer (pRNFL). The authors and others had previously described such a relationship for vigabatrin. This could easily be explained by the drugs' neurotoxic properties. Hitherto other studies in epilepsy have failed to convincingly demonstrate atrophy of the pRNFL in absence of vigabatrin.

There had been a number of theories on potential neurodegeneration in patients with severe epilepsy. These included cumulative doses of anti-epileptic drugs (AEDs), which had been associated with

localised brain atrophy elsewhere. There were arguments for shared biochemical pathways between vigabatrin and sodium valproate. The possible effects of combination therapy compared with monotherapy and treatment resistance have all been discussed, but not proven. In short, neurotoxicity can be unwanted side effect of AEDs, but the detection and monitoring remains challenging in clinical practice. It is against this background that the study by Balestrini et al. breaks new ground. The study is well powered and makes three points.

First, there is clearly atrophy of the pRNFL in patients with epilepsy who were not exposed to vigabatrin if compared with healthy controls. Importantly, relevant ophthalmological comorbidity was carefully excluded. A potentially relevant limitation is the lack of referring to an OCT quality control pipeline spanning every step from acquisition to evaluation. In the supplementary material, the authors refer to the device manufacturer software quality rating only, which ignores those points found relevant for measurement artifacts up to 40 μm . This may be relevant as the degree of pRNFL atrophy averaged at 10 μm on a group level.

Second, there was a linear relationship between the pRNFL with age and disease duration. This implies a cumulative effect. Whether due to cumulative drug toxicity or cumulative seizure-related damage to the central nervous system was not impossible to answer with this study.

Third, atrophy of the pRNFL was also related to the degree of intellectual disability. The authors carefully discussed the limitations of their study in this respect. But if proven prospectively, this might turn out to become a major point. There is emerging data from other quantitative retinal OCT data on a relationship of atrophy of the RNFL and also ganglion cell layer with cognitive functioning. Prospective, multi-centre data on such a potential functional structural relationship will be exciting to eventually read about.

Axel Petzold

Hidden in plain sight: AMN and PAMM

Bhavsar KV, Lin S, Rahimy E, Joseph A, Freund KB, Sarraf D, Cunningham ET. Acute macular neuroretinopathy: a comprehensive review of the literature. *Surv Ophthalmol* 2016;61: 538–565.

Neuro-ophthalmologists often evaluate patients with abstruse visual complaints. It behooves the practitioner to be aware of pathologies that cause these bothersome visual symptoms in the absence of obvious clinical examination findings. When working up a patient with paracentral scotomata, acute macular neuroretinopathy (AMN) must be on one's mind, as the retinal findings can be overlooked on both ophthalmoscopy and evaluation with optical coherence tomography (OCT). In this review of the literature, the authors more than double the number of cases previously analysed. Over 80% of cases were women, and over half were in their third decade of life. Approximately half reported a nonspecific flu-like associated illness. Spectral-domain OCT combined with near-infrared imaging is described as likely the most sensitive modality to detect the characteristic lesions seen in AMN. Fluorescein angiography was found to be truly helpful only in the exclusion of other possible aetiologies. Through presenting the conclusions of other studies, the authors argue that AMN is caused by noninflammatory ischaemia of retinal capillaries. The authors also report on a similar but distinct entity visualised on OCT, the paracentral acute middle maculopathy (PAMM). Although the lesions in AMN often develop at the junction of the outer plexiform layer (OPL) and outer nuclear layer (ONL), PAMM lesions are often seen at the level of the inner nuclear layer (INL). PAMM lesions have been noted in conditions such as non-proliferative diabetic retinopathy, sickle cell disease, and retinal vasculitis. Permanent INL or ONL thinning can later be seen in PAMM and AMN, respectively, and permanent scotomata can persist in both conditions.

Evan Price

Quantifying disc pallor

Nakano E, Hata M, Oishi A, Miyamoto K, Uji A, Fujimoto M, Miyata M, Yoshimura N. Quantitative comparison of disc rim color in optic nerve atrophy of compressive optic neuropathy and glaucomatous optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2016;254:1609–1616.

The authors report a computerised comparison of optic disc rim colour in compressive optic

neuropathy (CON), normal tension glaucoma (NTG), and normal eyes (NOR), calculated from the intensity of red, green, and blue pixels seen on colour photographs. Three disc colour indices (DCIs) for the intensity of redness were calculated and compared between groups. A statistically significant difference was found in all DCIs of COR eyes as compared with NOR eyes. When comparing mild COR and mild NTG eyes (those with Humphrey visual field mean deviation greater than -6 dB), the DCIs in the COR group were smaller. This difference was not found between the moderate-to-severe groups of COR and NTG patients. This attempt to effectively quantitate the amount of pallor on examination of the optic disc admittedly is dependent on the quality of the media. The authors note that they attempted to limit the contribution of the lens, vitreous, or any other pathologic ophthalmic tissue to the calculated DCIs through their relatively strict exclusion criteria, and they note that even the diameter of the vessels could complicate the accurate assessment of the disc. It is noted that a larger study with a more diverse population of patients would be helpful in clarifying the utility of the presented methodology.

Evan Price

Differential of combined hearing and vision loss

Kung NH; Bucelli RC, Van Stavern RB, Goebel JA, Van Stavern GP. A young man with progressive vision and hearing loss. *JAMA Neurol* 2016;73:880–883.

The authors use the case description of a 37-year-old man who presents to clinic with a combination of hearing and vision problems as a segue way to review the differential diagnosis for patients presenting with combined sensory deficits. Aetiologies such as Cogan syndrome, Susac syndrome, and Vogt-Koyanagi-Harada syndrome are all discussed in some detail. This is an approach other physicians can use in approaching patients of their own who may present with combined sensory problems. The case report concludes with a more targeted description of mitochondrial diseases.

John Pula

Low copper optic neuropathy

Rapoport Y, Lavin PJ. Nutritional optic neuropathy caused by copper deficiency after bariatric surgery. *J Neuroophthalmol* 2016;36:178–181.

The authors present a 47-year-old woman developed severe bilateral visual loss 4 years after gastric bypass surgery. Her serum copper level was low, and with supplementation her vision improved. This case highlights the importance of checking copper levels in addition to vitamin B₁, B₆, B₁₂, E, and serum folate in patients with suspected nutritional optic neuropathy after bariatric surgery, particularly if it involved a bypass procedure.

Michael Vaphiades

Optic neuropathy with CNS vasculitis

Benson CE, Knezevic A, Lynch SC. Primary central nervous system vasculitis with optic nerve involvement. *J Neuroophthalmol* 2016;36:174–177.

The authors present a 20-year-old woman presented with headache, painful visual loss, and bilateral optic disc edema. Brain magnetic resonance imaging (MRI) revealed enhancement of the leptomeninges and a brain biopsy showed vasculitis. The patient was treated with prednisone and cyclophosphamide resulting in improvement of her vision and systemic symptoms. The authors concluded that primary central nervous system (CNS) vasculitis is a rare condition that may affect the anterior visual pathways.

Michael Vaphiades

Eighteen years of LHON

Ohden KL, Tang PH, Lilley CC, Lee MS. Atypical Leber hereditary optic neuropathy: 18 year interval between eyes. *J Neuroophthalmol* 2016;36:304.

The authors report a 23-year-old man who experienced profound visual loss in his right eye at age 5 from the 11778 Leber hereditary optic neuropathy (LHON) mitochondrial point mutation. He maintained 20/20 vision in the left eye for 18 years when he then experienced loss of vision in the left eye. This

18-year interval between both eyes is the longest reported to date.

Michael Vaphiades

A review on paediatric optic neuritis

Yeh EA, Graves JS, Benson LA, Wassmer E, Waldman A. Pediatric optic neuritis. *Neurology* 2016;30;87(9 Suppl 2):S53–S58.

This article reviews the current knowledge of the clinical presentation and management of paediatric optic neuritis, with attention to associated syndromes and evaluative tools that may inform diagnosis and interventions. There are conflicting published reports in the literature particularly in terms of prognosis.

Michael Vaphiades

A review on NMO in children

Tenembaum S, Chitnis T, Nakashima I, Collongues N, McKeon A, Levy M, Rostasy K. Neuromyelitis optica spectrum disorders in children and adolescents. *Neurology* 2016;30;87(9 Suppl 2):S59–S66.

This article reviews the evolving diagnostic criteria of neuromyelitis optica spectrum disorder (NMOSD) and provides an update on the clinical and neuroimaging spectrum of the disorder in paediatric patients, including current knowledge on immunopathogenesis and treatment recommendations for children with NMOSD. More studies are necessary in children with NMOSD to have a better understanding of the disorder in the paediatric population.

Michael Vaphiades

Predictive risk factor for radiation optic neuropathy

Seibel I, Cordini D, Hager A, Tillner J, Riechardt AI, Heufelder J, Davids AM, Rehak M, Joussen AM. Predictive risk factors for radiation retinopathy and optic neuropathy after proton beam therapy for uveal melanoma. *Graefes Arch Clin Exp Ophthalmol* 2016;254:1787–1792.

The authors reviewed 1127 patients who had been treated with primary proton beam therapy

for uveal melanoma between 1998 and 2014. Mean follow-up was 53.4 months. They found that 463 (41.0%) patients developed radiation optic neuropathy after a median time of 19.8 months. In patients who did not develop any radiation-induced complication, their initial median visual acuity was 0.3 logMAR and the final visual acuity was 0.4 logMAR. However, for patients who developed radiation optic neuropathy, their visual acuities decreased from 0.3 logMAR before proton beam therapy to the final level of 1.5 logMAR. The authors found that independent risk factors for radiation optic neuropathy comprised a short distance and applied dose of the proton beam therapy to the optic disk.

An-Guor Wang

Retinal and optic nerve change in Parkinson's disease

Pilat A, McLean RJ, Proudlock FA, Maconachie GDE, Sheth V, Rajabally YA, Gottlob I. In vivo morphology of the optic nerve and retina in patients with Parkinson's disease. *Invest Ophthalmol Vis Sci* 2016;57:4420–4427.

This study recruited 25 patients with Parkinson's disease (PD) to evaluate the optic nerve and macular morphology using spectral-domain optical coherence tomography (SD-OCT). They found a significant thinning of peripapillary retinal nerve fibre layer (ppRNFL) in PD patients compared with controls. There is an associated foveal remodelling process consisted of retinal thinning, foveal pit widening, central outer plexiform layer thickening, and nasal retinal pigment epithelium (RPE) thinning in patients with PD. These specific findings of the ppRNFL thinning and fovea remodelling were correlated with disease severity and duration of PD, indicating that retinal and optic nerve change could be used as biomarkers for PD.

An-Guor Wang

Visual field loss in association with anterior visual pathway displacement

Boland MV, Lee IH, Zan E, Yousem DM, Miller NR. Quantitative analysis of the displacement of

the anterior visual pathway by pituitary lesions and the associated visual field loss. *Invest Ophthalmol Vis Sci* 2016;57:3576–3580.

Is there a relationship between the displacement of anterior visual pathway structures by pituitary tumors and the severity of visual field damage? The authors quantified the degree and laterality of visual field loss in static perimetry and the displacement of anterior visual pathway structures on magnetic resonance imaging (MRI) in 114 subjects with pituitary tumors. The authors found that both the total amount of visual field loss and the proportion of temporal visual field loss are significantly associated with the displacement of the anterior visual pathway on MRI. Thus, the anterior visual pathway displacement is predictive of the severity of visual field loss.

An-Guor Wang

"It's my hormones, doctor"

Markey KA, Uldall M, Botfield H, Cato LD, Miah MAL, Hassan-Smith G, Jensen RH, Gonzalez AM, Sinclair AJ. Idiopathic intracranial hypertension, hormones, and 11 β -hydroxysteroid dehydrogenases. *J Pain Res* 2016;9:223–232.

"It's my hormones, doctor"—perhaps you have heard this phrase from patients who struggle with weight loss? Ironically, this phrase comes to my mind on reading this interesting review about idiopathic intracranial hypertension (IIH) and its pathogenesis.

The authors present evidence to support the role of inflammation as a pathogenesis for IIH. Leptin has been one of the main adipokines (cytokines from adipose tissue) that has been the focus of IIH research. Evidence suggests that this is important, although not all studies support this. It is possible that a central leptin resistance is involved in the pathogenesis of IIH, although it is not clear how this occurs. Other cytokines were also reviewed, and the authors provide a comprehensive table summarising results various small studies.

Glucocorticoids have been reported anecdotally to cause raised intracranial pressure.

However, the systemic levels in IIH are normal. Therefore, looking at a cellular level may be of more relevance. The availability of glucocorticoid at a cellular level is regulated by 11β -hydroxysteroid dehydrogenase (11B-HSD1). There is a correlation of reduction of 11B-HSD1 level with a fall in intracranial pressure

following treatment of IIH. Inhibition of 11B-HSD1 is suggested as possible treatment modality. This paper puts us in anticipation of the results of an ongoing study by these investigators, due in 2017.

Sui Wong