ABSTRACTS

Neuro-Ophthalmic Literature Review

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Inflammatory optic neuropathies: A review

Boudreault K, Durand ML, Rizzo JF. Investigation-directed approach to inflammatory optic neuropathies. *Semin Ophthalmol* 2016;31:117–130.

The term “optic neuritis” is typically associated with demyelinative optic neuritis, the type affecting most patients in the Optic Neuritis Treatment Trial. Demyelinative optic neuritis typically affects one eye of young Caucasian females, causes painful visual loss without disc swelling, and can improve spontaneously without active treatment. In recent years, there is increasing awareness of other types of inflammatory optic neuritis. If these are not recognised and treated appropriately, they will lead to irreversible visual loss, unlike in typical optic neuritis. This is a comprehensive review of the whole spectrum of inflammatory optic neuropathies, including infectious optic neuritis and non-infectious optic neuritis. The latter is further classified into those with or without known antibodies and with or without association with systemic diseases. There is a particular emphasis on diagnosis using a stepwise approach of laboratory testing, imaging, and cerebrospinal fluid (CSF) analysis.

Carmen Chan

Levodopa AS treatment for acute naion?

Lyttle DP, Johnson LN, Margolin EA, Madsen RW. Levodopa as a possible treatment of visual loss in nonarteritic anterior ischemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2016;254:757–764.

There is currently no proven treatment for non-arteritic anterior ischaemic optic neuropathy (NAION). In this retrospective cohort study, the authors compared the visual outcomes of 33 eyes (33 patients) within 15 days of NAION onset, who

were treated with 25 mg carbidopa/100 mg levodopa three times a day for 12 weeks, with 26 eyes (26 patients) who were not treated. The method of group allocation was by patient preference, and the control group generally had better baseline visual acuity (though not statistically significant) and significantly better visual field mean deviation (VF MD) than the treatment group. Amongst those with initial visual acuity of 20/60 or worse, the treatment group ($n = 23$) had statistically significant improvement in visual acuity (mean: 7 Snellen lines), but the control group ($n = 14$) did not (mean: 3 Snellen lines). Eighty-three percent of the treatment group and 43% of the control group experienced visual improvement of at least 0.3 logMar units. The change in VF MD showed no significant improvements in both groups.

Previous studies by the same group showed that treatment of levodopa within 45 days of NAION onset and after 6 months of NAION resulted in 76.9% and 30% visual acuity improvement, respectively. The authors concluded that levodopa may improve the central vision of NAION patients and earlier treatment may be more beneficial. They speculated that the levodopa, a precursor of dopamine, promoted the up-regulation of anti-apoptotic pathways. Of course, whether levodopa is truly beneficial for NAION remains to be verified by multi-centre, randomised controlled studies.

Carmen Chan

Clinical characteristics of optic neuritis in HLA-B27 positive Chinese patients

Zhao S, Zhou H, Peng X, Zhu J, Wang W, Kang H, Chen T, Xu Q, Wei S. Optic neuritis with positive HLA-B27: characteristic phenotype in the Chinese population. *J Neurol Sci* 2016;362:100–105.

In ophthalmology, human leukocyte antigen (HLA)-B27 positivity is associated with acute

anterior uveitis but it is not usually associated with optic neuritis. In this retrospective review, the authors screened 410 optic neuritis patients from a tertiary referral centre in China, with a panel of autoimmune/inflammatory markers, including HLA-B27 and aquaporin-4 antibodies (AQP4-Ab). Here, 22/410 (5.4%) optic neuritis patients were identified to be HLA-B27 positive; the prevalence rate was similar to that in the general Chinese population (4–8%). 0.7% eventually turned out to have ankylosing spondylitis, slightly higher than the general population prevalence of 0.2–0.54%. 8/22 were also positive for AQP4-Ab, but the clinical features of their disease were similar to those who were AQP4-Ab negative in this cohort. Two patients met the diagnostic criteria for multiple sclerosis or neuromyelitis optica. 16/22 (72.7%) patients had bilateral involvement, 14/22 (63.6%) patients had recurrent episodes, and 22/38 (57.9%) of the involved eyes had visual acuity of <6/60 at presentation. The authors concluded the HLA-B27 positive optic neuritis patients were more likely to have bilateral severe visual impairment and recurrent episodes, compared with those with “typical” optic neuritis.

Carmen Chan

Comparing AQP4+ and MOG+ optic neuritis

Akaishi T, Sato DK, Nakashima I, Takeshita T, Takahashi T, Doi H, Kurosawa K, Kaneko K, Kuroda H, Nishiyama S, Misu T, Nakazawa T, Fujihara K, Aoki M. MRI and retinal abnormalities in isolated optic neuritis with myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies: a comparative study. *J Neurol Neurosurg Psychiatry* 2016;87:446–448.

In this short report, the authors tested 21 consecutive patients with isolated optic neuritis (ON), who were seronegative for anti-aquaporin-4 antibodies (anti-AQP4) for anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies. They found that 13 patients were anti-MOG+. All of them responded to intravenous prednisolone except one with previous untreated attacks of ON. The authors then compared the clinical, MRI, and spectral-domain optical coherence tomography (SD-OCT) features of the anti-MOG

+ ON eyes with 9 anti-AQP4+ eyes and 9 seronegative ON eyes. The OCT scans were performed 6 months after the ON episodes and were analysed for ganglion cell-inner plexiform layer (GCIPL) and retinal nerve fibre layer (RNFL) thickness.

Comparing anti-MOG+ ON eyes with those with anti-AQP4+, it was found that anti-MOG+ eyes were more likely to have severe optic nerve swelling at onset. They were also more likely to have MRI STIR/T2W (short-tau inversion recovery T2-weighted) hyperintensity extension to the canalicular and intracranial portions of the optic nerves. At 6 months, anti-MOG+ ON eyes had thicker peripapillary RNFL and GCIPL than anti-AQP4+ eyes. The authors concluded that although anti-MOG+ eyes had more extensive MRI abnormalities, they tended to have a good response to intravenous steroid treatment and there was less residual nerve damage in the long term compared with anti-AQP4+ eyes, as demonstrated by OCT.

Carmen Chan

Leber hereditary optic neuropathy: Bringing the lab to the clinic

Rasool N, Lessell S, Cestari DM. Leber hereditary optic neuropathy: bringing the lab to the clinic. *Semin Ophthalmol* 2016;31:107–116.

The authors describe the historical perspective and pathophysiology of Leber hereditary optic neuropathy (LHON). The authors then describe a case of point mutation G3460A with full recovery of vision, followed by typical clinical features and review of the literature on the potential for treatment and visual recovery. Although animal models are critical to understanding the disease process and early treatment investigations, these have been difficult to perform due to technical limitations of studying the mitochondrial genome. Treatments for LHON have been difficult to establish, and to date there exist no proven therapies. Instead, there is currently a focus on low-vision aids, psychological support, and education to avoid environmental toxins such as cigarette smoke and alcohol. A review of over 1300 articles and 12 randomised controlled trials failed to reveal any significant evidence for any intervention in the outcome of

this disorder. Antioxidants such as co-enzyme Q10, idebenone, and EPI-745 have been studied to varying degrees, but without much evidence of efficacy. The RHODOS (Study to Assess Efficacy, Safety, and Tolerability of Idebenone in the Treatment of Leber's Hereditary Optic Neuropathy) study was a prospective, randomised, placebo-controlled trial of idebenone in patients with LHON that demonstrated a non-statistically significant tendency towards better visual improvement in patients with idebenone. Finally, gene therapy has significant potential in LHON, but many obstacles that need to be overcome, including accessing and modifying mitochondrial DNA. There are many clinical trials looking at filling the knowledge gap and provide viable treatments in the future.

Peter MacIntosh

Investigation-directed approach to inflammatory optic neuropathy

Boudrealt K, Durand ML, Rizzo JF. Investigation-directed approach to inflammatory optic neuropathies. *Semin Ophthalmol* 2016;31:117–130.

The authors present a review of the literature on optic neuritis, starting with demyelinating optic neuritis (DON) and followed by a discussion on less common forms of inflammatory optic neuropathy. Neuromyelitis optica (NMO) is associated with the aquaporin-4 water channel antibody. Up to one quarter of patients with NMO-like picture but without NMO antibody may have a closely related autoimmune disorder with myelin-oligodendrocyte glycoprotein antibodies. These patients tend to have a better visual outcome following optic neuritis than do patients with NMO. The initial treatment of NMO is similar to DON with intravenous (IV) steroids, but the maintenance therapy shows better response to plasmapheresis, intravenous immunoglobulin (IVIg), rituximab, and azathioprine. Chronic relapsing inflammatory optic neuropathy (CRION) is a steroid-responsive optic neuropathy and may relapse after steroid withdrawal. Optic neuropathies with associated systemic conditions and autoantibodies include lupus optic neuropathy and paraneoplastic optic

neuropathy (PON). In PON, small-cell lung cancer is the most frequent associated neoplasm. An important clue to this diagnosis is vitritis or retinal infiltrates in addition to optic neuritis. Sarcoid optic neuropathy is another condition with systemic associations, but without autoantibodies. Important neuroimaging findings in sarcoid optic neuritis include an enhancing and enlarged nerve, with dural or leptomeningeal enhancement. The authors conclude with a discussion of infectious optic neuropathy, including syphilitic and Lyme and their important laboratory markers.

Peter MacIntosh

Intraorbital corticosteroid for IgG4-related ophthalmic disease

Andrew NH, Gajdatsy A, Selva D. Intraorbital corticosteroid injection for the treatment of IgG4-related ophthalmic disease. *Br J Ophthalmol* 2016;100:644–647.

In this retrospective study, the charts of 10 patients with biopsy-proven immunoglobulin G4 (IgG4)-related ophthalmic disease (IgG4-ROD) were reviewed. All had undergone intraorbital injection of 20 or 40 mg doses of triamcinolone acetonide. Complete clinical remission was achieved over a mean follow-up of 41 months in 50% of patients, and three of those patients required a single injection to achieve symptom control. In addition, peak improvement was noted in ≤ 7 days in 61% of injections. No complications were reported, aside from the discomfort of injection. One limitation of the study was that 80% of the cases reported received their first injection during the second week after orbital biopsy. It is possible that some of the perceived improvement in symptoms was actually due to the debulking effect of the procedure or the resolution of post-operative inflammation. Although the known possible adverse events must be weighed against the potential benefits of intraorbital corticosteroid injection, it seems that it may be a reasonable treatment option for IgG4-ROD, especially for those at higher risk for morbidity from the adverse effects of systemic immunosuppression.

Evan Price

Novel optic neuropathy identified in Chédiak-Higashi syndrome

Desai N, Weisfeld-Adams JD, Brodie SE, Cho C, Curcio CA, Lublin F, Rucker JC. Optic neuropathy in late-onset neurodegenerative Chédiak-Higashi syndrome. *Br J Ophthalmol* 2016;100:704–707.

In this descriptive case series, the authors expand our understanding of the ocular manifestations of Chédiak-Higashi syndrome (CHS) to include a progressive optic neuropathy in the late-onset neurodegenerative form of the disease. Three adult siblings with a family history of consanguinity are presented. All three siblings were confirmed to have the same homozygous *LYST* deletion, whereas their parents and two unaffected siblings were found to be heterozygous for the deletion. All three lacked the typical features of ocular albinism, and their vision loss could not be attributed to any foveal hypoplasia or nystagmus. However, optic nerve damage was diagnosed in all three siblings on the basis of loss of colour vision and contrast sensitivity, optic nerve head pallor, retinal nerve fibre layer thinning on optical coherence tomography (OCT), and abnormal visual evoked potential testing, with more severe dysfunction corresponding with sibling age and severity of neurological disease. An additional line was also seen on macular OCT in the interdigitation zone in the three cases and their father, but it was not seen in the two other siblings without CHS. The authors speculate that the line found on macular OCT may be caused by accumulation of detached retinal pigment epithelium (RPE) cells with atypical and/or enlarged melanosomes and secondary lysosomal residual bodies, or by enlargement of melanosomes in the RPE itself.

Evan Price

Is your patient starting topiramate? You may want to delay refractive surgery

Hesami O, Hosseini SS, Kazemi N, Hosseini-Zijoud SM, Moghaddam NB, Assarzaghan F, Mokhtari S, Fakhraee S. Evaluation of ocular side effects in the patients on topiramate therapy for control of migrainous headache. *J Clin Diagn Res* 2016;10:NC01–NC04.

The authors studied 66 eyes in 33 patients who were on titrating doses of topiramate from 25 mg to 50 mg over 1 week, with 3 patients increasing to 100 mg/day. Patients on topiramate were found to have a statistically significant myopic shift over time, from -0.23 dioptres as baseline to -0.61 dioptres after 3 months, correlating with an increase in central corneal thickness. One patient did develop the known adverse effect of angle closure glaucoma and discontinued topiramate, but no increase in intraocular pressure or decrease in anterior chamber depth was recorded in the other patients. Thus, it seems that the angle closure effect is idiosyncratic, but the statistical trend in refractive changes in patients starting topiramate should prompt caution in evaluation and timing of refractive surgery.

John H. Pula

Leber optic neuropathy gene therapy

Feuer WJ, Schiffman JC, Davis JL, Porciatti V, Gonzalez P, Koilkonda RD, Yuan H, Lalwani A, Lam BL, Guy J. Gene therapy for Leber hereditary optic neuropathy: initial results. *Ophthalmology* 2016;123:558–570.

The authors initiated a gene therapy trial to determine the safety and tolerability of escalated doses of an adeno-associated virus vector expressing normal ND4 (nicotinamide adenine dinucleotide dehydrogenase subunit) complementary DNA in patients with a guanine to adenine mutation at nucleotide 11778 of the mitochondrial genome in five legally blind patients with the G11778A Leber hereditary optic neuropathy (LHON) mutation. No one lost vision, and no serious adverse events were observed. The authors are planning an additional study follow-up of these and other participants planned for the next 4 years that is needed to confirm these preliminary observations.

Michael Vaphiades

Outcomes in paediatric pseudotumor cerebri

Gospe SM, Bhatti MT, El-Dairi MA. Anatomic and visual function outcomes in paediatric idiopathic intracranial hypertension. *Br J Ophthalmol* 2016;100:505–509.

The authors retrospectively investigated visual function, spectral-domain optical coherence tomography (SD-OCT), and enhanced depth imaging (EDI)-OCT findings in 31 children with papilloedema caused by idiopathic intracranial hypertension (IIH). They noted that high papilloedema grade on presentation was predictive of poor visual outcomes. They also noted a high proportion of study eyes had optic disc drusen, which was not associated with vision loss, but can be a diagnostic challenge in distinguishing true papilloedema from pseudopapilloedema.

Michael Vaphiades

The pescatorial sixth

Pellegrini F, Prosdocimo G, Barton JJ. The pescatorial sixth. *Surv Ophthalmol* 2016;61:248–254.

In a clinical challenges format, being presented as an unknown diagnosis, the authors present a case of a 56-year-old man with bilateral complete abduction deficits and areflexia without ataxia. Within a few days, he developed complete ophthalmoplegia and ataxia, consistent with a clinical diagnosis of Miller Fisher syndrome. The authors review this syndrome along with its differential diagnosis.

Michael Vaphiades

The demographics of ocular myasthenia gravis

Peragallo JH, Bitrian E, Kupersmith MJ, Zimprich F, Whittaker TJ, Lee MS, Bruce BB. Relationship between age, gender, and race in patients presenting with myasthenia gravis with only ocular manifestations. *J Neuroophthalmol* 2016;36:29–32.

The authors collected data on race, gender, and age at diagnosis of 433 patients diagnosed with ocular myasthenia gravis (OMG) and with no signs or symptoms of generalised myasthenia gravis (GMG). They detected a bimodal distribution for women peaking around 30 and 60 years. Men had a left skewed unimodal age distribution peaking at age 70. The authors acknowledge the inherent limitations of this study, including the

retrospective data collection and referral bias to tertiary care centres and that the data are based on patients with OMG at diagnosis who may have later converted to GMG. Furthermore, they noted that most rigorous clinical examination may miss subtle GMG. The authors concluded that the distribution of age at presentation in patients with OMG is different between men and women, similar to GMG, and that non-Caucasian patients tend to develop OMG at a younger age, yet it is unknown whether these differences affect prognosis, disease course, conversion to GMG, or responses to treatment.

Michael Vaphiades

Factors affecting visual fields in the IIHTT

Cello KE, Keltner JL, Johnson CA, Wall M; NORDIC Idiopathic Intracranial Hypertension Study Group. Factors affecting visual field outcomes in the Idiopathic Intracranial Hypertension Treatment Trial. *J Neuroophthalmol* 2016;36:6–12.

The authors examined a total of 165 participants with idiopathic intracranial hypertension (IIH) and mild visual loss who were randomised to either acetazolamide-plus diet or placebo-plus diet. Treatment failures (TF) were detected in 7/165 (4%) of the participants and performance failures (PF) were detected in 35/165 (21%) of the participants on at least one examination. Of the 2950 total IIHTT visual field (VF) examinations, 2.7% met PF criteria. The authors confirmed PF in 21% of subjects, and in 2.7% of the total number of VF examinations, however the diagnoses were reversible on repeat testing. They recommended retesting when perimetric worsening occurs in otherwise clinically stable or improving IIH patients, since the examinations returned to baseline levels on retest.

Michael Vaphiades

Cilioretinal artery infarction in papilloedema

Mahroo OA, Mohamed MD, Graham EM, Mann SS, Plant GT, Afridi SK, Hammond CJ. Cilioretinal artery territory infarction associated with papilloedema in a patient with neurofibromatosis type 2. *J Neuroophthalmol* 2016;36:58–60.

The authors present an 18-year-old woman with neurofibromatosis type 2 who developed a cilioretinal artery territory infarction in the setting of papilloedema in the left eye. The right eye was phthisical. There was no compressive optic nerve lesion on the left, but there was increased intracranial pressure from growth of a parasagittal meningioma. The authors suggest that cilioretinal artery infarction in the context of papilloedema is a rare, but real entity, and they propose two potential mechanisms.

Michael Vaphiades

Acquired colour vision deficiency

Simunovic MP. Acquired color vision deficiency. *Surv Ophthalmol* 2016;61:132–155.

Acquired colour vision deficiency occurs as the result of ocular, neurologic, or systemic disease. The authors review the pathophysiology of acquired colour vision deficiency, the data on its prevalence, theories for the preponderance of acquired S-mechanism (or tritan) deficiency, and discuss tests of colour vision. They also review the types of colour vision deficiencies encountered in ocular disease.

Michael Vaphiades

Impaired vascular endothelial function in naion

Yao F, Wan P, Su Y, Liao R, Zhu W. Impaired systemic vascular endothelial function in patients with non-arteritic anterior ischaemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2016;254: 977–981.

Endothelium dependent flow-mediated vasodilation (FMD) is a non-invasive method used to evaluate generalised endothelial function by ultrasound assessment of the brachial artery. It is measured as the percentage change of brachial artery diameter before and after cuff inflation. Cuff inflation will cause a shearing stress on the vessel wall and then induce endothelial nitric oxide release with subsequent vasodilation. The authors recruited 42 hypertensive patients with nonarteritic anterior ischaemic optic neuropathy

(NAION), 64 hypertensive controls, and 100 normal controls for a high-resolution ultrasonographic FMD examination. They found FMD decreased significantly in the NAION group ($6.02 \pm 1.87\%$) compared with the hypertension group ($7.86 \pm 2.94\%$, $p < 0.001$) and normal group ($8.99 \pm 2.44\%$, $p < 0.001$). They concluded that NAION may be associated with systemic vascular endothelial dysfunction.

An-Guor Wang

Visual fields in the IIH treatment trial

Wall M, Johnson CA, Cello KE, Zamba KD, McDermott MP, Keltner JL; NORDIC Idiopathic Intracranial Hypertension Study Group. Visual field outcomes for the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). *Invest Ophthalmol Vis Sci* 2016;57:805–812.

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) reported significantly improved perimetric mean deviation (MD) in the acetazolamide-plus diet group as compared with placebo-plus diet group. In the current study, the authors further analysed the point-wise visual field changes in these 165 IIH subjects over the 6-month study period. The results showed that visual field change from baseline to 6 months yielded percentages (acetazolamide, placebo) of 7.2% and 17.5% worse, 35.1% and 31.7% with no change, and 56.1% and 50.8% improved. They concluded that the acetazolamide-plus diet group had a significant point-wise improvement in visual field function, particularly in the nasal and pericentral areas.

An-Guor Wang

Surgical treatment for paralytic strabismus in CN3 palsy

Saxena R, Sharma M, Singh D, Dhiman R, Sharma P. Medial transposition of split lateral rectus augmented with fixation sutures in cases of complete third nerve palsy. *Br J Ophthalmol* 2016;100: 585–587.

Surgical management for the paralytic strabismus in third nerve palsy has been a challenge with

less than satisfactory outcomes. The authors reported a modification of the existing technique of medial transposition of the split lateral rectus by force augmentation through the use of equatorial fixation sutures. These sutures change the force vector of the transposed muscles and augment the force in the direction of action of the medial rectus. Satisfactory post-operative alignment was achieved in three cases.

An-Guor Wang

Trying to understand idiopathic intracranial hypertension

Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. *Lancet Neurol* 2016;15:78–91.

This is a thorough review on the current understanding of the pathogenesis and management of idiopathic intracranial hypertension (IIH). The section on pathogenesis was of particular interest. The pathogenesis is still unclear, and the following were considered:

- Cerebrospinal fluid (CSF) hypersecretion: limited evidence suggests that this is unlikely.

- CSF outflow obstruction: reabsorption may be delayed but limited evidence suggests that this may be unlikely.
- Venous sinus pressure: this is increasingly regarded as a relevant pathogenic factor, but evidence is conflicting. Venous sinus stenosis may be a consequence of IIH rather than the cause.
- Cerebral oedema: limited evidence suggests that this is unlikely.
- Obesity: this may be due to the inflammatory effects of obesity, as shown in two studies of CSF chemokines in IIH.
- Hormones: 11 β -hydroxysteroid dehydrogenase type 1, which is an enzyme that regulates local, tissue-specific glucocorticoid availability, may be relevant.

The authors went on to review the presentation, treatment options (weight loss; acetazolamide, furosemide, topiramate; potential surgical interventions) and visual prognosis (generally good but poorer in male, black ethnicity, early-onset reduced acuity). Future results of ongoing trials by this group (bariatric surgery and new drugs) are awaited with interest.

Sui Wong