ABSTRACTS

Neuro-Ophthalmic Literature Review

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“Doctor...what about my double vision?”

Rivera SS, Lee MS, Lunos S, Anderson JS, Bothun ED. Strabismus measurements in adults before and after pupil dilation. *Am J Ophthalmol* 2017;178:1–8.

How often have you heard that question just as you are wrapping up an examination? Your patient’s pupils have been dilated and you have just finished a thorough discussion of the findings when they bring up the fact that they have been experiencing diplopia. Instead of scheduling a second appointment for evaluation of ocular motility, many of us will proceed with alternate cover testing even though the pupils are already dilated. This study confirms that these measurements are valid.

This prospective study of 55 adult patients compared the measurement of their strabismus using the alternate prism cover test before pupil dilation with those obtained after pupil dilation. The pupils were dilated with 1% tropicamide and 2.5% phenylephrine. The two measurements were made by different certified orthoptists who were masked to each other’s findings.

The authors found no statistically significant difference in the measurements of both horizontal and vertical deviations at distance. Their findings were similar to the test–retest variability normally encountered in non-dilated patients. The study also demonstrated that there was no significant difference in near (1/3 m) measurements when using a +3.00 dioptre add.

David Bellows

A monoclonal antibody for thyroid eye disease

Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, Harris GJ, Antonelli A, Salvi M, Goldberg RA, Gigantelli JW, Couch SM, Shriver

EM, Hayek BR, Hink EM, Woodward RM, Gabriel K, Magni G, Douglas RS. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med* 2017;376:1748–1761.

For those of us who treat thyroid eye disease, a viable alternative to steroids and radiotherapy is especially welcome. In this double-masked clinical trial 88 patients with active, moderate-to-severe thyroid eye disease were randomised to receive placebo or teprotumumab, a human monoclonal antibody inhibitor of IGF-IR (insulin-like growth factor I receptor).

In this trial, patients received infusions every 3 weeks for a total of eight doses. Three factors: clinical activity score, proptosis, and quality of life scores, were used as end points. A response to the medication was defined as having at least a 2-point reduction in the Clinical Activity Score and at least a 2-mm reduction in proptosis.

The Clinical Activity Score at baseline in the treatment group was 5.1 points. Of those patients, 69% had a reduction of their Clinical Activity Score to 0 or 1 at the end of the trial. This improvement was noted to continue for at least another 7 weeks following the last infusion. The only clinically significant adverse event was hyperglycaemia.

David Bellows

Higher VEGF and lower IL-2 aqueous concentrations in NAION

Micieli JA, Lam C, Najem K, Margolin EA. Aqueous humor cytokines in patients with acute nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 2017;177:175–181.

The authors conducted a prospective study evaluating aqueous levels of various cytokines in patients with non-arteritic anterior ischaemic optic neuropathy (NAION). This is the first study evaluating the

aqueous levels of cytokines in NAION in humans. The study included 10 patients with acute NAION and 15 control patients who underwent cataract surgery. Using multiplex bead immunoassay, they measured the levels of vascular endothelial growth factor (VEGF), tumour necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-2, IL-6, and IL-8. Aqueous VEGF concentrations were higher in the NAION patients compared with controls, although the levels were less than seen in retinal vein occlusions, diabetic macular oedema, and proliferative diabetic retinopathy. Interestingly, there was a negative correlation between VEGF concentration and retinal nerve fibre layer (RNFL) thickness. This is counter-intuitive and suggests that VEGF is not as large of a factor in NAION compared with other retinal conditions known to respond to anti-VEGF therapy. The authors point out that the degree of optic disc oedema does not imply more severe disease. It would have been nice to see if the VEGF concentrations were correlated with the severity of vision loss.

The authors also found that IL-2 concentrations were lower in acute NAION, which has also been reported in glaucomatous optic neuropathy. It has been theorised that IL-2 acts as a neuroprotectant and decreased levels may contribute to further damage. Future studies on cytokines in NAION may provide more insight into the disease process and could provide therapeutic targets.

John Chen

Lamina cribrosa position in papilloedema

Garcia-Montesinos J, Munoz-Negrete FJ, de Juan V, Rebolleda G. Relationship between lamina cribrosa displacement and trans-laminar pressure difference in papilledema. *Graefes Arch Clin Exp Ophthalmol* 2017;255:1237–1243.

The authors conducted a prospective study evaluating the lamina cribrosa position in patients with papilloedema. Twelve eyes with newly diagnosed papilloedema were scanned with enhanced-depth imaging with Spectralis ocular coherence tomography (OCT) at baseline and after treatment of the papilloedema. They found that the translaminar lamina cribrosa pressure difference (TLCD) correlated with the anterior lamina cribrosa position at baseline and with lamina cribrosa movement following treatment. However, overall

there was no change in the average lamina cribrosa displacement with treatment. Interestingly, six eyes showed forward lamina cribrosa movement and six eyes had a backward movement after papilloedema resolution. The authors divided the eyes into a group with lower translaminar cribrosa gradient/lower intracranial pressure (ICP) and a group with higher translaminar cribrosa gradient/higher ICP. The patients with a higher TLCD had a posterior displacement of the lamina cribrosa after treatment, whereas there was a mild anterior displacement in the group with a lower TLCD after treatment. The authors had previously shown that patients with non-arteritic anterior ischaemic optic neuropathy had a posterior displacement of the lamina cribrosa, presumably due to the mechanical effects of optic disc oedema. Therefore, patients with papilloedema from raised ICP may have competing forces on the lamina cribrosa, with the optic disc oedema causing a posterior displacement and the raised ICP causing an anterior displacement. This may explain why the lamina cribrosa is anteriorly displaced with treatment in patients with a lower TLCD. Overall, this study provides evidence that the lamina cribrosa position is related to the TLCD in papilloedema.

John Chen

Pupillary responses in MS

Meltzer E, Sguigna PV, Subei A, Beh S, Kildebeck E, Conger D, Conger A, Lucero M, Frohman BS, Frohman AN, Saidha S, Galetta S, Calabresi PA, Rennaker R, Frohman TC, Kardon RH, Balcer LJ, Frohman EM. Retinal architecture and melanopsin-mediated pupillary response characteristics a putative pathophysiologic signature for the retino-hypothalamic tract in multiple sclerosis. *JAMA Neurol* 2017;74:574–582.

The authors demonstrated a significant reduction of blue light-induced sustained pupillary responses in multiple sclerosis (MS) patients who have alterations of retinal architecture. Melanopsin-expressing intrinsic photosensitive retinal ganglion cells (ipRGCs) project fibres into the pretectal olivary nucleus (retinomesencephalic tract) and the suprachiasmatic nucleus of the hypothalamus (retinohypothalamic tract). A measurement of melanopsin-mediated

persistent constriction response, which is a function of retinomesencephalic tract, might indicate the integrity of the retinohypothalamic tract. It can be useful in evaluating sleep disorders or circadian disruption in MS patients.

Panitha Jindahra

Optic neuritis study from a Russian cohort

Neroev VV, Eliseeva EK, Zueva MV, Lysenko VS, Zakharova MN, Tsapenko IV, Semenova NA, and Simaniv TO. Demyelinating optic neuritis: optical coherence tomography and multifocal electroretinography data correlation. *Hum Physiol* 2016;42:879–884.

The authors studied the correlation between optical coherence tomography (OCT) and multifocal electroretinogram (mfERG) data derived from the central retinal zone of 45 patients with the history of optic neuritis (ON). The cohort of the patients were divided into three groups according to the ON aetiology: (1) with confirmed relapsing-remitting multiple sclerosis (MS) and the history of ON (14 patients, mean age 33.4, corrected visual acuity [VA] on average 0.74 ± 0.24); (2) with isolated ON of unknown aetiology negative for MS lesions (19 patients, mean age 32.2, corrected VA on average 0.66 ± 0.33 , 62% of patients with normal fundoscopy); and (3) with proven infectious ON (12 patients, mean age 37.7, corrected VA 0.72 ± 0.35 , 68% with normal fundoscopy). OCT data from the parafoveal zone (1–3 mm) in group 1 showed a global decrease in the retinal thickness, more prominently in the temporal quadrant. Alternatively, in group 2, a decrease in the retinal thickness was localised to the inferior and temporal quadrants and was absent in the nasal and superior quadrants. The latter significantly distinguished ON with MS (group 1) from ON without MS lesions (group 2). Therefore, this suggested that a decrease in the retinal thickness in the nasal and superior quadrants of the central retinal zone in patients with isolated ON may be a marker of conversion to MS. Group 3 demonstrated increased retinal thickness in the nasal and temporal quadrants. Upon the density and amplitude of the P1 component of mfERG, group 2 differed from group 1 by multidirectional changes in density in the rings R1

and R2 and a significant decrease in amplitude in the rings R3 and R4. Moreover, it has been suggested that the calculation of the density ratio R1/Rx could additionally distinguish group 1 from group 2. Regarding the correlation analysis, the study found that the changes in the P1 latency in the second ring of the ON patients with MS are associated with the decreased total macular volume and central retinal zone thinning in all the quadrants except for the superior one. This is an interesting Russian article published in English and available in Scopus database. There is a lack of patients' characterisation in groups 2 and 3 of the study. Therefore some study results should be interpreted with caution.

Rauan Kaiyrzhanov

Vision training improves visual field performance

Cavanaugh MR, Huxlin KR. Visual discrimination training improves Humphrey perimetry in chronic cortically induced blindness. *Neurology* 2017;88:1856–1864.

The authors prospectively investigated if visual discrimination training improves performance on Humphrey visual fields analysed for 17 chronic cortically blind stroke patients prior to and following visual discrimination training, as well as in 5 untrained, cortically blind controls. They found that trained patients recovered <108 degrees of vision squared on average, whereas untrained patients spontaneously improved over an area of <16 degrees squared. The authors concluded that in adults with chronic cortical visual impairment, the blind field border appears to have enhanced plastic potential, which can be recruited by gaze-controlled visual discrimination training to expand the visible field.

Michael Vaphiades

Awakening amaurosis

Bouffard MA, Cornblath WT, Rizzo JF 3rd, Lee MS, DeLott LB, Eggenberger ER, Torun N. Transient monocular vision loss on awakening: a benign amaurotic phenomenon. *J Neuroophthalmol* 2017;37:122–125.

The authors performed a retrospective observational case series of the 29 patients we studied who experienced transient monocular vision loss (TMVL) on awakening. Brain magnetic resonance imaging and vascular imaging (magnetic resonance angiography, computed tomographic angiography, or carotid Doppler) were performed in 69% and 55% of cases, respectively, and were uniformly negative. In 14 patients for whom clear follow-up data could be obtained, no medically or visually significant sequelae of this syndrome were found, and 50% experienced resolution of symptoms. The authors concluded that these patients' evaluation were negative. This visual phenomenon may represent an autoregulatory failure resulting in a supply/demand mismatch during low-light conditions. Recognising this is a benign entity will impact clinical management and may help avoid costly and unnecessary testing.

Michael Vaphiades

Paediatric ocular motor abnormalities

Brodsky MC, Marshall M, Parks Memorial Lecture: Ocular motor misbehavior in children: where neuro-ophthalmology meets strabismus. *Ophthalmology* 2017;124:835–842.

The term “genius” seems to be used ubiquitously in our culture. However, one application of the term should be reserved for individuals who fundamentally change the way we as physicians think about certain topic. In his Marshall M. Parks Memorial Lecture, Dr. Michael Brodsky reviews the recent paradigm shifts that have transformed our understanding of paediatric ocular motor disease at the prenuclear and infranuclear levels. The pathogenesis of complex ocular motor disorders, such as paradoxical pupillary constriction to darkness, benign tonic upgaze of infancy, congenital fibrosis syndrome, and the constellation of unique eye movements that accompany Joubert syndrome, are elucidated.

Michael Vaphiades

An anatomical study of the optic canal

Liugan M, Xu Z, Zhang M. Reduced free communication of the subarachnoid space within the

optic canal in the human. *Am J Ophthalmol* 2017;179:25–31.

In this human cadaveric study, 9 cadaveric heads (subject age 54–87 years) without optic neuropathy were prepared as sets of transverse, coronal, and sagittal plastinated sections. This study identified and traced the fibrous components within the optic canal and revealed their nature, architecture, and relationship with surroundings and concluded that in the human, free communication of the intracranial subarachnoid space between the intracranial cavity and optic nerve sheath was significantly reduced. This is a cadaveric study and does not necessarily mimic the anatomy in living tissue; thus, the result must be interpreted with caution as it relates to human pathophysiologic states. The clinical significance may relate to why some patients with elevated intracranial pressure do not manifest papilloedema or only unilateral papilloedema.

Michael Vaphiades

Diplopia and epiretinal membranes

Veverka KK, Hatt SR, Leske DA, Brown WL, Iezzi R Jr, Holmes JM. Causes of diplopia in patients with epiretinal membranes. *Am J Ophthalmol* 2017;179:39–45.

In this retrospective observational case series, 50 patients with an epiretinal membrane (ERM) were evaluated for diplopia. Twenty-five patients had symptomatic diplopia, and 25 had no diplopia. Unexpectedly, 15 of 25 patients without diplopia (60%) had evidence of retinal misregistration. Owing to the retrospective design, there were not complete data on every clinical parameter. Patients with ERM and presenting diplopia may have one of several causes of diplopia, most commonly retinal misregistration (central-peripheral rivalry-type diplopia). Nevertheless, diplopic patients with retinal misregistration may also have treatable strabismus or optical/refractive error as the primary barrier to single vision and therefore many potential barriers to single vision should be considered.

Michael Vaphiades

Paediatrics, autoimmunity, and demyelination

Amorim ALM, Cabral NC, Osaku FM, Len CA, Oliveira EML, Terreri MT. Association between demyelinating disease and autoimmune rheumatic disease in a pediatric population. *Rev Bras Reumatol Engl Ed* 2017;57:224–228.

The authors retrospectively studied 22 patients younger than 21 years old with multiple sclerosis (MS) or neuromyelitis optica (NMO) diagnosed before the age of 18. They found a prevalence of females (68.1%). Two patients (9%) had a history of associated autoimmune rheumatic disease: one case of juvenile dermatomyositis in a patient with NMO and another of systemic lupus erythematosus in a patient with MS. Three patients (13%) had a family history of autoimmunity in first-degree relatives. Antinuclear antibody was found positive in 80% of patients with NMO and 52% of patients with MS. About 15% of antinuclear antibody-positive patients were diagnosed with rheumatologic autoimmune diseases. The authors concluded that there was a high frequency of antinuclear antibody positivity but a lower association with rheumatologic autoimmune diseases than that observed in studies conducted in adults.

Michael Vaphiades

Lumbar drains and pseudotumour

Jiramongkolchai K, Buckley EG, Bhatti MT, Muh CR, Wiggins RE, Jiramongkolchai P, El-Dairi MA. Temporary lumbar drain as treatment for pediatric fulminant idiopathic intracranial hypertension. *J Neuroophthalmol* 2017;37:126–132.

Fulminant idiopathic intracranial hypertension (FIIH) is a subtype of idiopathic intracranial hypertension (IIH) characterised by rapid, severe, progressive vision loss. Surgical intervention is often performed either as a cerebrospinal fluid (CSF) shunt procedure or an optic nerve sheath fenestration or, at times, both. These surgical procedures carry a significant risk of morbidity and failure. The authors present 2 patients in whom a temporary lumbar drain was successfully used in the management of medically undertreated paediatric FIIH and circumvented the need for surgical intervention. The authors provide another option

to ventriculoperitoneal (VP) shunt in medically refractory fulminant idiopathic intracranial hypertension.

Michael Vaphiades

The obesity epidemic is associated with a risk to vision

Kilgore KP, Lee MS, Leavitt JA, Mokri B, Hodge DO, Frank RD, Chen JJ. Re-evaluating the incidence of idiopathic intracranial hypertension in an era of increasing obesity. *Ophthalmology* 2017;124:697–700.

This is a retrospective population-based cohort study of residents of Olmsted County in Minnesota between January 1990 to December 2014. All cases of idiopathic intracranial hypertension (IIH) were identified using the Rochester Epidemiology Project, which is a record-linkage system of medical records for all patients-physician encounters among Olmsted County, Minnesota, residents. All medical records were reviewed to confirm a diagnosis of IIH and the incidence of obesity in Minnesota over the same period. 63 new cases of IIH were identified between 1990 and 2014. The annual incidence rate increased from 1.0 per 100000 (1990–2001) to 2.4 per 100000 (2002–2014; $p = 0.007$). A strong correlation was observed between IIH incidence rates and obesity rates in Minnesota ($R^2 = 0.70$, $p = 0.008$).

As expected, 92.1% of patients affected were female. Over 80% (82.6%) were obese, more than half of whom were morbidly obese (52.6%). Almost 90% (88.9%) were of White ethnicity, likely related to the homogenous population. Patients without papilloedema were excluded, which would avoid misdiagnosis. However, some patients with IIH without papilloedema may have therefore been excluded, i.e., the incidence of IIH may have been a slight under estimation.

This study is important in highlighting the problems that come with the current obesity epidemic. Obesity puts patients at risk of visual loss from IIH. This further emphasises the urgent need for population wide intervention for obesity.

Sui Wong