Neuro-Ophthalmic Literature Review

David Bellows, Noel Chan, John Chen, Hui-Chen Cheng, Peter MacIntosh, John H. Pula, Michael Vaphiades, and Konrad P Weber

Fluorescein angiography is best in distinguishing pediatric pseudopapilledema

Chang MY, Velez FG, Demer JL, Bonelli L, Quiros PA, Arnold AC, Sadun AA, Pineles SL. Accuracy of Diagnostic Imaging Modalities for Classifying Pediatric Eyes as Papilledema Versus Pseudopapilledema. *Ophthalmology* 2017;124:1839-1848

One of the more frequent referrals that we see in the neuro-ophthalmology clinic is the child with suspected papilledema. Accurately distinguishing papilledema from pseudopapilledema in children can have life-threatening consequences. The heavy responsibility this places on our shoulders can compel us to employ multiple imaging modalities in the belief that more imaging will yield more correct diagnoses.

25 eyes with pseudopapilledema and 10 eyes with papilledema (confirmed by lumbar puncture) were included in this study. The authors compared the accuracy of multiple imaging modalities (read by three masked neuro-ophthalmologists) in distinguishing papilledema from pseudopapilledema. The modalities they compared were B-scan ultrasonography, fundus photography, autofluorescence, fluorescein angiography, and optical coherence tomography.

Fluorescein angiography was found to be the most accurate in correctly identifying papilledema with not a single case being misrepresented after the images were reviewed by the three neuro-ophthalmologists. However, fluorescein angiography is not infallible. It was noted that the rate of misrepresentation by an individual neuro-ophthalmologist ranged from 3% to 17%.

Fundus photography was the second most reliable modality in identifying papilledema. Important to note, however, is that fundus photography misrepresented an unacceptably high number of eyes (30%) with papilledema.

The bottom line is that many of us will continue to use multiple imaging modalities to aid us in distinguishing papilledema from pseudopapilledema. After reading this study I am now more inclined to subject my pediatric patients to fluorescein angiography in order to make this important distinction.

David Bellows

A less invasive angiography for ischemic optic neuropathy?

Balducci N, Morara M, Veronese C, Barboni P, Casadei NL, Savini G, Parisi V, Sadun AA, Ciardella A. Optical coherence tomography angiography in acute arteritic and non-arteritic anterior ischemic optic neuropathy. *Graefes Archive for Clinical & Experimental Ophthalmology* 2017;255(11):2255-2261.

As a new non-invasive technology, there is an increasing number of studies evaluating the use of optical coherence tomography angiography (OCT-A) in different neuro-ophthalmic conditions. Previous study by Sharma *et al* reported global and sectorial reduction of retinal and choroidal peripapillary flow densities in acute NAION. This retrospective study reported early OCT-A findings of 5 eyes with acute anterior ischemic optic neuropathy (AION) and compared them with traditional fluorescein angiography (FA) and indocyanine green angiography (ICG). OCT-A was able to visualize the boundaries of optic

nerve head non-perfusion areas in 2 out of 4 non-arteritic AION eyes which were also detectable with FA as disc filling defects. However, this finding was not dissimilar to that of arteritic AION (1 eye). In the remaining 2 eyes with non-arteritic AION, there were sectorial peripapillary capillary network reductions without non-perfusion defects while FA only demonstrated diffused leakage only. In these 2 eyes, FA only confirmed the presence of disc leakage and yet underlying peripapillary vascular changes were masked. The authors concluded that OCT-A was able to identify microvascular defects and vessel density reduction in acute AION. However, limited by the small sample size and motion artefacts, further studies and software improvements will be required for future clinical implication.

Noel Chan

Myelin oligodendrocyte glycoprotein antibody associated disease

Hacohen Y, Mankad K, Chong WK, Barkhof F, Vincent A, Lim M, Wassmer E, Ciccarelli O, Hemingway C. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. *Neurology* 2017;89:269–278

This is a large retrospective study describing the clinical features of a cohort of 110 children with relapsing demyelinating syndrome (RDS) with a mean follow up duration of 4 years. About half of these patients (56.4%) were diagnosed with multiple sclerosis (MS), 25.4% with neuromyelitis optica spectrum disorder (NMOSD) or MOG-Ab (myelin oligodendrocyte glycoprotein antibody) associated disease, 12.7% with multiphasic disseminated encephalomyelitis, and 5.5% with relapsing optic neuritis. In the MS group, only about one fifth (19.4%) presented with optic neuritis at onset as compared to approximately one third (35.4%) in the non-MS group. 82.9% of patients in the non-MS RDS were either aquaporin-4 antibody (AQP4-Ab) or MOG-Ab positive while MOG-Ab was more commonly found (63.4% vs 19.5%). 42.3% of MOG-Ab positive children presented with acute demyelinating encephalomyelitis (ADEM) while none of AQP4-Ab positive children did. Children with MOG-Ab were younger, less

likely to present with area postrema syndrome, had lower disability and longer time to relapse. Thus, the authors concluded the importance of isolating MOG-Ab positive children as a distinctive phenotype and to be incorporated as an essential part in the algorithm for the management and workup of children with central nervous system demyelinating disease. They also proposed 4 main distinct phenotypes: MS, NMOSD with AQP4-Ab, MOG-Ab-associated disease, and seronegative RDS, for future clinical use.

Noel Chan

Clemastine fumarate: a promising remyelinating therapy for multiple sclerosis?

Green AJ, Gelfand JM, Cree BA, Bevan C, Boscardin WJ, Mei F, Inman J, Arnow S, Devereux M, Abounasr A, Nobuta H, Zhu A, Friessen M, Gerona R, von Büdingen HC, Henry RG, Hauser SL, Chan JR. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. *Lancet* 2017;390, 2481–2489.

This single center, double-blind, randomized, placebo-controlled, crossover phase 2 clinical trial evaluated the use of clemastine fumarate, a first generation antihistamine capable of inducing oligodendrocyte differentiation, as a remyelinating therapy for multiple sclerosis (ReBUILD). Our current treatments for multiple sclerosis focus on prevention of demyelinating events, but we do not have any treatments to promote remyelination after damage has already occurred and therefore this trial has garnered a lot of excitement. They enrolled 50 patients with chronic multiple sclerosis and randomly assigned them to clemastine fumarate for 90 days followed by placebo for 60 days (25 patients) vs. placebo for 90 days followed by clemastine fumarate for 60 days (25 patients). The primary outcome was P100 latency on visual evoked potentials (VEP).

The trial found that clemastine fumarate treatment resulted in a reduced latency of 1.7ms/eye on VEP ($p=0.0048$). There was a trend toward improvement in low-contrast

letter acuity that reached significance of an increase of 1.6 letters per eye ($p=0.022$) in the post-hoc delayed-treatment analysis. There were no changes on magnetic resonance imaging (MRI) or optical coherence tomography (OCT). There were no serious adverse events, but some patients reported fatigue with treatment.

While the results were promising, there were a few limitations. Although the primary outcome was visual function, only 56% patients had a prior history of optic neuritis. A cohort with only patients with prior optic neuritis may have provided more robust results as suggested by their post-hoc analysis. Visual field data would also be helpful in detecting possible changes/improvements in visual function. Lastly, the mild improvements in visual evoked potential latency and low-contrast letter acuity were small and unlikely clinically meaningful to the patient.

Regardless of the potential shortcomings, this is first randomized controlled trial to demonstrate possible efficacy of a remyelinating drug for chronic demyelination in multiple sclerosis. Larger trials will be required to confirm these results and determine the optimal dosing and duration of therapy. It has yet to be determined if these improvements will be sustained beyond the period of the study. In addition, the mechanism of action of clemastine fumarate will need to be further explored and potentially optimized. In summary, this trial provides promise for future potential treatments for multiple sclerosis and other demyelinating diseases, but more work will need to be done.

John Chen

OCT as a window to the brain in multiple sclerosis

Petzold A, Balcer LJ, Calabresi PA, Costello F, Frohman TC, Frohman EM, Martinez-Lapiscina EH, Green AJ, Kardon R, Outteryck O, Paul F. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurology* 2017 16-(10):797-812

This large meta-analysis evaluated the utility of using spectral domain optical coherence tomography (SD-OCT) for the detection of neurodegeneration from multiple sclerosis. The authors reviewed all SD-OCT studies on multiple sclerosis between November 22, 1991 and April 19, 2016 and included 40 studies that met criteria for meta-analysis, which totaled 1667 eyes with multiple sclerosis-related optic neuritis, 4109 eyes with multiple sclerosis without optic neuritis, and 1697 healthy control eyes.

The largest differences between eyes with multiple sclerosis and controls were seen in the peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell layer and inner plexiform layer (GCIPL). When compared to controls, there was an average thinning of $-20.10\mu\text{m}$ in the peripapillary RNFL among eyes with prior multiple sclerosis-related optic neuritis and $-7.41\mu\text{m}$ in eyes with multiple sclerosis and no history of optic neuritis (both $p<0.0001$). The mean thinning of the macular GCIPL was $-16.42\mu\text{m}$ for eyes with prior optic neuritis and $-6.31\mu\text{m}$ for multiple sclerosis eyes without a history of optic neuritis when compared to controls (both $p<0.0001$). There was macular RNFL thinning in eyes with multiple sclerosis, but this was less prominent than the thinning seen in the peripapillary RNFL and macular GCIPL. Interestingly, there was mild thickening of the inner nuclear layer in eyes with prior MS-related optic neuritis compared to control eyes and eyes with multiple sclerosis without prior optic neuritis, which has been proposed to represent inflammation-mediated changes from optic neuritis. The outer retina was mostly spared in multiple sclerosis.

The main limitation of any meta-analysis is the dependency on prior studies that have heterogeneity in data collection and methods. The authors did an excellent job of going through 25,497 records and identifying 40 studies that were suitable for meta-analysis, which cut down on this potential bias. While this cannot replace a large prospective study, the large numbers garnered from this well-designed meta-analysis

is useful in providing a robust summary of the literature to date.

This meta-analysis on SD-OCT in multiple sclerosis now takes the place of a prior meta-analysis using time domain OCT published in 2010. This study confirms that SD-OCT is able to detect neurodegeneration from multiple sclerosis, especially within the peripapillary RNFL and macular GCIPL, and provides evidence for the use of these parameters in both clinical care and future clinical trials on multiple sclerosis.

John Chen

Postpartum is high-risk time neuromyelitis optica spectrum disorder

Klawiter EC, Bove R, Elson L, Alvarez E, Borisow N, Cortez M, Mateen F, Mealy MA, Sorum J, Mutch K, Tobyn SM, Ruprecht K, Buckle G, Levy M, Wingerchuk D, Paul F, Cross AH, Jacobs A, Chitnis T, Weinshenker B. High risk of postpartum relapses in neuromyelitis optica spectrum disorder. *Neurology* 2017;89:2238-44

Pregnancy is a well-established modulatory factor for autoimmune diseases. In multiple sclerosis (MS), the relapse rate may decrease during pregnancy and increase after delivery. However, little was known about pregnancy and neuromyelitis optica spectrum disorder (NMOSD).

Klawiter *et al* conducted a retrospective study of 217 women with NMOSD from 7 medical centers. They found that NMOSD relapse rate was increased during pregnancy and postpartum period, especially first 3 months postpartum, compared to baseline (annualized relapse rate [ARR] = 0.44, 0.69, 1.33, and 0.17 respectively). Breastfeeding was not associated with risk of relapse of NMOSD, contrary to its protective role in multiple sclerosis (MS). Regarding the initial NMOSD symptom onset during postpartum period, the observation risk (10.5%) exceeds the expected risk (3.65%) by a factor of 2.9. Future prospective studies are needed to investigate the treatment strategies and outcomes of pregnancy management in patients with NMOSD.

Hui-Chen Cheng

A novel video goggle as an alternative to Hess screen test for strabismus measurement

Weber KP, Rappoport D, Dysli M, Schmuckle Meier T, Marks GB, Bockisch CJ, Landau K, MacDougall HG. Strabismus Measurements with Novel Video Goggles. *Ophthalmology* 2017;124:1849-56

Traditional Hess screen test can provide informative data for ocular alignment. However, it has limitation in patients with visual suppression, and requires experienced technicians. Weber *et al* designed binocular video goggles with a head-mounted laser turret, which can project targets in a 0+/-15° 9-point grid onto a white screen at 0.5 meter distance. Binocular eye position was recorded by a digital infrared camera continuously. Binocular horizontal and vertical eye positions were calculated from the images. The eyes were alternately occluded with a liquid crystal display (LCD) shutter and 3 cycles of alternate eye occlusion were done at each gaze position. The authors then enrolled 41 patients with congenital or acquired paralytic or comitant strabismus and 17 health volunteers to test the agreement between the novel goggles and the Hess screen test. They found good agreement between the goggles and Hess screen test in measurements of horizontal and vertical deviation. In addition, the strabismus video google could be applied to measurement in patients with comitant strabismus and visual suppression, which was limited in the Hess screen test. We look forward to the implantation of ocular cyclotorsion measurement and more clinical data to validate the results of these novel strabismus video goggles.

Hui-Chen Cheng

What does the bladder have to do with the eye?

Takizawa T, Kijimoa M, Suzuki S, Osada T, Kitagawa S, Nakahara J, Takahashi S, Suzuki N. New onset of myasthenia gravis after intravesical Bacillus Calmette-Guerin. *Medicine* (Baltimore). 2007 Nov; 96(46):e8757

In this case report and review of the literature, the authors present a patient with bladder cancer

treated with transurethral resection followed by six weeks of intravesical Bacillus Calmette-Guerin (BCG). Four days after his final injection, he developed ptosis and diplopia. Testing was significant for a positive Tensilon test and positive anti-acetylcholine receptor antibodies, consistent with myasthenia gravis (MG). His response to pyridostigmine was incomplete, but he had good response to methylprednisone 1g/d for 3 days, after which his symptoms resolved and have not recurred in 1 year of follow up.

In the discussion, the authors acknowledge that BCG triggers an immune response including pneumonitis, though no prior report of MG was found in the literature. Other noxious medications that may induce MG included anticonvulsants, antibiotics and various immunotherapies. The most frequently reported medication was D-penicillamine. Another drug class, the immune checkpoint inhibitors (ICI) including antibodies against programmed death-1 (nivolumab, and pembrolizumab) and antibodies against cytotoxic T-lymphocyte-associated antigen 4 (ipilimumab) have a strong association with new-onset MG. Importantly, the medications need not be given systemically, as in this case it was given locally to the bladder only. Other local medication administrations related to new onset MG have included beta blocker eye drops for glaucoma and periocular botulinum toxin given for blepharospasm. The authors note the limitations of their paper including the single case report which cannot support a definite association between BCG and MG, but it does highlight the importance of being aware of the secondary MG effects of some medications, particularly D-penicillamine and immune checkpoint inhibitors.

Peter MacIntosh

In search of the Holy Grail

Weiss JN, Levy S, Benes SC. Stem Cell Ophthalmology Treatment Study: bone marrow derived stem cells in the treatment of non-arteritic ischemic optic neuropathy (NAION). *Stem Cell Investig.* 2017;4:94

The authors present a series of 10 patients with sequential NAION treated with autologous bone marrow derived stem cell (BMSC) therapy as part of the Stem Cell Ophthalmology Treatment Study (SCOTS). SCOTS is an IRB-approved clinical study of BMSC in the treatment of various optic nerve and retinal diseases.

The patients in this study had vision loss from NAION on average for 9.8 years (range 1-35 years). The affected eye was treated with either retrobulbar, subtenons and IV BMSC or with vitrectomy and intra-optic nerve, subtenons and IV BMSC. Primary outcome was visual acuity as measured by Snellen or converted to LogMAR.

The authors report 80% of patients with improved Snellen binocular vision and an average of 3.53 Snellen lines of vision improvement per eye at no later than 6 months after treatment. The authors conclude that BMSC can achieve meaningful visual improvements. The mechanism of action is unknown, but the authors postulate several mechanisms including paracrine secretion of proteins and hormones, transfer of mitochondria, release of messenger RNA.

The authors report impressive results for patients many months to years after vision loss from NAION. At this long interval since onset of vision loss, we would expect a certain amount of optic nerve atrophy, so the potential for visual recovery in this situation seems attractive. However, some shortcomings of this study include the lack of randomization and control group. The data provided focus mostly on visual acuity, and visual fields. Some macula thickness data is included, but for an optic nerve problem, RNFL might be also helpful. There is no mention of RAPD or color vision, which are other important neuro-ophthalmic markers of visual function. Another concern with this study is that it is patient funded, though the costs or details of funding are not specified. Certainly this type of treatment needs significant more research before we understand its implications for patients.

Peter MacIntosh

Don't ignore the sinuses

Chen L, Jiang L, Yang B, Subramanian PS. Clinical features of visual disturbances secondary to isolated sphenoid sinus inflammatory diseases. *BMC Ophthalmol.* 2017 Dec 6;17(1):237

The authors report a retrospective evaluation spanning ten years. They describe cases of sphenoid sinus disease having neuro-ophthalmologic manifestations. They excluded describing non-inflammatory cases such as malignancy, and they excluded any cases where pathology was localized anywhere outside the sphenoid sinus. In all, they found 67 cases of isolated sphenoid sinus disease, although only 23 were included in the report. It would have been helpful if they reported why the other cases were not included, but it is possible these were the non-inflammatory cases. The authors noted that neuro-ophthalmologic manifestations are non-specific, and include optic neuropathy, third nerve, and sixth nerve palsy. Fungal sinusitis was the most common diagnosis where post-operative pathology differed from preliminary radiographic diagnosis. Sphenoidotomy with drainage was the main treatment in all patients, and the authors recommend NOT treating with steroids until the infectious lesion is cleared. They found patients with diplopia responded much better to treatment than patients with optic neuropathy.

John Pula

Space Brain

Hamid SHM, Whittam D, Roberts DR, Albrecht MH, Collins HR, Asemani D, Chatterjee AR, Spampinato MV, Zhu X, Chimowitz MI, Antonucci MU. Effects of spaceflight on astronaut brain structure as indicated on MRI. *N Engl J Med* 2017;377:1746-53

This prospective study used non-contrasted brain magnetic resonance imaging (MRI) to compare images of 34 astronauts: 18 brain MRIs before and after missions of long duration involving stays on the International Space Station, and 16 brain MRIs before and after missions of short duration involving participation in the Space Shuttle Program. Narrowing

of the central sulcus occurred in 17 of 18 astronauts after long-duration flights (mean flight time, 164.8 days) and in 3 of 16 astronauts after short-duration flights (mean flight time, 13.6 days). Cine clips from a subgroup of astronauts showed an upward shift of the brain after all long-duration flights (12 astronauts) but not after short-duration flights (6 astronauts) and narrowing of CSF spaces at the vertex after all long-duration flights (12 astronauts) and in 1 of 6 astronauts after short-duration flights. Three astronauts in the long-duration group had optic-disk edema, and all 3 had narrowing of the central sulcus. A cine clip was available for 1 of these 3 astronauts, and the cine clip showed upward shift of the brain. The limitations include 2 different MRI systems, the cine clips were not used in all patients and the small number of patients who had not flown before. This paper is important because it adds to the body of evidence that space flight, especially long trips, can cause changes in the brain on MRI and also elevated ICP.

Michael Vaphiades

Vision loss and diplopia in giant cell arteritis

Ross M, Burszty L, Superstein R, Gans M. Multiple Cranial Nerve Palsies in Giant Cell Arteritis. *J Neuroophthalmol.* 2017;37:398-400

The authors present 2 patients with biopsy-proven giant cell arteritis (GCA) associated with multiple cranial nerve palsies. The authors described 2 patients with GCA who developed vision loss because of posterior ischemic optic neuropathy (PION) and multiple cranial nerve palsies including cranial nerve 3, 4, or 6. Interestingly their visual loss persisted though the extraocular motility deficits improved or resolved. The main limitation of the study is the small sample size. This paper highlights the fact that GCA can cause multiple cranial nerve palsies, including the 4th cranial nerve, and the optic neuropathy may not improve even if the extraocular motility defect does improve or resolve.

Michael Vaphiades

Younger is not better in pediatric pseudotumor cerebri

Tovia E, Reif S, Oren A, Mitelpunkt A, Fattal-Valevski A. Treatment Response in Pediatric Patients With Pseudotumor Cerebri Syndrome. *J Neuroophthalmol.* 2017;37(4):393-397

In this retrospective study of 60 pediatric patients treated for pseudotumor cerebri syndrome (PTCS), 46 patients responded well to acetazolamide therapy (76.6%), with full resolution of symptoms, including papilledema. Of the 14 patients with no response to treatment, 9 required surgical intervention. Non-responders tended to be younger at presentation than responders (mean 8.7 vs 11.5 years respectively). Twelve patients experienced relapse after acetazolamide was discontinued. The group that experienced relapse was significantly younger than the non-relapsers (mean 8.9 vs 12.1 years respectively). The main limitation of the study is its retrospective nature. In pediatric patients with PTCS, younger age was found to be a risk factor for treatment failure or relapse. This is an important paper because in younger patients with PTCS, physicians should be extra vigilant due to treatment failure with acetazolamide is common and thus visual loss may be profound.

Michael Vaphiades

Infliximab for CNS sarcoidosis

Gelfand JM, Bradshaw MJ, Stern BJ, Clifford DB, Wang Y, Cho TA, Koth LL, Hauser SL, Dierkhising J, Vu N, Sriram S, Moses H, Bagnato F, Kaufmann JA, Ammah DJ, Yohannes TH, Hamblin MJ, Venna N, Green AJ, Pawate S. Infliximab for the treatment of CNS sarcoidosis: A multi-institutional series. *Neurology* 2017;89(20):2092-2100

Six United States centers retrospectively identified patients with central nervous system (CNS) sarcoidosis treated with infliximab, including only patients with definite or probable neurosarcoidosis following rigorous exclusion of other causes. Of 66 patients with CNS sarcoidosis treated with infliximab for a median of 1.5 years, there was clinical improvement in 77.3% of patients, with complete neurologic recovery in 28.8%, partial improvement in 48.5%, clinical stability in 18.2%, worsening in

3%, and 1 lost to follow-up. MRI evidence of a favorable treatment response was observed in 82.1% of patients with imaging follow-up, with complete remission of active disease in 51.8% and partial MRI improvement in 30.1%; MRI worsened in 1 patient (1.8%). Limitations of this study include potential biases inherent in any retrospective case series, including the absence of a comparison of outcomes to a noninfliximab-treated group. Most patients with CNS sarcoidosis treated with infliximab exhibit favorable imaging and clinical treatment responses, including some previously refractory to other immunosuppressive treatments. This is an important study given the potential devastating neurologic and ophthalmological effects of this disease, side effects with long-term corticosteroid use and the failure of some steroid-sparing immunosuppressive treatments to control this disease.

Michael Vaphiades

Pediatric Pseudotumor Cerebri

Phillips PH, Sheldon CA. Pediatric Pseudotumor Cerebri Syndrome. *J Neuroophthalmol.* 2017;37 Suppl 1:S33-S40.

This review addresses the revised criteria, demographics, diagnosis, and treatment of pediatric primary pseudotumor cerebri syndrome (PTCS). Prepubertal children with primary PTCS have an equal gender distribution and less frequent obesity compared with adult patients. However, female gender and obesity are risk factors for primary PTCS in postpubertal children. Compared with adults, children with PTCS more frequently present with ocular motility deficits and more often have associated medical conditions that increase the risk of developing PTCS. In non-sedated, non-obese children, an ICP greater than 25 cm H₂O exceeded the 90th percentile. The ICP is greater than 28 cm H₂O in the 90th percentile of the remainder of children with this disorder. This is an important review because it highlights the differences between pediatric and adult PTCS, more specifically the equal gender distribution and less obesity in prepubertal children and the higher ICP of greater than previously recognized.

Michael Vaphiades

What are the most common causes of fourth nerve palsy?

Dosunmu EO, Hatt SR, Leske DA, Hodge DO, Holmes JM. Incidence and Etiology of Presumed Fourth Cranial Nerve Palsy: A Population-based Study. *Am J Ophthalmol* 2018 Jan;185:110-114

A population-based database was used to identify all cases of isolated fourth nerve palsy in Olmsted County, Minnesota, USA diagnosed over a 15-year period. Seventy-three patients were identified with a mean age at presentation was 41.8 years. The most common etiology was presumed congenital (49%), followed by hypertension (18%), and trauma (18%). One patient (1%) had fourth nerve palsy owing to a known intracranial neoplasm. For 3 patients (4%) the cause of fourth nerve palsy was undetermined. The most common decade of presentation overall was the fourth decade, including for presumed congenital cases. The population studied was predominately white and thus the results may have been different with a more diverse population. This is an important review because it highlights the different etiologies of 4th cranial palsies and further supports that a vasculopathic etiology is just as common as head trauma, and not less common. Also, in no case was an isolated fourth nerve palsy the presenting sign of an intracranial tumor.

Michael Vaphiades

The role of the mitochondria explored

Bargiela D, Chinnery PF. Mitochondria in neuroinflammation - Multiple sclerosis (MS), leber hereditary optic neuropathy (LHON) and LHON-MS. *Neurosci Lett*. 2017 Jun 28. pii: S0304-3940(17)30543-8.

Mitochondrial dysfunction is associated with neuroinflammation and neurodegenerative disease, but its role as a driver in these processes is uncertain. Understanding the pathogenesis of inherited mitochondrial disorders may help us to uncover mechanisms involved during acquired mitochondrial dysfunction. The authors review the mechanisms of mitochondrial dysfunction in Leber's hereditary optic

neuropathy and multiple sclerosis and discuss shared clinical and molecular features in both conditions. Targeting mitochondrial pathways involved in inflammation or apoptosis may be a possible therapeutic approach in multiple sclerosis.

Michael Vaphiades

Breast cancer in a male metastasizing to the eye

Wang Y, Mettu P, Maltry A, Harrison A, Mokhtarzadeh A. Metastatic Breast Carcinoma to the Superior Oblique in a Male. *Ophthalmol Ther*. 2017 Dec;6(2):355-359.

The authors report a 66-year-old man with a history of left breast carcinoma who presented with headaches and intermittent diplopia. MRI of the orbit revealed a $0.7 \times 1.4 \times 1.9$ cm mass in the region of the left superior oblique muscle. Biopsy of the superior oblique revealed metastatic breast carcinoma. While rare, male breast cancer can metastasize to the orbit. In more than half of the cases, metastatic disease is found in lymph nodes at time of presentation, and may involve any of the extraocular muscles. It may present as nodular, fusiform with tendon sparing or diffuse with tendon involvement. The imaging presented in this case could be mistaken for orbital inflammatory or thyroid eye disease (yet axial cuts if presented likely would have shown tendon involvement unlike thyroid eye disease).

Michael Vaphiades

Vestibulo-ocular reflex deficits in medial longitudinal fasciculus lesions

Aw ST, Chen L, Todd MJ, Barnett MH, Halmagyi GM. Vestibulo-ocular reflex deficits with medial longitudinal fasciculus lesions. *J Neurol*. 2017 Oct;264(10):2119-2129

This study thoroughly examines the vestibulo-ocular reflex (VOR) in multiple sclerosis (MS) patients with internuclear ophthalmoplegia (INO) due to lesions of the medial longitudinal fasciculus (MLF). For this purpose, the authors measured the

head impulse test in the direction of all six semicircular canals with binocular 3D scleral search coils in 27 MS patients. In unilateral INO, they found not only an impaired horizontal VOR of the adducting eye, but also of the contralateral posterior semicircular canal. In bilateral INO, they found VOR deficits in all six semicircular canals, but predominantly in both posterior canals. From the relative sparing of the horizontal VOR with marked slowing of the horizontal catch-up

saccades in the adducting eye, the authors concluded that part of the horizontal VOR is mediated by the adjacent ascending tract of Deiters, while the catch-up saccades are mediated by the MLF. The study nicely explains why patients with INO due to MS not only suffer from double vision on lateral gaze, but also from oscillopsia, especially with vertical head movements.

Konrad P. Weber