· Education ·

Recent developments in neuro-ophthalmology

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[**Abstract**] Some recent advances in neuro-ophthalmology including clinical trials, diagnostic testing and newly elucidated disease entitites were summarized in present paper, such as neuromyelitis optica spectrum disorder. The review goes into great detail regarding recent clinical trials in neuro-ophthalmology. These trials have investigated the management of idiopathic intracranial hypertension as well as treatment of Leber hereditary optic neuropathy and optic nerve glioma. The potential gene therapy for Leber hereditary optic neuropathy seems very promising and may have a significant clinical impact within the next few years. This review also includes an extensive discussion about the application of optical coherence tomography (OCT) and OCT-angiography (OCTA) in neuro-ophthalmology. OCT has important clinical relevance not only for the diagnosis and management of optic neuropathies, such as optic neuritis, ischemic optic neuropathy and chiasmal compression, but also for retro-chiasmal injury. In terms of OCTA, recent studies have demonstrated increased vessel density in acute stage of ischemic optic neuropathy (NAION) and optic neuritis, but decreased vessel density in severe papilloedema and late stage of optic atrophy of any cause. These serve as the potential foundation for future clinical applications. Ophthalmologists should pay more attentions to these recent progress in neuro-ophthalmology.

[**Key words**] Neuro-ophthalmology; Clinical trials, intracranial hypertension; Leber´s optic neuropathy; Optical coherence tomography; Optical coherence tomography angiography; Optic neuritis; Ischemic optic neuropathy

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神经眼科学最新研究

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【**摘要**】 本文回顾了神经眼科学在临床试验、诊断性检测及新的疾病分型例如视神经脊髓炎谱系病(NMOSD)等方面的研究进展, 详尽总结了特发性颅内高压、Leber 遗传性视神经病变及视神经胶质瘤等疾病的临床试验最新成果。Leber 遗传性视神经病变的基因治疗效果令人振奋, 可能在未来几年内产生重大的临床影响力。近年来光相干断层扫描(OCT)及光相干断层扫描血管成像(OCTA)在神经眼科的疾病诊疗中发挥了重要作用, OCT 不仅可对视神经病变进行辅助诊断, 用于视神经炎、缺血性视神经病变、视交叉压迫病变的诊断和治疗过程监测, 而且对视交叉以后的视路病变的诊断也有较大的参考价值。最新研究也表明, 借助于 OCTA 检查可发现, 急性期缺血性视神经病变(NAION)或视神经炎患者视盘血管密度是增加的, 而严重视盘水肿和不同原因视盘萎缩的患者视盘血管密度则是降低的。眼科医生应该关注这些视神经疾病诊疗方面的最新进展。

【**关键词**】 神经眼科; 临床试验; 颅内高压; Leber 遗传性视神经病变; 光相干断层扫描; 光相干断层扫描血管造影; 视神经炎; 缺血性视神经病变

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This review covers some recent studies and findings from the 42nd and 43rd annual meetings of the North American Neuro-Ophthalmology Society (NANOS) meeting held in Tuscon, AZ and Washington DC in 2016 and 2017 respectively as well as recent issues of *Journal of Neuro-Ophthalmology*. The hot topics were well

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outlined by Dr. Neil Miller from Johns Hopkins Hospital and updates about ongoing clinical trials investigating idiopathic intracranial hypertension (IIH), Leber hereditary optic neuropathy (LHON), giant cell arteritis (GCA) and optic pathway glioma (NANOS, 2017). One point of interest was a significant increase in studies evaluating the use of optical coherence tomography-angiography (OCTA) for neuro-ophthalmic diseases. The number of accepted abstracts on the topic increased by several folds.

Part I: Hot topics in NANOS, 2017

1　Current neuro-ophthalmology clinical trials

1.1　Idiopathic Intracranial Hypertension Treatment Trial

Run by the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) and funded by National Eye Institute (NEI, US). Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) prospectively enrolled 165 participants with mild visual field loss to assess whether acetazolamide (diamox) plus dietary management was superior to placebo tablets plus dietary management in improving visual function. Goal of the study was to determine if weight loss alone is as effective as weight loss combined with diamox for mild/moderate pseudotumor cerebri (PTC) or IIH. The severity of disease was characterized by degree of papilledema and mild Humphrey visual field deficits. The dosage of diamox started at 500 mg 2 times/day, and could be increased up to 4 g/day at the discretion of investigator given its acceptable safety profiles. The most common dose for initial treatment is 500 mg three times daily by mouth. The results showed that (1) weight loss with diamox has better visual outcome than weight loss alone, and (2) the effects of diamox is not due to solely to its effect on weight loss. Headache is the most common symptom of IIH. The IIHTT study also found that cerebrospinal fluid (CSF) pressure and headache are independent features of IIH.

1.2　Leber hereditary optic neuropathy

New developments have been made in gene therapy using adeno-associated viral (AAV) vector carrying ND4 genetic materials. Most common Leber's mutation 11778, ND4 subunit gene of complex I of the oxidative phosphorylation chain in mitochondria and reduce ATP production. There have been three previous and current clinical trials in different countries. (1) A prospective, open label trial from China included 9 patients (1 – 17 year's disease history) with Leber hereditary optic neuropathy (LHON) G11778A mitochondrial mutation (worst prognosis among 3 common Leber's mutations). Single intravitreal injection of rAAV-ND4 was used for the patients, 8 patients received unilateral injection, and 1 patient bilateral injection. A 3-year follow-up was performed to determine safety and efficacy. Improvement of vision in both groups (some treated and some untreated eyes, not the same object) may be attributed to young age of some patients (<10 years). These patients have some chance to recover even without treatment. Visual field improved in all treated eyes and some untreated eyes. In the treatment group, the P-100 latency of visual evoked potential (VEP) demonstrated a statistically significant decrease. The increase in the P-100 amplitude was not deemed statistically significant. OCT exhibited no effectiveness on nerve fiber layer thickness. No serious adverse effects, including liver and kidney function, occurred during the follow up in any patients[1-2]. (2) A phase 1 prospective open label trial of LHON patients with G11778A mutation from United States published in 2016. Patients were assigned into different groups based on onset of disease and severity of visual loss. Five patients with unilateral injection of self-complementary AAV-P1ND4v2 and an adaptive plan to identify the maximum tolerated dose. Results showed 3-line improvement of vision in 2 out of 5 patients. The patients were followed up from 3-6 months, without serious ocular and systemic side effects[3]. (3) Additionally a trail is ongoing in Europe for the patients with G11778A mutation, with single intravitreal injection to one eye (rAAV2/2-ND4) and the other eye received sham injection. Fifteen patients divided into 3 groups in a dose-escalation fashion. There are no final results yet but there was a recent press release. No significant adverse events at 48 weeks post treatment. The treated eyes showed significant improvement in those patients who lost vision within two years of disease onset when compared to the untreated eyes. The treatment effects were stable beyond 48 weeks[3].

Two new phase 3 trials are set to begin. The RESCUE study led by Nancy Newman (Emory University, GA, US)

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with onset within 6 months and the REVERSE study led by Patrick Yu-Wai Man (Moorfields Eye Hospital, London, England) with onset within 7–12 months.

1.3 Giant cell arteritis

Giant cell arteritis (GCA) and arteritic anterior ischemic optic neuropathy (AAION) are relatively rare in China. The study is to investigate the use of steroid sparing agents in the prevention of relapse of GCA[4]. One previous randomized clinical trial with methotrexate (MTX) as an adjunctive agent showed no efficacy. Tocilizumab (TCZ) is an anti-interleukin (IL)-6 receptor antibody. It is currently approved for use in treatment of both rheumatoid arthritis and juvenile idiopathic arthritis. A randomized control trial in GCA demonstrated that 85% in the TCZ treated group experienced no relapse by the end of trial at week 52. Only 20% of the placebo treated group had the same outcome.

1.4 Optic pathway glioma

Most optic nerve gliomas in children in NF-1 are relatively benign and stable over the years. However, optic pathway, especially chiasmal glioma in sporadic cases can be very aggressive with poor visual prognosis. A case series study included 5 children with optic nerve glioma and severe optic atrophy (Italy). The patients received 10-day course of topical murine nerve growth factor (NGF) (eye drops). VEP amplitude increased in all cases and continued past 90 days. By 180 days, the amplitude had declined but remained above baseline[5]. The same research group had a follow up study that was a randomized phase 2 clinical trial. They enrolled 18 patients with optic pathway gliomas and treated them with a 10-day course of NGF. There were no adverse events. The treated group showed significant improvement in all parameters (vision, visual field, VEP, OCT-NFL and MRI). The placebo group showed worsening of the visual field[6].

2 OCT in neuro-ophthalmology

2.1 OCT and multiple sclerosis

This is an area of great interest to both ophthalmologists and neurologists. OCT findings are closely relate to the degree of brain injury/atrophic changes in multiple sclerosis (MS) patients. In 1999, the first study of OCT-retinal nerve fiber layer (RNFL) in MS-optic neuritis (MS-ON), showed that RNFL thickness was reduced by 46% with history of optic neuritis. The fellow eye without optic neuritis history was also found to be reduced by 28%. This was an asymptomatic and subclinical finding[7]. In 2005, Trip et al [8] reported similar finding with time domain-OCT (TD-OCT), but also found retinal ganglion cells (RGCs) loss. In 2006, Costello et al[9] reported that 75–80 μm NFL thickness to be "threshold level." Below this, patients will have visual function impairment. The normal value of TDOCT-NFL is about 105 μm. Physiological loss due to aging is about 10–20 μm loss over 60 years. Further study found NFL reduction of about 20 μm in MS-ON, and 7 μm in MS without optic neuritis, with maximal loss at 3–6 months after the acute event.

As noted in Gabilondo et al[10] in 2015, the loss of ganglion cell layer (GCL) precedes NFL thinning by a few weeks and is more accurate to determine the treatment window. The first detectable NFL thinning occurs at about 6–7 weeks. In some situations, OCT-NFL can be complicated by areas of disc swelling (in 1/3 of cases, early stage ON can have associated mild disc swelling) and axonal loss. This confounds the testing and shows less change in the average thickness of nerve fiber layer.

OCT-NFL thickness has been shown to reflect volumes of brain white and grey matter. It is better correlated with MRI measurement of brain atrophy in patients without optic neuritis, and could be a marker for brain atrophy in MS. A meta-analysis of NFL and GCL in MS-ON demonstrated that OCT-retinal ganglion cells (RGCs) is as important as OCT-NFL. Britze et al reviewed 42 out of a total of 251 studies involving 4,745 subjects. GCL thinning was measurable within the first 5 weeks, earlier than NFL thinning. GCL thinning at 1–2 months after acute optic neuritis predicted recovery of visual function at 6 months. Degree of GCL thinning was associated with loss of visual function in most studies, particularly low contrast visual acuity (LCVA). Most of the studies found a significant inverse correlation between GCL thickness and expanded disability status scale (EDSS) scores.

2.2 OCT in non-arteritic ischemic optic neuropathy

Similar to MS-ON, OCT-RGC loss was detected earlier than NFL loss in non-arteritic ischemic optic neuropathy

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(NAION). It was first detectable at about 1 month, continued at 3 months, and stabilized at 6 months[11]. However, the study chose the time point as acute, 1 month, 3 months, 6 months when the GCL thinning could be earlier than 1 month (1 – 2 weeks, author's unpublished observation). This is correlated to the previous study of NAION animal model[12]. Hauptman and Hauptman (Australia) (NANOS 2017) demonstrated that OCT-GCL is better than visual field in early stage of glaucoma and demyelinating disease. On the other hand, late glaucoma is best tracked by Humphrey visual field. The authors propose that correlating structure and function is the best approach and Humphrey visual field, OCT-GCL and OCT-NFL being excellent complements.

2.3 OCT-RGC in chiasmal compressive optic neuropathy

In chiasmal compressive optic neuropathies, nasal retinal RGC loss in both eyes is typical presentation with corresponding bi-temporal Humphrey visual field loss[13]. Visual field defects correlate more with GCL than NFL thickness. Thinning of GCL may be detected in some patients before Humphrey visual field defects indicating that Humphrey visual field may not be as sensitive as OCT-RGC. The combination of Humphrey visual field and Goldmann visual field may be as sensitive as RGC loss but this has not been formally investigated and tested (Author's observation). In some situations, visual field defects could be more sensitive than RGC loss, such as in acute/subacute chiasmal compression from pituitary apoplexy/pituitary tumor. We have seen many patients clinically that OCT-RGC and NFL both are completely normal, but with severe temporal visual field defects, and these patients usually have excellent visual prognosis.

After surgery, even though chiasmal compression relieved, the visual field improves but there is a persistent RGC loss, indicating some previously injured optic nerve axons and RGCs by compressive lesions are irreversible.

So due to complexity of various optic neuropathies, early detection by OCT or Humphrey visual field may depend on the speed of pathological process. In chronic disease process, such as open angle glaucoma, OCT will be more sensitive than Humphrey visual field. In acute ON diseases, such as NAION or optic neuritis, Humphrey visual field will be more sensitive than OCT. But in chiasmal compression, it depends on the speed of tumor growth and the development of compression. So combination of OCT and Humphrey visual field is most important approach at the present time.

2.4 Multi-focal VEP in chiasmal compressive optic neuropathy

MfVEP amplitudes were able to differentiate eyes with temporal hemianopia in pituitary tumor and were significantly correlated with Humphrey visual field and OCT findings, suggesting that it may be a useful addition for detecting visual abnormalities in patients with chiasmal compression.

2.5 OCT-NFL and visual function

Thecorrelation of OCT-NFL and VEP showed that VEP-latency was found to be sensitive for demyelination, while VEP-amplitude correlated with NFL thickness changes[14]. The correlation of OCT-NFL and visual function showed that visual function is associated with NFL thickness. It is estimated that for every 1 line decease in low contrast letter acuity, the mean NFL thickness decreased by 4 μm[15].

2.6 Trans-synaptic degeneration

In the past, people believe retro-chiasmal pathology will not cause significant retinal & GCL changes. However, many recent studies proved this is not the case with the OCT testing. RGC and RNFL loss are associated with post-lateral geniculate nucleus (LGN) pathology due to retrograde degeneration (US). Homonymous visual field loss is also sometimes seen with increase in C/D ratio, due to loss of ON axons.

Anterograde trans-synaptic degeneration was also studied in patients with MS-Optic Neuritis[16]. After optic neuritis, there is progressive damage to the optic radiations, and it is greater in patients with early optic atrophy, indicating anterograde neuronal degeneration.

3 OCT angiography in the evaluation of retinal and choroidal and optic nerve vasculature

3.1 OCTA and migraine

Chang et al showed (US) (NANOS 2017) migraine with aura, but not without aura, is associated with an enlarged FAZ (foveal avascular zone) and decreased macular vessel density at the superficial capillary plexus level. Further studies are needed to determine if retinal vascular

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abnormalities correlate with cerebrovascular changes and risk of ischemic complications in migrainers.

3.2 OCTA and NAION

OCTA shows the increased vessel density of the optic nerve in the setting of acute stage NAION (US) (Ghannam et al, NANOS 2017). Chronically with optic atrophy, the vessel density will decrease below the normal levels, specifically along the area that was affected by ischemia.

3.3 OCTA and papilledema

Fell et al. (US) (NANOS 2017) used customized OCTA post-processing software (current OCT machine frequently gets segmentation error in papilledema) and demonstrated significantly decreased peripapillary capillary density in high-grade papilledema and post-papilledema optic atrophy. This decrease might be related to visual functional damage in patients with severe papilledema but further evaluation is required. Clinically only patients with severe papilloedema are associated with poor visual prognosis.

3.4 OCTA and optic atrophy

All chronic optic neuropathies lead to a decrease in the peripapillary capillary density on OCTA. The study found this is not specific to optic neuropathies that are thought to have an underlying ischemic mechanism, such as glaucoma. Future studies evaluating the time course and severity of peripapillary capillary density changes may provide some ability to distinguish optic neuropathies.

3.5 OCTA in other optic nerve diseases

Optic nerve OCTAfindings varied in different etiologies of optic neuropathy (US) (Gaier et al, NANOS 2017). In LHON patients, temporal peripapillary capillary dilation was noted in both the acutely affected eyes and the fellow eyes. The patients with optic nerve head drusen showed focal capillary drop-out in the areas associated with superficial drusen. Acute NAION patients showed dilation of the peripapillary capillary network that corresponded to focal ON edema and visual field loss. Arteritic ischemic optic neuropathy (AAION) demonstrated areas of capillary drop-out in a non-sectoral pattern (segmental disc swelling is the feature of NAION).

Part II: Neuro-Ophthalmology diseases

1 NAION

Pakravan et al treated NAION patients with steroid plus erythropoietin. The study found no beneficial effect of either systemic steroid alone or combined with erythropoietin in the visual outcome of NAION patients (treatment started <14 days). Some NAION patients associated with macular edema/deformation and Kupersmith et al did an OCT study to see if it affects visual prognosis. The study found retinal deformation/macular edema and their resolution are not correlated with vision loss or recovery, likely due to local tissue changes and extracellular fluid accumulation, and most vision loss is due to optic neuropathy by ischemic injury. Micieli et al studied the vascular endothelial growth factor (VEGF) and IL-2 levels in 10 NAION patients and found acute NAION (<14 days) is associated with increased intraocular VEGF and a decreased IL-2 in aqueous humor. This may have implications for future therapeutic interventions and diagnostic testing in NAION patients.

2 Optic neuritis (ON)

2.1 NMOSD

Neuromyelitis optica (NMO), now called neuromyelitis optica spectrum disorder (NMOSD), is diagnosed on clinical and radiological criteria. It is more common in Asian (NMOSD ratio to MS: US or Europe 1∶50; Asian 1∶3). The 2006 criteria used clinical findings of ON and transverse myelitis, and two or more of the following: anti-aquaporin 4 antibodies, brain MRI that is not consistent with multiple sclerosis, and a spinal cord lesion three or more vertebral segments in length.

The current 2015 criteria are more complex, and distinguish NMOSD with and without antibodies to aquaporin 4. They also broaden the clinical and radiological requirements. Major diagnostic criteria are NMO antibody positive: plus one core feature (ON, spinal cord or atypical brain lesion); NMO antibody negative: plus two core criteria (optic neuritis and transverse myelitis or atypical brain lesion, one core feature must be optic neuritis or acute myelitis).

NMO antibody testing: Cell based FACS is the most sensitive test, showing 76.7% sensitivity; NMO-IgG positivity correlates with higher risk of relapsing disease process. Typical core clinical features are ON: Bilateral severe vision or visual field loss, extensive optic nerve and chiasmal enhancement on MRI; Acute myelitis: spinal

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lesions (>2 contiguous segments); Atypical MS brain lesions (not periventricular, in the postrema, brainstem or diencephalon)[17].

Anti-MOG antibody (anti-myelin oligodendrocyte glycoprotein, located on the myelin sheath): Some NMO-IgG negative patients (15%-40%) could be anti-MOG positive, which has been shown to be associated with better prognosis and monophasic (no relapse). Test is still not commercially available as a diagnostic tool.

In treatment of acute onset NMOSD, it is available to have the intraveneous injection of steroid and plasma exchange/plasmapheresis (PLEX), next line intraveneous injection of immunoglobulins (IVIG). For the chronic treatment, rituximab, azathioprine, and cellcept can be used. MS medication, such as interferon (INF)-beta 1a (Avonex) and fingolimod (Gilenya) may have deleterious effects on the relapse rate of NMOSD patients.

Despite the rarity of NMOSD-related ON among the predominantly Caucasian American population, Vanikieti et al studied the NMOSD patients between Thai and Caucasian population and found the clinical characteristics and long-term visual outcome were not statistically different from those observed in the Thai population.

2.2 Pediatric optic neuritis

Pediatric optic neuritis (PON) is different from adult ON. It is more commonly bilateral, with disc swelling and severe visual loss at presentation but most of them with good visual recovery. Risk for MS included white matter lesion and older age at presentation, oligoclonal bands on lumber puncture (LP). Sex and laterality (uni- or bilateral) not associated with the risk for MS. One study from Korea found a 7.7% conversion rate to MS for about 1 year follow-up, which could be similar to Chinese population[18]. Study from Children´s Hospital of Boston (Harvard affiliated hospital) found about 50% of PON associated with systemic diseases (39% MS, 7% ADEM, 7% NMOSD)[19]. Final visual outcome was not associated with vision at presentation, sex, bilateral involvement, optic nerve edema, and underlying diseases, but with poor vision at 3 months. So final visual outcome was associated with nothing at baseline. 81% has vision of 20/20 at 1 year f/u, 89% better than 20/40. Recovery time to almost normal vision: vision at presentation >CF, recovery takes 1 month; vision at presentation < CF, recovery takes 3 months. Anti-MOG antibody was found to be associated infrequently with demyelination, such as MS or ADEM, but maybe more important in NMO antibody negative NMOSD.

Regarding treatment, there is no clinical trial for the optimal treatment. Usually intraveneous injection of methylprednisolone for 3-5 days is given. If not effective, intraveneous injection of IG or plasmapheresis is used.

2.3 Pediatric Optic Neuritis Prospective Outcome Study

Pediatric Eye Disease Investigator Group (PEDIG) and NORDIC co-sponsored (funded by NEI) pediatric optic neuritis(PON) prospective trial, to study the features of PON and whether able to enroll sufficient numbers of PON patients for future study about treatment[20]. Study enrollment includes the children aged 3- to 15-year old, at least 1 eye with PON within 2-week onset, MRI brain and orbit. Exclusion criteria included neuroretinitis, previous episode on the same eye, or any infectious or other etiology except demyelinating etiology. Baseline testing included high and low contrast vision using electronic visual system, and NMO antibody testing done at Mayo Clinic, treatment depending on investigator.

2.4 LHON

Lyseng-Williamson[21] reviewed the therapeutic effects and mechanism of idebenone in the treatment of LHON. Idebenone is the only disease-specific drug approved to treat LHON patients in Europe. The mechanism involves its antioxidant properties and ability to act as a mitochondrial electron carrier. Idebenone overcomes mitochondrial complex Ⅰ respiratory chain deficiency in patients with LHON by transferring electrons directly to mitochondrial complex Ⅲ (by-passing complex Ⅰ, while 11778 mutation affecting ND4 subunit and complex Ⅰ), thereby restoring cellular energy (ATP) production. Previous studies showed that oral idebenone 900 mg/day for 24 weeks has persistent beneficial effects in preventing further vision impairment and promoting vision recovery in patients with LHON. LHON is an important cause of mitochondrial blindness among young adults. Yu-Wai-Man et al.[22] evaluated the therapeutic potential of idebenone in LHON. The study investigated the four quinone analogues (CoQ_1, CoQ_{10}, decylubiquinone and idebenone) in compensating for the deleterious effect of the m. 11778G> A mitochondrial DNA mutation. The LHON

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fibroblast cell lines exhibited reduced cell growth, impaired mitochondrial bioenergetics and elevated levels of reactive oxygen species (ROS). Only idebenone consistently increased ATP production and reduced ROS levels, although the effect was partial. He also studied metabolic pathways in mitochondrial optic neuropathy and found oxidative stress, impaired phospholipid metabolism and dysregulated steroidogenesis as important metabolomics signatures in patients with mitochondrial optic neuropathies (LHON, dominant optic atrophy DOA, Wolfram syndrome).

Levin[23] from Canada studied the mechanism of parvocellular optic neuropathy with PM (papillo-macular) bundle defects. He proposed that superoxide generation and oxidation are the common pathway for optic neuropathies with ceco-central scotoma, including hereditary (LHON, DOA), nutritional (commonly B12 and folate deficiency), toxic (most common ethambutol, a TB drug). PM bundle is more sensitive to superoxide or other type of injury, could be due to the smaller axons in the bundle. Arndt and Arndt (France) (NANOS 2017) found in most patients with parvocellular (PM bundle) optic neuropathies, the blood samples demonstrated a deficiency of micronutrients involved in mitochondrial function and these deficiencies could contribute parvocellular axonal loss particularly sensitive to mitochondrial dysfunction.

2.5 Papilledema *vs.* pseudo-papilledema

Thompson et al studied whether the horizontal diameter in Bruch membrane opening (BMO) can distinguish papilledema from pseudo-papilledema using OCT. The size of BMO is enlarged in eyes with papilledema and reverses as papilledema resolves. BMO may be used to help distinguish papilledema from pseudo-papilledema. A prospective study by Pineles et al found fluorescence angiography (FA) was the best imaging modality for differentiating pseudo-papilledema from disc edema in children (100% sensitivity and specificity). Non-calcified and buried disc drusen in children are difficult to diagnose clinically, and the distinction between pseudo-papilledema and disc edema in children may be best accomplished by evaluating for disk leakage (disc edema) on FA. But very early stage of papilledema may not have leakage on FA. B-scan is usually considered very sensitive for calcified disc drusen, but with relatively high false positivity. In the future, new generation OCT, EDI-OCT (Enhanced Depth Imaging-OCT) may have deeper penetration and offer best diagnosis for disc drusen.

2.6 Idiopathic intracranial hypertension

Chang et al studied the correlation between intracranial pressure (ICP) and papilledema severity in patients with IIH. The study confirms a correlation between ICP and papilledema severity, but less than perfect ($R = 0.4$), suggesting that disc edema is not a function of ICP alone. The data also suggests even less correlation for trans-laminar pressure gradient (TPG), and intraocular pressure (IOP) may have no significant influence on papilledema severity.

2.7 IgG4 disease

A retrospective histopathological analysis on IgG4 related orbital disease (ROD) were performed[24]. The study reviewed 65 cases of either biopsy confirmed non-granulomatous idiopathic orbital inflammation (IOI) or orbital benign lymphoid hyperplasia (OBLH). The study found that 50% of the cases diagnosed as OBLH and 23.6% of the cases diagnosed as IOI would be classified as IgG4 ROD. A retrospective chart review looked at the clinical efficacy and safety of 5 patients that were treated with rituximab for IgG4 ROD[25]. All cases that were treated were either dependent on or resistant to steroids. Three of the cases achieved complete clinical remission and two achieved partial clinical resolution. There were no cases of relapse in the 33 months following treatment for those on rituximab or mycophenylate maintenance therapy.

3 Others

The human body has naturally occurring electrical currents that have been shown to exert neurotropic effects on motor neurons and dorsal root ganglion cells. The effects of an electrical field (EF) on RGC growth, however, have never been tested before. Gokoffski et al showed for the first time that RGC axons grow directionally towards the cathode when exposed to an EF. In the absence of an EF, RGC neurites demonstrated indiscriminate directional growth from the tissue edge. EF does not affect the length or rate of RGC axon growth. So electrical currents may be of great help to direct the

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growth of newly transplanted RGCs.

Kayabasi studied the trans-corneal electrical stimulation (TES) in optic neuropathies. Twenty patients with NAION and 10 patients with traumatic optic neuropathy were stimulated 40 minutes per day for 10 consecutive days by the TES device. Patients with optic neuropathy were treated at least 2 months after the acute event. In both groups, improvement in vision and visual field was achieved. The average visual acuity improvement was 2 Snellen lines.

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自我刊开通网上投稿以来，作者均采用将 Word 文档从网上在线投稿的方式，但部分来稿中所包含的图片像素较低，这些图片便于网上审稿，并不能用于制版印刷。因为显示器与彩印纸品的色彩形成截然不同，显示器应用红、绿、兰的三原色原理发射光线形成图像，这种色彩形成的原理被称为 RGB 模式；而彩色印刷品是兰、红、黄、黑四色油墨印制在纸制品上来形成彩色图像，这种原理被称为 CMYK 模式。那些在显示器上看起来比较清晰但分辨率较低的图片在实际印刷时不能转换为高质量 CMYK 模式的图片。为了保证论文的刊出质量及本刊的印刷出版质量，如果作者的来稿中附有组织病理图、免疫荧光染色图、免疫组织化学图、细胞图，请作者将原图保存为 TIFF 格式或 JPG 格式，图片的分辨率至少 300 dpi。

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