Pathoanatomical abnormalities of COVID-19: a comparative analysis using OCTA

Coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a contagious pathogen that evolved into a global pandemic moving humanity into health and economic jeopardy. Despite increasing knowledge of various clinical presentations, much is still unknown about how COVID-19 will affect people over time. Months after recovery from COVID-19 infection, non-specific symptoms of chronic fatigue syndrome or complex extreme fatigue with little activity have persisted. The long-term effects on ocular health have also garnered interest in recent months.

In this issue, a comparative cross-sectional observational study by Abrishami and colleagues sheds light on the impact on the foveal avascular zone (FAZ) and vessel density of the deep and superficial macular capillary plexus in patients recovered from COVID-19 compared to age-matched healthy control subjects.1 Thirty-one patients with at least one positive COVID-19 reverse-transcriptase polymerase chain reaction test were enrolled. Confounding variables such as ocular comorbidities (retinal disease, glaucoma, refractive error >5D), media opacity, or best-corrected vision less than 20/20 were excluded. These study patients, along with 21 age-matched healthy controls, underwent optical coherence tomography angiography (OCTA). The study revealed that vessel density of mean macular superficial capillary plexus (SCP) and deep CP (DCP) were significantly reduced in the COVID-19 cohort compared to the age-matched controls. However, the total FAZ area in the COVID-19 group was comparable to the control group. There were no significant differences in these parameters between hospitalized and non-hospitalized COVID-19 patients.1

Similarly, findings from another study suggested an impairment in the blood supply to the peripapillary retinal nerve fiber layer in patients who recovered from SARS-CoV-2, but microvascular impairment was more evident in older patients and in patients with systemic hypertension.2 However, the study by Abrishami and colleagues included patients who were young and otherwise healthy. Only one of their patients was medically managed for hypertension. The small sample size and younger patient demographics may explain why the FAZ area was greater in the COVID-19 group but did not show statistical significance.

Although OCTA demonstrated post-infectious microvascular capillary disturbances in Abrishami’s study, the clinical implications of these changes remain minimal as most patients retained their baseline 20/20 visual acuity after recovery. Further, microvascular endothelial or ischemic damage on OCT or in clinical exam were not present. By contrast, a recent study by Invernizzi and colleagues demonstrated that dilation in retinal arteries and veins, assessed by computer-based analysis, was significantly greater in the COVID-19 patients than in healthy controls, implying an inflammatory response or endothelial damage from COVID infection.3 In addition, angiotensin-covering enzyme (ACE) receptors, which mediate the infectious cascade of COVID infection, have been found in the choroid, muller cells, ganglion cells, retinal vascular endothelial cells, and photoreceptors.4 Therefore, pathoanatomical abnormalities can be expected following severe infections in older adults. Moreover, the integrity of the DCP is needed for photoreceptor metabolism. The consequences of the progressive rarification of the SCP and DCP post-COVID-19 is unknown; however, it should be noted that in diabetic retinopathy, these locations are commonly associated with capillary dropout and subsequent ischemia.5

In conclusion, Abrishami and colleagues have demonstrated that alterations of retinal microvasculature are found subsequent to COVID-19 infections compared to healthy control patients. Although these changes do not translate to changes in visual acuity, the study highlights the importance of evaluating the retina in all COVID-19 patients regardless of visual disturbances. Larger and diverse cohorts, especially those with clinically symptomatic keratoconjunctivitis or severe systemic illness treated in the intensive care unit should be included to better understand the long-term clinical implications of COVID-19 on ocular health.

Prima Moinul, PGY-5

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There have been significant advances in corneal transplantation surgery with the development of lamellar keratoplasty techniques. While these confer particular advantages over traditional penetrating keratoplasties (PKs), such as less invasiveness and lower risk for immune rejection, PKs are still commonly used after trauma, postinfection opacities, and keratoconus. Real-world outcomes of PK grafts have been reported in the literature, often with the assistance of graft registries.2,4 In this issue, Ahmad and colleagues report on their investigation of real-world survival and failure rates of PK grafts in the United States using data from a large claims-based database.5 All adult, primary PKs from 2011 to 2017 who received transplants for a variety of indications (grouped as infectious disease, ocular surface disease, corneal dystrophies and degeneration, congenital corneal diseases, traumatic diseases, keratoconus, and miscellaneous diseases) were included in the study. Outcomes for a total of 596 patients were analyzed using Kaplan-Meier survival curves. The survival rates for 3, 5, and 7 years were 78% (confidence interval [CI]: 73%-82%), 76% (CI: 70%-80%), and 73% (CI: 66%-79%), respectively. This is lower than survival rates previously reported from other U.S.-based graft outcome studies—at 5 years, the Cornea Donor Study (CDS) reported an 86% survival, and Thomson and colleagues reported 90%.6,7 However, the 5-year rates are comparable to those reported from registry data in Australia and Singapore (73% and 64%, respectively).8,9 The studies by CDS and Thomson and colleagues were more restrictive about the types of patients included in analysis and the indications for transplantation. They have a known centre effect, where higher survival rates may be related to more strict inclusion criteria, surgeon experience, and quality of the postoperative management.

The indications for PK have changed over the years as lamellar keratoplasty techniques have been increasingly used as an alternative to PK. For example, PKs used to be the treatment of choice for conditions such as Fuchs dystrophy, pseudophakic bullous keratopathy, and keratoconus. More recently, endothelial keratoplasty and crosslinking treatment have changed the proportion of patients requiring PK for the aforementioned causes. Thus, PKs are now more commonly performed for indications that have a higher chance of failure. Since graft survival is dependent on preoperative diagnosis, Ahmad and colleagues also proposed the development of a risk stratification score that takes preoperative factors into consideration. Regional differences exist in disease incidence and pathology among countries and even provinces or states, so to take a Canadian spin on their proposal, the development of a Canadian-based risk scoring system may be of benefit for Canadian patients and for resource allocation in our large patient population.

However, there are limitations to this study. Only 596 patients were included; this may not be a representative sample as more than 15,000 grafts are performed annually in the United States. Additionally, claims-based databases can have inaccuracies and lack specificities in coding, influencing the accuracy of analysis and results. Nevertheless, this work by Ahmad and colleagues further emphasizes the importance of a national graft registry to accurately track outcomes. It would also provide information needed to create a risk stratification scheme for corneal transplantation, which in turn could optimize postoperative management and patient outcomes.

Jenny Qian, PGY-2

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Resident Perspective: Referral outcomes from a vision screening program for school-aged children

Early detection of ophthalmic disease in children is key in ensuring timely treatment and favourable outcomes, especially in cases of amblyopia. Children from underserved or marginalized populations are especially vulnerable, with previous studies demonstrating higher prevalence of risk factors for amblyopia in children from these populations.

In this issue, Silverstein and colleagues describe ocular diagnoses and follow-up patterns of children referred to pediatric ophthalmology after the Wills Eye Vision Screening Program for Children (WEVSPC) in Philadelphia. Between January 2014 and June 2015, 10,726 children were screened; of these, 509 (5%) were found to have decreased visual acuity not attributable to refractive error, and were referred for a comprehensive ophthalmic assessment. Following this assessment, refractive error was found to be the most common diagnosis, representing 76% of the cases referred. The next most common diagnosis was amblyopia (43%), followed by strabismus (16%), and anisometropia (13%).

This study provides further evidence to support the use of school-based vision screening programs, especially in underserved populations. The majority of children (84%) referred to the pediatric ophthalmology service in this study were diagnosed with at least one ocular condition. Amblyopia was diagnosed in 54 children as a result of the vision screening program, allowing for earlier intervention and supporting the use of mandated school-based vision screening programs in Philadelphia. However, the authors acknowledged that the amblyopia detection rate reported in their study is lower than the population prevalence, suggesting that this may be due to a lack of follow-up. The authors postulated several reasons for a minority of screened patients attending follow-up and listed suggestions for tackling many of these challenges, including restructuring grant funding to pay for the first eye examination and alleviating transportation costs to and from appointments.

It should be noted, however, that the study does have some important limitations. As the authors acknowledged, they had a small sample size due to low consent form return rates. Changes that incentivize follow-up and consent form return rates may increase sample size for any follow-up studies. In addition, given that this study analyzed data collected in the United States, where lack of insurance is a much larger issue for low-income families compared to countries with universal public health care, this study may not be generalizable to school districts in Canada or other countries. Lastly, another variable that may decrease generalizability of this study is the distribution of demographics of racial and ethnic backgrounds of study subjects. More than half of the subjects in this study were African American, while only 0.8% were of Pacific Islands or Caucasian decent. It would be beneficial to objectively analyze whether the rates of these demographics truly reflect the general population of students attending public schools in Philadelphia or other cities in North America.

In summary, Silverstein and colleagues have described the results of ophthalmic assessment and follow-up patterns of children identified through a school-based vision screening program in Philadelphia. Further studies investigating a larger sample size and analysis of objective barriers to follow-up may allow for a better understanding of ways to improve school-based vision screening programs.

Helya Aghazadeh, PGY-3

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Resident Perspective: Successes and shortfalls of community Plusoptix photoscreening

Amblyopia, clinically defined as a difference of >1 line of best corrected visual acuity between the 2 eyes in the absence of structural ocular disease, occurs in about 2% of preschool-aged children in high-income countries. Risk factors include media opacities, strabismus, anisometropia, or high ametropia.

Because amblyopia is preventable and reversible if timely treatment is instituted, both the Canadian Pediatric Society and US Preventive Services Task Force recommend screening in all children aged 3-5 years. However, both groups acknowledge that evidence supporting this recommendation is weak, in part because of high rates of false positive screening results in low-prevalence populations. Evidence to support vision screening in even younger children is lacking because existing studies have suffered from high levels of untestability.

In Canada, some provinces have established universal amblyopia screening programs for preschoolers. Other provinces and territories, including the 2 most populous, instead cover children’s optometric services in their health insurance plans in an attempt to encourage parents to access screening examinations for their children. Unfortunately, the latter strategy may result in as little as 45% of children being screened.

In the current issue, Kiatos and colleagues evaluated a community-based amblyopia screening program for preschool children in Southwestern Ontario. The program used a handheld, non-mydriatic autorefractor device, known as a photoscreener, to detect amblyopia and its risk factors with 80% sensitivity and 95% specificity. This screening strategy has the benefit of being portable and can be administered by lay operators. In addition, the study found very low untestability rates, even for children aged 18-36 months. Overall, 6.8% of children failed the screening exam and were referred for a comprehensive eye exam with an optometrist. Anisometropia was the most common reason for failed screening, followed by high ametropia, then strabismus. Perhaps the most arresting finding of the study, though, was that a mere 25% of referred children had a documented confirmatory examination. Furthermore, for those children who were examined, documentation of the findings was of inconsistent quality.

For me, this study suggests 2 clear areas for future action. First, further photoscreening trials with 1-3-year-old children are warranted so as to bolster the evidence base for the effectiveness and cost-effectiveness of screening in this age group. Second, provincial and national amblyopia screening programs ought to include built-in strategies to address any barriers that may prevent children from reaching appropriate and adequate follow-up care, including ensuring buy-in from parents and eye care professionals.

Gareth D. Mercer, PGY-4

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Resident Perspective: Microvascular changes in diabetic macular edema following IVB

Anti-vascular endothelial growth factor (anti-VEGF) therapy has become a mainstay of diabetic macular edema (DME) treatment. However, previous studies using fluorescein angiography have suggested mixed effects on the macular vascularization with some studies suggesting that anti-VEGF injections slow the progression of capillary drop out while others have suggested that the medications can induce macular ischemia.1,2 A few smaller studies have looked at the impact of anti-VEGF injections using optical coherence tomography (OCTA) but these studies have often been limited by smaller sample sizes, combined with different underlying diseases, different types of anti-VEGF agents, and segmentation error.3,4

In this issue, Mirshahi and colleagues evaluated the quantitative changes in different retinal layers and choriocapillaris after bevacizumab injections using careful segmentation procedures.5 The authors conducted a case series of consecutive patients who received intravitreal bevacizumab (IVB) for center-involving DME and obtained en face OCTA images at baseline and 1 month after receiving IVB. Using a combination of manual and automatic methods that were cross-checked by two graders, the authors calculated the vascular density (VD), vascular diameter index (VDI), vascular length density (VLD), foveal avascular zone (FAZ) area, and foveal density (FD)-300. The VD and VDI measurements were performed in the superficial capillary plexus (SCP), deep retinal capillary plexus (DCP) and choriocapillaris. Automatic detection was used to calculate the capillary nonperfusion area (CNPA) in the whole 3 mm x 3 mm enface image area and in the four smaller consecutive rings around the foveal center.

Twenty-three eyes of 19 patients were analyzed in the study at baseline and one month post injection. No significant differences were noted in the FAZ area, FD-300, and the VD of the foveal and parafoveal superficial and deep capillary plexuses. There were no significant differences in the CNPA. There was a significantly increased VD in the choriocapillaris, with a mean change of 1.64 +/- 2.88, p=0.005. Thus, the authors found no significant changes in the FAZ or macular vascular densities in the retinal capillary networks but did find an improvement in the vascular density of the choriocapillaris 1 month post-IVB injection.

The results of the study are consistent with two previous studies on OCTA microvascular changes in post anti-VEGF DME patients. One study was previously published by the authors on patients with DME and RVO who received different anti-VEGF agents that showed no significant differences in the microvasculature3. Similarly, another study by Busch et al. which looked at microvascular density post intravitreal aflibercept injections for DME from 3 to 25 months also did not show any differences.4 Compared with the other two OCTA studies, the present study was conducted on only DME patients with a single anti-VEGF agent and included manual correction of segmentation errors by two graders. Some of the limitations of the present study include a small sample size, short follow up time, and lack of control groups that received other anti-VEGF injections. However, the study does provide valuable evidence suggesting that there is not significant macular ischemia one month following bevacizumab injections. Further studies are required to compare different anti-VEGF injections, with longer term follow up to further understand the effects of anti-VEGF injections on retinal vasculature the choriocapillaris.

Aishwarya Sundaram, PGY-5

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