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Neuro-Ophthalmic Implications of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Related Infection and Vaccination

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Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic created a unique opportunity to study the effects of infection and vaccination on disease. The year 2020 was dominated by infection and its consequences. The year 2021 was dominated by vaccination and its consequences. It will still take several years for full maturation of databases required for robust epidemiological studies. Therefore, this review on the implications for neuro-ophthalmology draws on resources presently available including reported adverse reactions to vaccination. Illustrative clinical cases are presented.

The spectrum of pathology following infection with SARS-CoV-2 falls into 4 main categories: autoimmune, vascular, sequelae of brain damage, and miscellaneous. This review is exhaustive, but the most common conditions discussed relate to headaches and associated symptoms; vertigo, diplopia, and nystagmus; vascular complications of the eye and brain; cranial nerve (mono-)neuropathies; photophobia, ocular discomfort, and optic neuritis. Of the 36 main adverse reactions reviewed, vaccine-induced immune thrombotic thrombocytopenia is a novel complication requiring specific hematological management. Updated diagnostic criteria are summarized. It is relevant to remember taking a medication history because of side effects and to recognize the relevance of comorbidities. The clinical assessment can frequently be performed virtually. Consensus recommendations on telemedicine and the virtual assessment are summarized in a practical and compressed format.

The review concludes with an epidemiological tetralogy to interrogate, in future studies, associations with (1) SARS-CoV-2 pandemic infection, (2) SARS-CoV-2 worldwide vaccination, and (3) the possibility of a rebound effect of infections in the pandemic aftermath.

Key Words: COVID-19, neuro-ophthalmology, SARS-CoV-2

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious disease that triggered a pandemic that started in Wuhan, in the Hubei province of China in December 2019. Hence, the other name used in the literature, Corona Virus Disease 2019 or otherwise commonly known as "COVID-19."

The number of individuals reported to be infected with SARS-CoV-2 worldwide was 298,040,180 [Johns Hopkins Coronavirus Resource Center (https://coronavirus.jhu.edu) visited on January 6, 2022]. This is more than what was reported for the previous SARS-CoV outbreak in the Guangdong province with 8096 cases in 2002.[1] Infection with SARS-CoV-2 requires binding of the viral spike(S) protein to angiotensin-converting enzyme 2.[1]

Vaccinations against SARS-CoV-2 became available within the year 2020.[2] The protective immune-response following infection with SARS-CoV-2 and vaccination against SARS-CoV-2 is variable and can wane over time. Emerging viral mutations pose a continuous challenge. There are also side effects to SARS-CoV-2 vaccination. The vaccination trials were underpowered to detect rare adverse reactions (ADR).[2] The total number of reported vaccinations, synchronized in date and time to the above number of SARS-CoV-2 infections, was 9,330,607,312 [Johns Hopkins Coronavirus Resource Center (https://coronavirus.jhu.edu) visited on January 6, 2022]. The number of vaccinations is, therefore, larger than the number of infections. This needs to be remembered when interpreting the frequency of side effects from vaccination.

In clinical practice, questions are asked regarding vaccination ADR and SARS-CoV-2 infection. For this reason, the present review of the neuro-ophthalmological issues encountered in the context of the current pandemic will discuss consequences of infection and vaccination in parallel.

METHODS

Two lines of evidence are combined in this review:

1. ADR reporting [openly accessible, the English National Immunisation (National Immunisation Management Service) Database of COVID-19 vaccination, national data for mortality, hospital admissions, and SARS-CoV-2 infection data[2]]
2. a systematic literature search, including case reports

However, a major limitation of this approach remains that the pandemic is still ongoing. New observations are likely to emerge. A truthful and authoritative systematic review of the literature on the subject remains still premature. Therefore, citations were

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selected with preference to open access (URLs provided in this review) and comprehensive reference lists. Following the website links, the reader will have access to relevant references not included in this review because of space restrictions.

The reader is also reminded that regarding ADR, anything can be reported. There is no strictly defined terminology. Symptoms, signs, and diseases are lumped together. For clinical practice, this is still relevant because similar terminology is frequently used in the phrasing of a referral letter to the neuro-ophthalmology service. The United Kingdom (UK) "yellow card" ADR reporting was last accessed by the author on November 15, 2021, through the UK government website and all data used are provided as Supplementary Digital Content, Files 1–6, http://links.lww.com/APJO/A139, http://links.lww.com/APJO/A140, http://links.lww.com/APJO/A141, http://links.lww.com/APJO/A142, http://links.lww.com/APJO/A143, http://links.lww.com/APJO/A144 (Medicines and Healthcare Products Regulatory Agency, UK, https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions). At time of last access yellow card reporting covered the period between December 9, 2020, to November 3, 2021. The data were evaluated statistically using SAS (v9.4m7, 100 SAS Campus DriveCary, NC 27513-2414, US). The cumulative percentage of selected ADR from all vaccines reported was presented in Table 1. This required 1 extra round of revision by harmonizing the terminology used for the 278 different ADR. For example, "Bell palsy" (n = 587), "Facial paralysis" (n = 357), "Facial nerve disorder" (n = 8), and "Facial paresis" (n = 168) were all collated to "Facial nerve palsy" (n = 1120). Likewise, palsies of the third, fourth, and sixth nerve were summarized under "Diplopia" together with variations over the term "Extraocular muscle disorder" for the purpose of this review. The UK yellow card reporting of ADRs was contrasted with published data from the UK National Immunisation Management Service using incidence rate ratios (IRR) for the risk of a neurological complication.[2] For transparency this mixed bag of terms is summarized in Table 1, but a clinically more structured approach has been used for the main text. The basal cranial nerves were not included in this neuro-ophthalmology-focused review. In clinical practice, it remains relevant to ask for bulbar symptoms including swallowing and breathing and assessment of the gag reflex in suspicious cases. The conditions were grouped into 3 groups: vascular, autoimmune, and sequels to brain pathology.

Next, the terms found in the UK yellow card reporting were used as search terms in combination with "COVID-19," "SARS-CoV-2," and "vaccination" in the systematic literature search. Two databases were searched: PubMed and Google Scholar. Finally, the anecdotal reports presented in the Figures came through the author's neuro-ophthalmological service. For the 3 individual cases reported, permission for publication was requested and granted by the R&D Department (Study numbers CaRS-22, CaRS-24, CaRS-27).

Table 1. Overview on the ADR Following SARS-CoV-2 Vaccination as Reported in the UK Yellow Card Scheme

UK Yellow Card Reporting		UK NIMS IRR*		
ADR	**Number**	**AZ**	**PF**	**SARS+**
1. Vascular				
Stroke	1231	n/a	n/a	n/a
ICH		1.02	1.24	0.85
SAH		1.01	1.05	1.51
CVST	385	n/a	n/a	n/a
Giant cell arteritis	59	n/a	n/a	n/a
Vasospasm	54	n/a	n/a	n/a
TMVL	11	n/a	n/a	n/a
Retinal disorder	177	n/a	n/a	n/a
Macular disorder	74	n/a	n/a	n/a
2. Autoimmune				
Demyelination	65	0.07	1.02	1.67
Myasthenia gravis	27	1.23	1.18	3.01
Optic neuritis	85	n/a	n/a	n/a
Bell palsy	2092	1.07	1.06	1.34
Other cranial nerve palsies	745	n/a	n/a	n/a
Uveitis and vitritis	58	n/a	n/a	n/a
3. Sequelae from brain pathology				
Headache and migraine related	84793	n/a	n/a	n/a
Vertigo and dizziness	36795	n/a	n/a	n/a
Tinnitus	2001	n/a	n/a	n/a
Nystagmus	23	n/a	n/a	n/a
Oscillopsia	4	n/a	n/a	n/a
Visual hallucination	646	n/a	n/a	n/a
IIH/ICP related	65	n/a	n/a	n/a
Pupil abnormality	125	n/a	n/a	n/a
4. Miscellaneous				
Optic disc appearances	28	n/a	n/a	n/a
Eye pain	3325	n/a	n/a	n/a
Color vision impaired	29	n/a	n/a	n/a
Blepharospasm	19	n/a	n/a	n/a
Facial spasm	94	n/a	n/a	n/a
Ptosis and eyelid involvement	74	n/a	n/a	n/a
Photophobia	1549	n/a	n/a	n/a

For comparison data from UK NIMS are presented, were available, based on 20,417,752 individuals who received the ChAdOx1nCoV-19 vaccine, 12,134,782 people who received the BNT162b2 mRNA vaccine and 2,005,280 individuals who had a positive SARS-CoV-2 test (in those vaccinated).[2]

ADR indicates adverse drug reaction; AZ, ChAdOx1nCoV-19 vaccine; CVST, cerebral venous sinus thrombosis; ICP, intracerebral pressure; IIH, idiopathic intracranial hypertension; IRR, incidence rate ratios; n/a, not available; NIMS, National Immunisation Management Service; PF, BNT162b2 mRNA vaccine; SAH, subarachnoid hemorrhage; SARS+, positive SARS-CoV-2 test; TMVL, transient monocular visual field loss; UK, United Kingdom.

*IRR/incidence rate ratios greater than 1 mean an increased relative risk.

VASCULAR

Stroke

A stroke is one of the many thromboembolic complications of SARS-CoV-2.[3] An acute ischemic stroke (AIS) with large vessel occlusion does affect a younger population compared to ischemic strokes in the prepandemic period.[4] The outcome for an AIS after SARS-CoV-2 infections seems to be worse compared to other causes.[5,6] A prospective US study found the mortality of AIS due to SARS-CoV-2 infection to be 39.1%, which was significantly higher than the mortality in non–SARS-CoV-2 AIS (4.8%, $P = 0.01$).[4] Consistent with this observation the functional outcome on the modified Rankin Scale was poorer for SARS-CoV-2 AIS (39.5%) compared to non–SARS-CoV-2 AIS (17.8%, $P = 0.01$). It is relevant to note the high proportion of African Americans (46.2%) in this study[4] because of the impact ethnicity has on the clinical outcome in SARS-CoV-2.[7]

There are also reports on intracranial hemorrhages (ICH) that tend to be more frequently located lobar and/or multifocal with an overall poorer outcome compared to ICH in other contexts.[5] The

overall reported IRRs for an ICH are 1.02 (0.90–1.15) for the ChAdOx1nCoV-19 vaccine, 1.24 (1.07–1.43) for the BNT162b2 mRNA vaccine, and 0.85 (0.57–1.26) after a positive SARS-CoV-2 test.[2] These data apply to the full 28-day observation period mentioned in the method section. If shorter epochs are used, then an increased risk of ICH becomes apparent at onset (day 0) after a positive SARS-CoV-2 test result compared to vaccination[2]:

1. positive SARS-CoV-2 test IRR 12.42 [95% confidence interval (CI): 7.73–19.95]
2. ChAdOx1nCoV-19 vaccination IRR 0.37 (95% CI: 0.18–0.78)
3. BNT162b2 mRNA vaccination IRR 0.59 (95% CI: 0.27–1.33)

If the posterior visual pathways are involved, then the stroke will be associated with a binocular visual field defect.[8] Retinal emboli manifesting as a central retinal artery occlusion, branch occlusion, or ophthalmic artery occlusion in monocular loss of vision.[9] There may be a risk for overdiagnosing and embolic stroke due to SARS-CoV-2 infection and other etiologies should not be overlooked.[10] Pituitary apoplexy, in the context of SARS-CoV-2 infection, must not be missed because it is life threatening.[11] Short lasting, transient binocular loss of vision is frequently hemodynamic in origin. If a swollen disc is seen acutely, a nonarteritic anterior ischemic optic neuropathy needs also to be considered and requires management of cardiovascular risk factors as there is a risk to the other eye.

Eye movement disorders, a facial drop, and vertigo are part of the brainstem stroke syndromes. A ptosis due to a midbrain stroke is always bilateral due to bilateral innervation of the levator palpebrae from the Edinger-Westphal nucleus. Transient diplopia or blurring of vision triggered by rapid horizontal eye movements point to an internuclear ophthalmoparesis that can be the result of a small ischemic insult to the medial longitudinal fasciculus. Blurred vision triggered by self-motion suggests impairment of the vestibulo-ocular reflex in the context of a posterior circulation stroke. Depending on the topology of the stroke, this can be associated with any form of nystagmus. A periodic alternating nystagmus requires patience during examination and points to cerebellar involvement. Cerebellar strokes also result in an increase of fixation losses, saccadic intrusions, and dysmetric saccades. Taken together, the history can be vague and clinical signs subtle, but activation of a stroke care pathway is important.

Cerebral Venous Sinus Thrombosis

The incidence of a cerebral venous sinus thrombosis (CVST) is increased after infection with SARS-CoV-2 (39.0 per million people) compared to 2-week epochs pre–SARS-CoV-2.[12] This is about 10-fold higher than the incidence reported for CVST following messenger ribonucleic acid (mRNA) vaccination.[12] There is, however, an increased risk for CVST after vaccination with the adenovirus vector vaccine ChAdOx1 (Oxford-AstraZeneca).[12,13] A characteristic feature is thrombocytopenia and the London index case that lead to discovery of this association[13] is discussed alongside patients with fundus images of the acute and chronic phase of CVST (Fig. 1).

Up to 90% of patients with vaccine-induced immune thrombotic thrombocytopenia (VITT) report headaches,[12] but it was acknowledged that there are many other reasons for this as discussed[12,14] above. The association of headaches with either

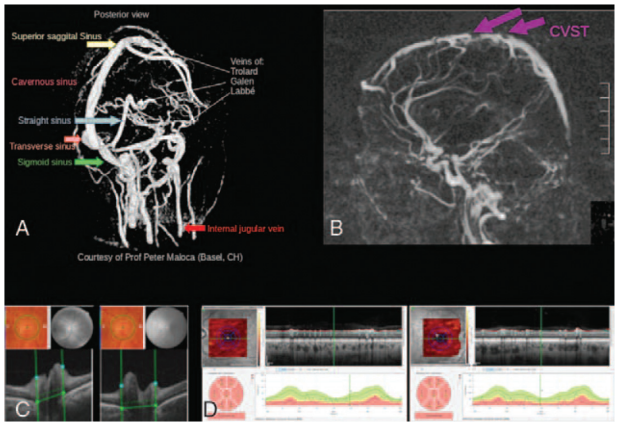

Figure 1. Composite image of the anatomy, presentation, and consequences of cerebral venous sinus thrombosis (CVST). A, The anatomy of the intracranial veins in a 3D vascular reconstruction. A thrombus can be present anywhere and the risk is that clot expansion eventually affects the entire superior sagittal, transverse, straight, and sigmoid sinuses all the way down into the jugular vein. To help with the 3D visualization of the vascular network a video is provided as Supplementary Digital Content, Video 1, https://links.lww.com/APJO/A143 (courtesy of Professor Peter Maloca). B, A CVST of the superior sagittal sinus (purple arrows) in an own case.[70] In this patient the venous outflow problem eventually led to extensive swelling of the brain and herniation of the brain stem into the foramen magnum and death. C, If seen acutely the venous outflow problem from a CVST causes bilateral swollen optic discs as seen here. The OCT image does show the elevated, swollen retinal nerve fiber layer with wrinkles. D, Another risk of persistent optic disc swelling is irreversible axonal damage and optic atrophy as seen in the individual about 1 year after suffering from a CVST. Case report of CVST in vaccine-induced immune thrombotic thrombocytopenia (VITT) in a 30-year-old woman (Case 1 in[13]). Within 2 weeks after SARS-CoV-2 vaccination, she had developed headaches and computed tomography (CT) brain imaging showed CVST. This was followed by extensive thrombosis of the mesenteric and portal veins. Her platelet count remained low at around 20×10^9/L throughout. Her initial management was with intravenous heparin and platelet transfusion. This did not work. She was the index case from London leading to the discovery of anti-PF4 antibodies and description of VITT.[13] Subsequent, successful, treatment was with rivaroxaban, prednisolone, and intravenous immunoglobulins.

unilateral or bilateral sixth nerve palsies, optic papilledema, visual symptoms, and tinnitus suggest an increase of the intracranial pressure (ICP) that can be due either to CVST or idiopathic intracranial hypertension (IIH) (discussed with images below). Seizures are more frequent in CVST and generally not observed with IIH. There is a weak association between the anatomy of the thrombosed sinus and focal neurological signs.[12] The sagittal sinus is affected in about 62% of cases, giving raise to bilateral focal neurological signs.[12]

The laboratory guidelines on assessment of VITT continue to evolve, but the cutoff of a platelet count of 150×10^9/L is likely to remain.[15] Confirmatory of the diagnosis is testing for platelet factor 4 (PF4) antibodies using enzyme-linked immunosorbent assay (eg, Immucor, Stago) and/or a functional assay (ie, PF4 platelet activation assay).[12,13,15] There remain subtle differences in management guidelines between continents.[12,14,15] Heparin products must be stopped and nonheparin anticoagulants be started.[12,15] There is anecdotal evidence that intravenous immunoglobulins are helpful.[12,14,15] A multidisciplinary approach that involves hematology experience in heparin-induced thrombocytopenia is strongly recommended.[12] If medical treatment fails,

progression to brain herniation can be rapid. Decompressive hemicraniectomy may be required.[14] The procedure was performed in 13 individuals of the prospective UK VITT cohort and had a high mortality of 54%[14] compared to the 16% mortality reported in CVST before, with earlier intervention in less severely affected individuals representing a potential statistical bias.

Novel diagnostic criteria were proposed, and it was recommended to use the first symptom of a venous thrombosis, even if of extracranial origin, for assessing the time interval since vaccination:

1. Definite VITT-associated cerebral venous thrombosis
   - Postvaccine cerebral venous thrombosis (proven on neuroimaging and with first symptom of venous thrombosis within 28 days of vaccination against COVID-19) and
   - Thrombocytopenia (lowest recorded platelet count 150 × 109/L or documented platelet count decrease to less than 50% of baseline) and
   - Anti-PF4 antibodies (detected on enzyme-linked immunosorbent assay or functional assay)
2. Probable VITT-associated cerebral venous thrombosis
   - Postvaccine cerebral venous thrombosis and
   - Either thrombocytopenia or anti-PF4 antibodies and
   - Coagulopathy (D-dimer 2000 μg/L or fibrinogen 2.0 g/L with no other explanation such as severe sepsis, malignancy, or recent trauma or surgery) or extracranial venous thrombosis (clinical or imaging evidence with onset since vaccination against COVID-19)
3. Possible VITT-associated cerebral venous thrombosis
   - Postvaccine cerebral venous thrombosis and
   - Either thrombocytopenia or anti-PF4 antibodies

Giant Cell Arteritis

There is an association of giant cell arteritis (GCA) both with SARS-CoV-2 infection and vaccination. Patients with GCA are more severely affected by SARS-CoV-2 if elderly, male, suffering from multiple comorbidities, or on more than 10 mg prednisolone.[16] Following vaccination, an increased risk for GCA has been implied with a reporting odds ratio (OR) of 2.7 (95% CI: 2.3–3.2).[17] This was, however, not significant if compared to use of influenza vaccines (0.5, 95% CI: 0.4–0.7).

Vasospasm

Vasospasm with SARS-CoV-2 infection and vaccination has been described systemically and involves the brain and eye. Retinal vasospasm causes transient monocular visual field loss as one of many manifestations.[18] The classical description of vasospasm is that of Raynaud phenomenon and complications have been reported with SARS-CoV-2 infection.[19]

Retinal Disorders

The majority of retinal disorders included in Table 1 were also vascular in origin. There is vascular damage to the retina with SARS-CoV-2 infection.[20] Venous vascular occlusion is thought to be related to hypercoagulability.[21] In a postmortem study of 6 patients who died from SARS-CoV-2 infection due to respiratory failure, there was evidence for more severe inflammation in the retina (Fig. 2). The described pathology of the retinal vasculature gained more attention because of optical coherence tomography angiography.[22,23]

Macular Disorders

A mild form of cystoid macular edema can be seen in Figure 3. Other macular conditions reported in the yellow card scheme were acute macular neuroretinopathy and macular edema. One symptom reported was metamorphopsia. Testing for metamorphopsia with an Amsler chart is rapid and straightforward and can be done online/virtually. Following SARS-CoV-2 infection, there is a suggestion of an increased incidence of acute macular retinopathy.[24] Involvement of the deep vascular plexus in postinfectious and postvaccination acute macular neuroretinopathy shows similarities to what is observed in other systemic diseases with vascular involvement.[23]

AUTOIMMUNE

Demyelination

The 2 main demyelinating diseases drawing attention in the pandemic were Guillain-Barré syndrome (GBS) (discussed below with cranial nerve 7) and multiple sclerosis (MS). There is substantial evidence that the outcome in individuals suffering from MS is adversely affected by SARS-CoV-2 infection.[25] There is an increased risk of death from SARS-CoV-2 infection in MS.[26] The main contributing factors are higher age, more severely affected individuals with MS, and treatment with CD20 immunosuppressive drugs.[26] Adjusting for these risk factors gives a pooled statistical mortality of 1.97% (95% CI: 1.61–2.33).[26] In individuals with MS, a relapse can be triggered by SARS-CoV-2 infection and vaccination.[27,28] In a cohort of 211 individuals with MS, the third dose of the BNT162b2 mRNA vaccine was associated with a transient increase of MS symptoms in 3.8% and a relapse in 3.3%.[29] Increased mortality and reduced efficacy of vaccination in MS are related to anti-CD20 therapies that reduce the *B*-cell count and can cause hypogammaglobulinemia.[26,29] The IRR for an acute demyelinating event is higher in the 28 days following[2]

1. Positive SARS-CoV-2 test IRR 1.67 (95% CI: 0.93–3.00)
2. ChAdOx1nCoV-19 vaccination IRR 0.97 (95% CI: 0.78–1.22)
3. BNT162b2 mRNA vaccination IRR 1.02 (95% CI: 0.75–1.40)

Taken together the data are in favor of vaccination of individuals suffering from MS.

Myasthenia Gravis

Patients with a neuromuscular junction disorder have a slightly increased mortality following SARS-CoV-2 infection, which is associated with comorbidities such as diabetes mellitus.[30] Onset of myasthenia gravis (MG) after infection[31] and vaccination against SARS-CoV-2 has also been reported.[32] The IRR for MG is higher in the 28 days following[2]

1. Positive SARS-CoV-2 test IRR 3.01 (95% CI: 1.70–5.36)
2. ChAdOx1nCoV-19 vaccination IRR 1.23 (95% CI: 0.94–1.62)
3. BNT162b2 mRNA vaccination IRR 1.18 (95% CI: 0.88–1.59)

The data are in favor of vaccination of individuals with MG.

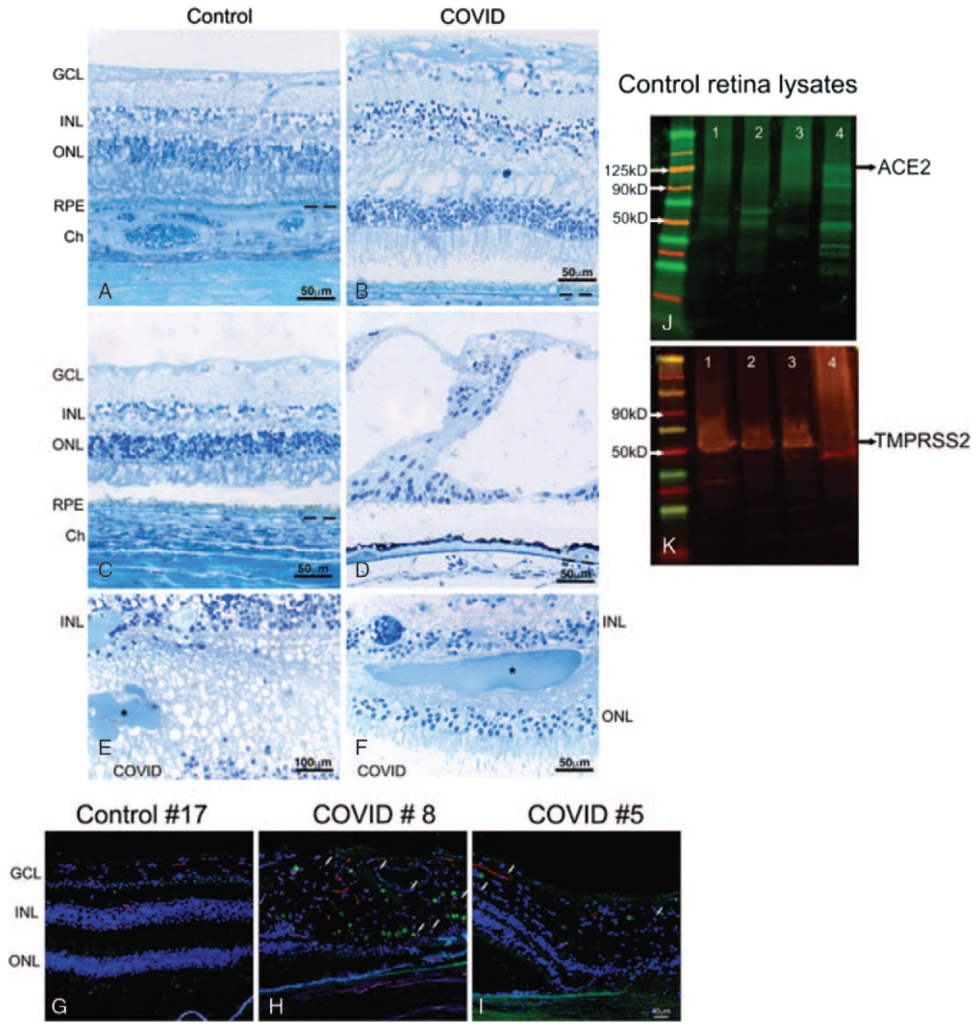

Figure 2. Histology and immunohistology of COVID-19 donor eyes. Representative toluidine blue-stained plastic 1 μm sections of retinas from COVID-19 donors (B, D, E, F) and age-similar controls (A, C). Morphology of the control retina displayed typical retinal lamina (C), whereas cystoid degeneration was observed in the central retina of several COVID-19 eyes (D). Two of the COVID-19 retinas showed hemorrhages of various sizes (E, F, asterisk) in the outer plexiform layer close to the optic nerve head. Immunofluorescence of 2 COVID-19 retinas labeled with antibodies to SARS-CoV-2 S protein (H, I, green) showed the presence of several positive cells (arrows) when compared to control (G). J and K, Protein blots of retinal tissue from 4 healthy controls from the age group 75, probed with ACE2 and TMPRSS2 antibody indicates that these proteins are expressed in the retina. Note that the level of ACE2 is very low in control#1 and control #2, whereas control#3 did not show any positive signal. TMPRSS2 is detected in all controls. Scale bar A–D, F = 50 μm, E = 100 μm, G–I = 40 μm. (Figure and legend reproduced with permission from[71]). ACE2 indicates angiotensin-converting enzyme 2; Ch, choroid; GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; POS, photoreceptor outer segments; RPE, retinal pigment epithelium; TMPRSS2, transmembrane serine protease 2.

Cranial Nerve 1

The prevalence of anosmia in SARS-CoV-2 infection is 70% to 90%.[33] This is thought to be either a consequence of obstruction of the narrow passages at the upper part of the nasal cavities; infection of the angiotensin-converting enzyme 2 expressing olfactory neurons and sustentacular cells; or injury to the olfactory bulb.[33] Speed and extent of recovery are variable. Similar anosmia after vaccination has not been reported. Therefore, the combination of new-onset anosmia together with any neuro-ophthalmological conditions suggests infection with SARS-CoV-2 to be likely of etiological relevance.

Cranial Nerve 2

There are very few reports on post–SARS-CoV-2 optic neuritis (ON).[34] It is important to remember that statistically more people were vaccinated than being infected with SARS-CoV-2. Hence the absolute number of postvaccination ON might seem higher (85 reports in Table 1), but could proportionally be similar. In our experience, recovery of high contrast visual acuities in post–SARS-CoV-2 vaccination is good with a group average of logMAR 0.0.[35] Inner retinal layer atrophy can be substantial despite the good functional outcome as illustrated in Figure 4. Interestingly, a proportion of individuals with postvaccination ON were myelin oligodendrocyte glycoprotein seropositive. A personal case is shown in Figure 5. It is very likely that the incidence of SARS-CoV-2–related postinfectious and postvaccination ON is very low compared to the incidence of ON generally.[35]

In the UK the incidence of ON was stable at 3.74 per 100,000 persons in the 22 years predating the current pandemic.[36] From these data we calculated the odds of a prior diagnosis of infection diagnosis with syphilis amongst those with incident ON compared to matched controls was 5.76 ($P = 0.02$), mycoplasma (OR 3.90, $P = 0.04$) or Epstein Barr virus (OR 2.3, $P = 0.001$).[36] The absence of prepandemic data on postvaccination ON suggests odds and incidence values to be

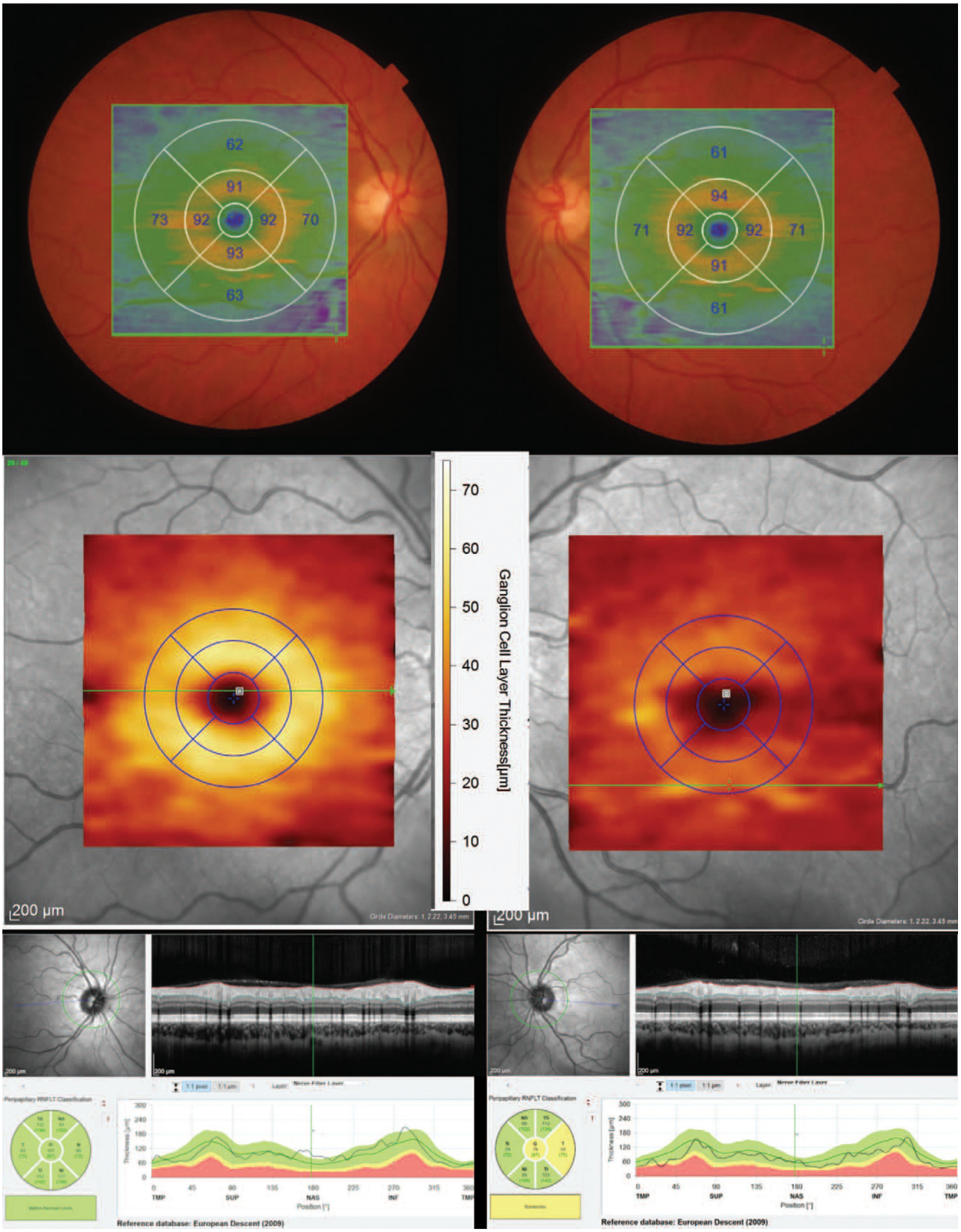

Figure 3. Postinfectious IIH in an 18-year-old woman. Onset within about 1 month after testing positive for SARS-CoV-2 associated with anosmia and headaches. The top right OCT image shows her left eye before infection with SARS-CoV-2 (framed in red). This OCT had been taken because after successful treatment of an episode of uveitis. The next OCT B scan, matched in location to baseline, shows the severe optic disc swelling with the edema affecting the nuclear layers (INL, ONL), reaching the macula (CMO). At this time there were enlarged blind spots on automated perimetry (Humphrey 24−2 SITA). The MRI revealed bilateral tortuous and prominent optic nerve sheath complex, flattening of the posterior sclera, and mild bilateral proptosis. There is intrasellar arachnoid herniation (a ``partially empty sella''). There was no evidence for CVST or sinus stenosis. The lumbar puncture opening pressure was 65 cm H_2O. Her symptoms improved after removal of 20 mL cerebrospinal fluid. She started on acetazolamide 250 mg twice daily. The series of subsequent optic disc OCT volume scans illustrate gradual improvement of disc swelling over the next 2 months. Opening of Bruch membrane finally aligned horizontally after having been lifted upwards into the optic disc (= flattening of the posterior sclera on MRI). In this case, there was no development of PHOMS which have also been associated with IIH.[72] CMO indicates cystoid macular edema; CVST, cerebral venous sinus thrombosis; IIH, idiopathic intracranial hypertension; INL, inner nuclear layer; MRI, magnetic resonance imaging; OCT, optical coherence tomography; ONL, outer nuclear layer; PHOMS, peripapillary hyperreflective ovoid mass-like structures.

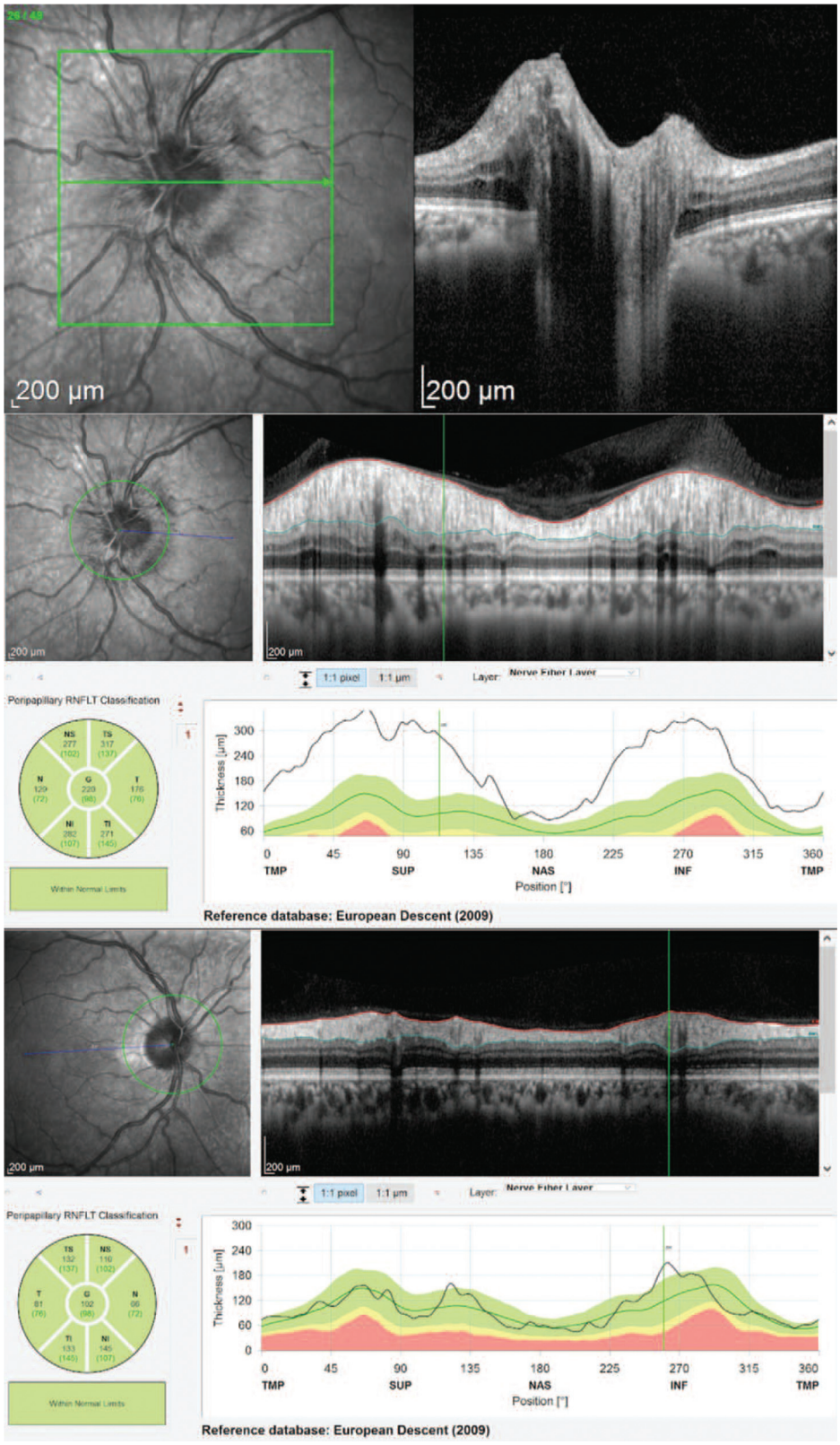

Figure 4. Postvaccination ON in a 42-year-old woman. Onset 2 to 3 weeks after mRNA vaccination against SARS-CoV-2 with discomfort on eye movements on the left and progressive loss of vision to hand movements only. There was a left RAPD. The top images show the swollen optic disc on the left (EDTRS grid overlay mGCIPL thickness). The development of inner retinal layer atrophy on the left over the following 3 months is documented in the lower images (mGCL and pRNFL). Spontaneous recovery of vision to 6/4. EDTRS indicates Early Treatment Diabetic Retinopathy Study; mGCIPL, macular ganglion cell-inner plexiform layer; mGCL, macular ganglion cell; mRNA, messenger ribonucleic acid; ON, optic neuritis; pRNFL, peripapillary retinal nerve fiber layer; RAPD, relative afferent pupillary defect.

lower than what was reported for presumed postinfectious ON. Future studies will need to calculate the IRR for Table 1, similar to what was done for demyelination.[2]

Cranial Nerves 3, 4, and 6

Diplopia has been reported with SARS-CoV-2 infection.[37] Diplopia following infection with SARS-CoV-2 can be due to the

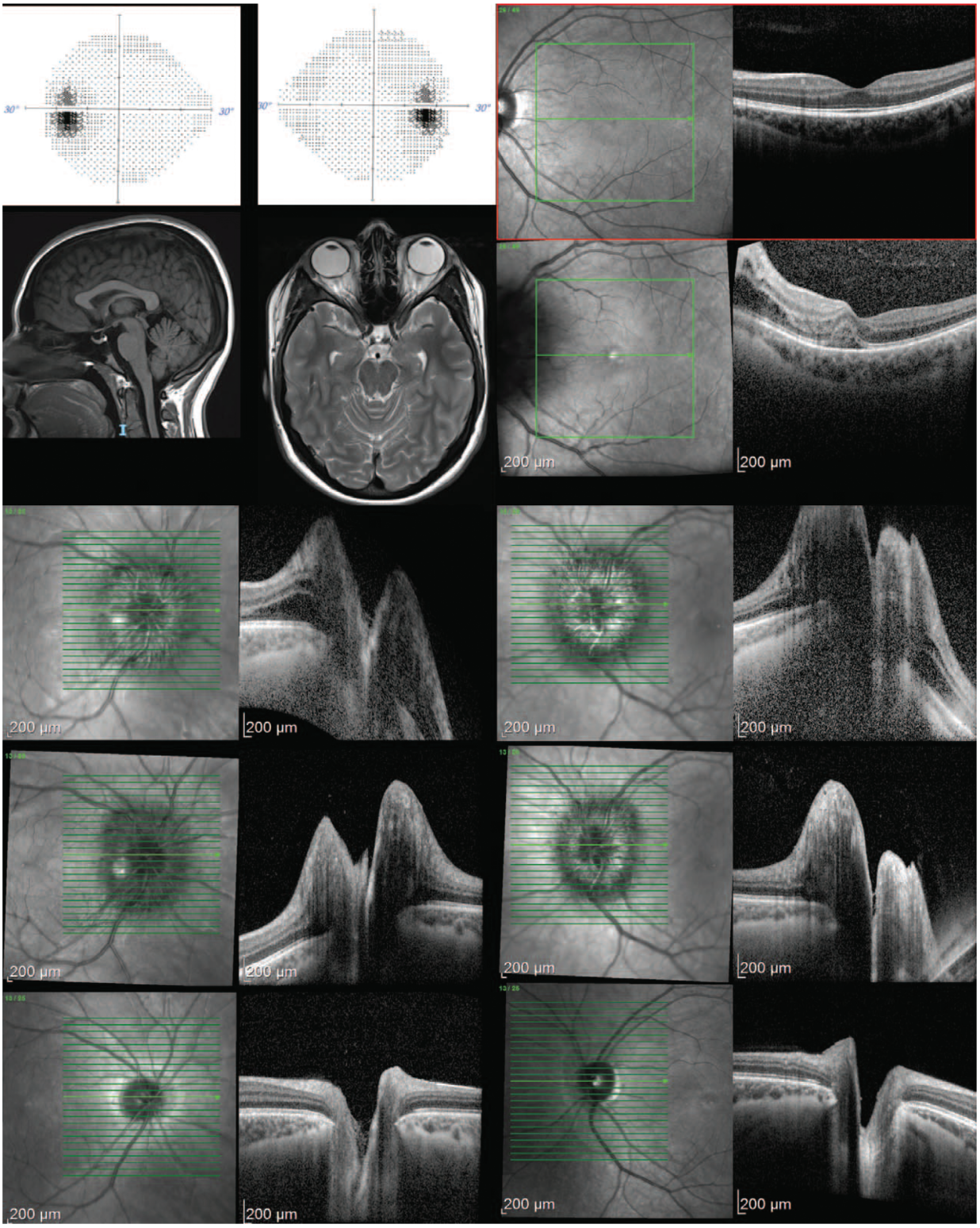

Figure 5. Postinfectious MOG-ON in a 30-year-old woman. Onset 2 to 3 weeks after testing positive for SARS-CoV-2 with retrobulbar pain on the left, worsening on eye movements. Two days later vision started to decline which progressed to perception light only. There was a left RAPD and the swollen disc can be seen in the image. Spontaneous recovery of vision to hand movements. MOG-ON indicates myelin oligodendrocyte glycoprotein–optic neuritis; RAPD, relative afferent pupillary defect.

Miller-Fisher syndrome variant of GBS,[38] a third-nerve palsy,[39] a fourth-nerve palsy,[40] a sixth-nerve palsy,[41] or ocular MG (discussed above). Extremely rare associations are diplopia associated with acquired Brown syndrome.[42] There are no systematic outcome data available yet, but good recovery is typical from microvascular etiology.

Cranial Nerve 5

Both infection and vaccination can affect the trigeminal nerve.[43] Trigeminal neuralgia has been reported as the presenting symptom in SARS-CoV-2 infection[44] and also as infection triggered reactivation.[45]

Cranial Nerve 7

There is good evidence for postvaccination Bell palsy predating the current pandemic and diagnostic criteria have been setup by the Brighton collaboration. There are reports on an association of SARS-CoV-2 vaccination and infection with Bell palsy from Israel.[46] Of 2,594,990 subjects without prior history of Bell palsy, 132 developed a Bell palsy within 21 days after the first dose of the BNT162b2 mRNA vaccine.[46] A second dose of the same vaccine was given to 2,434,674 subjects and 152 developed a Bell palsy within 30 days.[46] This calculates to a 21-day risk of 5.09 per 100,000 and 30-day risk of 6.24 per 100,000. These data are in line with ADR self-reporting from the US (vaccine adverse event reporting system) with an OR of 1.84 (95% CI: 1.65–2.06) for BNT162b2 mRNA vaccination and 1.54 (95% CI: 1.39–1.70) for mRNA-1273 vaccination (referenced in[46]). The study did not compare the risk of a Bell palsy due to infection with vaccination, but the UK data shows that the IRR for a Bell palsy is highest in the 28 days following infection[2]:

1. Positive SARS-CoV-2 test IRR 1.34 (95% CI: 0.91–1.97)
2. ChAdOx1nCoV-19 vaccination IRR 1.07 (95% CI: 0.94–1.21)
3. BNT162b2 mRNA vaccination IRR 1.06 (95% CI: 0.90–1.26)

A much rarer cause for a facial nerve palsy is postvaccination GBS. Taken together it was estimated that the excess risk of a Bell palsy was very small even in the highest risk group (≈ 4.5 per 100,000 in older females) with an excellent recovery rate of ≈ 90% within 9 months.[46]

Cranial Nerve 8

The second most frequent postvaccination complication recorded in the UK yellow card scheme is vertigo, which includes vestibular migraine (Table 1). Following SARS-CoV-2 infection, the frequency of dizziness was estimated as 1.3% in a systematic review.[47]

A frequent differential diagnosis is benign paroxysmal positional vertigo.[48] Virtual assessment can be performed.[48] The test requires video monitoring of the eyes whilst the patient leans backward and bows forward. The effect of self-treatment maneuvers can also be reevaluated virtually.[48] There is an international consensus for virtual assessment of vertigo and dizziness.[49] It was advised to combine general observations with a revision of signs of symptoms related to the binocular eye position, nystagmus, saccades, pursuit, convergence, the vestibulo-ocular reflex and its suppression, hearing, stance, and gait. For a video examination, the patient has to fixate the camera in primary fixation with a close-up of both eyes being well illuminated. The 5-step assessment is broken down to:

1. Nystagmus
   - Assessment of eye movements in all gaze directions (each ≈ 15 degrees for 10 seconds) with lids to be elevated on downgaze
   - Nystagmus evaluation with eyes closed (corneal bulges, penlight/smartphone flashlight cover)
2. Saccades
   - Shift gaze horizontally to eccentric position
   - Shift gaze vertically to eccentric position
3. Pursuit
   - Fixate the camera whilst moving it smoothly to the right and left
4. Binocular alignment
   - Inspect for asymmetry of the corneal light reflex
   - Patient to cover/uncover 1 eye on command
   - Patient to alternate the cover between eyes on command
5. Head impulse test
   - Hold camera tight and fixate a central visual target in the screen whilst rapidly moving the head from right to left

Finally, tinnitus is a frequent symptom, but there seems to be an association with SARS-CoV-2 infection[50] and vaccination.[51] The association of tinnitus with diplopia, visual obscuration, and headaches is rarer and raises the differential diagnosis of increased ICP as discussed further down.

Uveitis and Vitritis

Noninfectious uveitis was reported to be higher following SARS-CoV-2 infection, but a recent claims-based analysis suggests that this may be related to the preexisting comorbidities and immunosuppressive treatments.[52] Reactivation of uveitis with vaccination is possible but proof of causality remains complex.[53] This includes keratouveitis related to herpes zoster reactivation but affects many other cranial nerves as carefully reviewed and referenced in.[54] There is some evidence for vitritis that can be associated with uveitis.[55] Vitritis can also be present with some of the macular pathology discussed above.

SEQUELAE OF BRAIN PATHOLOGY

Headache and Migraine Related

Headaches are the most frequently reported problem after vaccination to SARS-CoV-2 (Table 1) and after infection with SARS-CoV-2 with presently over 1237 reports on PubMed alone. The estimated prevalence ranges from 3.47% to 82.6%.[56,57] The most frequent presentation was a tension-type headache, followed by headaches with migrainous features.[56,57] Headaches are also present in long COVID-19.[57] In contrast to postinfectious migrainous features, the frequency of postvaccination migrainous features may be lower, accounting for 2.78% of the reported yellow card complications in Table 1. These migrainous features are a frequent reason for referral to the neuro-ophthalmological service because they include a migrainous visual aura. The spectrum of referral diagnoses includes photopsia, scintillations, scotomas, visual field defects, blurred vision, ophthalmoplegic migraine, vestibular migraine, "retinal migraine," and other autonomic symptoms associated with migraine.

In addition to classical migraine headaches as defined by the International Headache Society (ichd-3.org), there are a plethora of visual symptoms related to migraine that can be acephalic.[58] Both SARS-CoV-2 infection and vaccination may worsen preexisting migraine.[59,60] The features of vestibular migraine are discussed next.

Visual Hallucinations

Yellow card reporting on visual hallucinations in Table 1 is extensive (see Supplementary Digital Content, File 5, https://links.lww.com/APJO/A144). A stroke can be the sole manifestation of the Alice in Wonderland syndrome. Charles Bonnet syndrome is associated with poor vision and neurodegenerative

conditions. Exacerbation of Charles Bonnet syndrome was associated with social implications of the pandemic, for example, prolonged period of self-isolation.[61] Autoscopy is an illusory visual experience during which one sees oneself externally. It has been associated with stroke and seizures. Of the plethora of other visual hallucinations described, glare, photopsia, scintillating scotoma, and visual snow syndrome are most frequent. There are no specific treatment options other than exposure prophylaxis and management of underlying conditions such as migraine.

Idiopathic Intracranial Hypertension

The differential diagnosis of increased ICP in the pandemic includes CVST and ICH (discussed above) and idiopathic IIH. The association of headaches with blurred disc margins has led to an increase in urgent referrals from opticians to neuro-ophthalmology services in general. The number of referrals has increased further in the pandemic, likely because of the frequency of pseudo-papilledema in the general population and headaches being one of the most frequent symptoms reported with both, SARS-CoV-2 infection and vaccination. Figure 3 was already mentioned because of the mild cystoid macular edema but is more illustrative regarding the development of IIH after SARS-CoV-2 infection. The pathology for this association remains uncertain. It has been reported that there has been an increase of weight in 58% of individuals suffering from IIH during the lockdown and related delay in monitoring and treatment.[62] Scores for anxiety increased by 64% and for depression in 51% of subjects. There was an increase of optical coherence tomography quantifiable papilledema by an average of 15.5 μm. Vision-threatening papilledema triggered emergency cerebrospinal fluid diversion surgery in 13% of subjects, which is almost double the historical rate of 7.6%.[62]

Pupil Abnormalities

The pupil abnormalities reported after vaccination and included in Table 1 were Holmes-Adie pupil, Horner syndrome, miosis, mydriasis, pupil fixed, pupillary deformity, pupillary light reflex tests abnormal, pupillary reflex impaired, and "pupils unequal." After SARS-CoV-2 infection, there are reports on Holmes-Adie syndrome[40,63] and Horner syndrome.[64,65] Patients who develop a fixed, dilated pupil or a new Horner syndrome will require urgent imaging.[66,67] It was also pointed out that there is a need to consider increased ocular pressure in patients who are ventilated in a prone position.[64,68]

OUTLOOK

There are important questions around the pandemic for epidemiological research. One contribution neuro-ophthalmology can make to the field is to provide very well-defined and electronically coded diagnoses of pathologies discussed in this review. For example, incidence rates from CVST, VITT, ON, and Bell palsy should be interrogated. It may take several years for databases to have fully maturated to answer the following 4 questions inspired by our own observations.[35]

First, the worry at onset of the pandemic was that the incidence of many conditions triggered by infection may increase. The early impression on one such condition, postinfectious ON, does not give a signal in that direction. In contrast, it may well be that the worldwide implementation of infection control has led to an overall decrease of postinfectious ON. If one was to extrapolate from this impression to other diseases similar may be found. The first question therefore is, "What is the epidemiological burden of overall postinfectious pathology between 2019, 2020, and 2021, compared to the prepandemic period?" This will be easy for ON, where a 22-year epidemiological study on over 121 million patient follow-up years was just completed[36] and worldwide epidemiological data are available.[69]

Second, is there a true post–SARS-CoV-2 infectious epidemiological signal that is masked statistically by the effect of infection control? In other words, the total incidence argument used in several survey studies presently may not be entirely watertight. The second question therefore is, "Is there evidence for a true post–SARS-CoV-2 infectious signal in longitudinal epidemiological data correcting for other covariables?"

Third, a contentious point is a relationship between SARS-CoV-2 vaccination and postvaccination complications. Causality has been proven for VITT, but this is an extremely rare condition. To prove causality for most of the conditions reviewed here will be difficult if not impossible. Therefore, the relevance of epidemiological data to address this issue indirectly cannot be overestimated. The third question therefore is, "What is the epidemiological burden of overall postvaccination pathology for the same time period and comparison as addressed in the first question?"

Fourth, the underlying assumption to the first 3 questions is that there is a link between infection or vaccination and pathology. If this is correct, then it is possible that this relationship will be modified over time by change of exposure to infection and vaccination. Therefore, the fourth question is, "Is there evidence of rebound postinfectious pathology in the aftermath of the pandemic?"

Taken together, these questions apply to all of medicine and can be addressed most comprehensively by a worldwide epidemiological burden approach. Regarding neuro-ophthalmology, it may be worthwhile considering postinfectious and postvaccination autoimmune phenomena of deep phenotyped cases. Table 1 may be found useful as a template to calculate the IRR for conditions seen in neuro-ophthalmological practice.

CONCLUSIONS

In conclusion, there are 3 main pathological mechanisms by which infection with SARS-CoV-2 and vaccination against SARS-CoV-2 cause neuro-ophthalmological problems:

Vascular through hypercoagulability and thromboembolic complications. The majority of these manifest as a stroke with a CVST in the context of the novel described VITT being a life-threatening emergency.

Autoimmune phenomena can be postinfectious or postvaccination. They manifest as ON, labyrinthitis, vestibulitis, or other cranial nerves (mono-) neuropathies of which Bell palsy is most frequent.

Sequelae from brain pathology that include symptoms frequently related to headache disorders including IIH and migraine.

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