Non-arteritic anterior ischaemic optic neuropathy sequential to SARS-CoV-2 virus pneumonia: preventable by endothelial protection?

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SUMMARY

We present a case of non-arteritic anterior ischaemic optic neuropathy (NAION) with no ocular or systemic risk factors in a patient who recovered from a recent SARS-CoV-2 pneumonia. NAION is the most common acute optic neuropathy among individuals over 50 years of age. It results from a transient hypoperfusion of the optic nerve head circulation, especially in patients with low vascular compliance due to ocular or systemic risk factors. We attribute the ophthalmological condition to a SARS-CoV-2 virus-associated endotheliopathy that can be prevented with timely protection of endothelial function with vitamins D and K_2.

BACKGROUND

Late complications, mostly cerebral and cardiac, after COVID-19 pneumonia are reported in increasing numbers. These have been linked with hypercoagulability and associated lupus anticoagulant antibodies. However, endothelial dysfunction has also been implied. Non-arteritic anterior ischaemic optic neuropathy (NAION) has not been reported as a sequela of COVID-19 so far.

CASE PRESENTATION

A 64-year-old Caucasian man presented at the emergency eye clinic with a 4-day history of right eye visual field reduction. Four weeks earlier, he had been discharged after 5-day hospitalisation for COVID-19 pneumonia. In summary, the patient was admitted to hospital because of dyspnoea 1 week after first symptoms of COVID-19. CT of the thorax showed typical ground-glass opacities with a score 15 of 25, compatible with COVID-19 pneumonia. PCR was positive for SARS-CoV-2.

For 4 days he was treated with high-flow nasal cannula oxygen without the need for mechanical ventilation or intubation. He was further treated with hydroxychloroquine (2×400 mg a day for 6 days) and acetaminophen (4×1 g a day for 5 days). Oxygen saturation was always above 90%. Blood pressure during hospitalisation ranged from 123/64 mm Hg to 136/82 mm Hg. No other therapy was given. The patient used no medication, is a non-smoker, had no previous ophthalmological disease, no diabetes, no obesity, no hypercholesterolaemia nor other systemic diseases. No ocular or systemic risk factors for NAION were present.

INVESTIGATIONS

Ophthalmological findings showed a relative afferent pupillary defect in the right eye, relative desaturation of colour perception and unilateral sectorial papillary oedema (figure 1). Visual acuity was preserved. No crowded disc was observed in the other eye. Automatic perimetry demonstrated an inferior altitudinal defect (figure 2). Fluorescein angiography excluded cilioretinal artery occlusion or embolic choroidal hypoperfusion (figure 3). Laboratory investigations are shown in table 1.

DIFFERENTIAL DIAGNOSIS

Embolism of short posterior ciliary arteries of optic nerve head is a rare cause of NAION.[1] Embolic occlusion of these arteries is seen on fluorescein fundus angiography as hypoperfusion choroidal area. Fluorescein fundus angiography did not show signs of short posterior ciliary artery embolism (figure 3).

A hypercoagulable state due to antiphospholipid antibodies[2] was ruled out. Also, anticardiolipin and lupus anticoagulant were negative, D-dimer had normalised and Von Willebrand factor antigen was normal (table 1).

Arteritic anterior ischaemic optic neuropathy (AION) is a mandatory differential diagnosis to rule out in patient presenting with an ischaemic optic neuropathy.[1] The primary cause of AION is giant cell arteritis (GCA).[1]

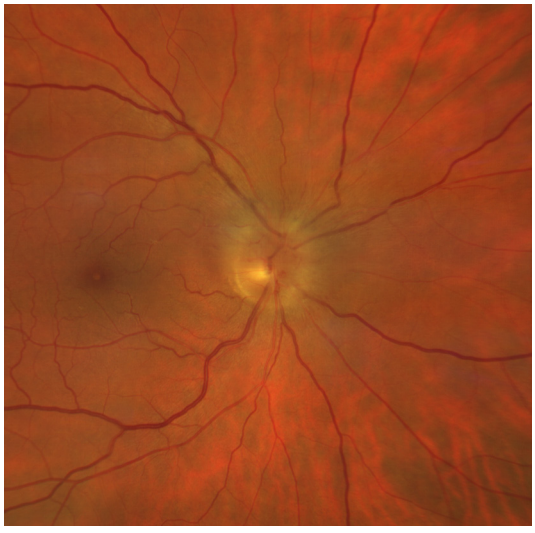

Figure 1 Fundus examination of right eye shows a pale optic nerve disc with sectorial swelling, dilated capillaries in the disc surface and some intrapapillary haemorrhages. The macula appears within normal limits with no signs of cilioretinal artery occlusion.

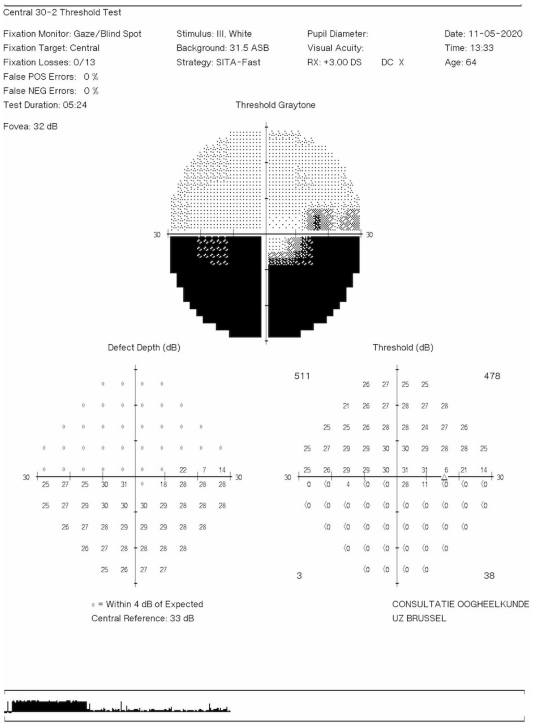

Figure 2 Inferior altitudinal defect in right visual field at the presentation in the eye clinic.

The differential diagnosis between NAION and GCA of posterior ciliary arteries is based on systemic and clinical features.

The patient had no clinical signs of GCA, that is, no jaw claudication, no headache, no scalp tenderness or other features.

Erythrocyte sedimentation rate increased in GCA was completely normal the day of the patient's presentation at the eye clinic (10 mm/hour) and in 2-month follow-up time (4 mm/hour). At presentation, C reactive protein (CRP) was within normal range (12.7 mg/L) and significantly decreased compared with hospitalisation value (170.2 mg/L). At 2-month follow-up,

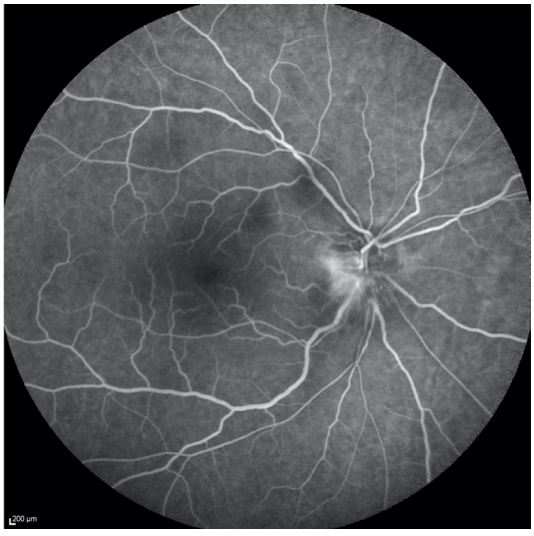

Figure 3 Fluorescein angiography of the right eye shows optic nerve fluorescein leak from superficial dilated capillaries during the retinal venous phase and the classical hyperfluorescence of superficial and deep portions of the optic disc in the late phase. No signs of cilioretinal artery occlusion were found.

Table 1 Laboratory findings during hospital admission and discharge for COVID-19 pneumonia, at eye clinic presentation and at follow-up

Laboratory findings	Hospital admission for COVID-19 pneumonia	Hospital discharge for COVID-19 pneumonia	Eye clinic presentation	Follow-up	Normal range
PCR detection of COVID-19 (SARS-CoV-2)	Positive				
Clinical chemistry blood					
Glucose (mg/dL)	120 !				70–100
pH	7.487 !				7.35–7.45
$PaCO_2$ (mm Hg)	30.6 !				35–45
PaO_2 (mm Hg)	87.7 !				90–100
Bicarbonate (mmol/L)	23.1				22–26
Total CO_2 (mmol/L)	24.1				22–27
Base excess (mmol/L)	0.7				–2 +2
Oxygen content (%)	96.8				>97%
Lactate (mmol/L)	0.8				0.7–2.1
Urea (mg/dL)	32	28			19–43
Creatinine (IDMS-norm) (mg/dL)	0.92	0.89	0.87	0.95	0.67–1.17
eGFR (MDRD-IDMS) (mL/min/1.73 m²)	>60	>60	>60	>60	>60
eGFR (CKD-EPI-IDMS) (mL/min/1.73 m²)	88	90	91	84	>60
Ionogram					
Sodium (mmol/L)	136 !	141			137–145
Potassium (mmol/L)	3.7	3.7			3.4–5.0
Chloride (mmol/L)	101	100			98–107
Calcium (mmol/L)	2.18	2.08 !			2.10–2.55
Bicarbonate (mmol/L)	25	32			22–30
Anion gap (mmol/L)	14	13			
CRP (mg/L)	170.2 !	145.5 !	12.7 !	0.8	<5
Creatine kinase (U/L)	75	86	107		55–170
Lactate dehydrogenase (U/L)	888 !	654 !	481		313–618
Aspartate aminotransferase (U/L)	57	37			17–59
Alanine aminotransferase (U/L)	55	55			21–72
Alkali aminotransferase (U/L)	55	55			29–33
Gamma-glutamyl transferase (U/L)		45			9–48
Cholesterol (mg/dL)				165	<190
HDL-cholesterol (mg/dL)				50	>40
Non-HDL cholesterol (mg/dL)				114	<130
LDL cholesterol (mg/dL)				108	<100
Triglyceride (mg/dL)				118	<150
Bilirubin total (mg/dL)	0.67				0.2–1.3
Haematological profile					
Platelet ($x10^9$/L)	215	305	217	219	158–450
Red blood cell ($x10^{12}$/L)	5.0	4.4	4.4	5.0	4.2–5.7
Haemoglobin (g/L)	144	130	150	151	130–165
Haematocrit (%)	43.9	39.4 !	45.2	45.3	39.6–49.2
MCV (fL)	88.5	89.8		91.3	83.0–98.0
MCH (pg)	29.0	29.6		30.3	27.0–33.0
MCHC (g/dL)	32.8	32.9	33.2	33.2	32.0–35.0
White cell count ($\times10^3$/mm³)	5.4	6.3	5.5	5.8	3.6–9.6
Formula					
Neutrophile (%)	68.7	66.8	60.0	59.8	41.0–74.0
Basophile (%)	0.1	0.2	0.3	0.2	0.0–2.0
Eosinophile (%)	1.5	3.0	3.1	2.6	0.0–6.0
Lymphocyte (%)	16.4 !	17.2 !	26.3	26.5	19.0–44.0
Monocyte (%)	13.3 !	12.8	10.3	10.9	3.0–13.0

Continued

Table 1 Continued

Laboratory findings	Hospital admission for COVID-19 pneumonia	Hospital discharge for COVID-19 pneumonia	Eye clinic presentation	Follow-up	Normal range
Erythrocyte sedimentation velocity (mm/hour)			10	4	0–10
Haematocrit (%)	46.6				39.6–49.2
Coagulation profile					
PT (%)	80		104		>70
PT (INR)	1.2		1.0		0.8–1.3
APTT (s)	29.8				22.2–34.4
Von Willebrand factor antigen (%)			104		>52
D-dimer (ng/mL)	832 !		300	<215	<500
Lupus anticoagulant			Negative		
Cardiolipine antibody IgG (U/mL)			<2.6		<20
Cardiolipine antibody IgM (U/mL)			4.2		<20
Radioimmunology					
Hydroxy vitamin D (µg/L)			11.4 !	22.3	20–50
Ferritin (µg/L)	411 !		113		30–400
Serology					
Mycoplasma pneumonia IgM–IgG	Negative				
Humoral immunology					
Antinuclear antibody			Negative		
Antineutrophilic cytoplasm antibody			Negative		

APTT, activated partial thromboplastin time; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IDMS, isotope-dilution mass spectrometry; INR, international normalised ratio; LDL, low-density lipoprotein; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; MDRD, Modification of Diet in Renal Disease; n/a, not available; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; PT, prothrombin time.

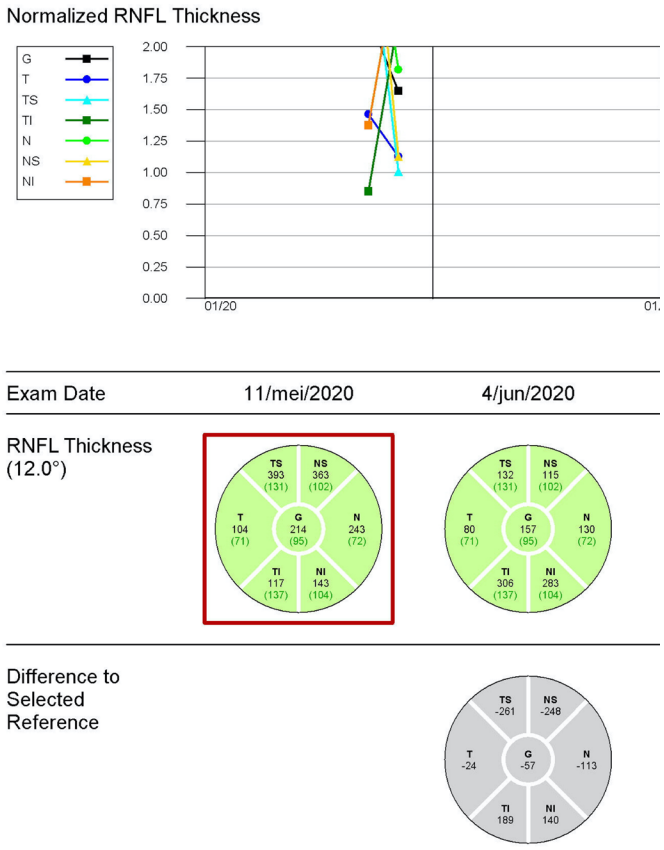

Figure 4 Pseudo-thickening of the nerve fibre layer of the right eye due to papillary oedema. The abnormal thickening reduced in 2-month follow-up examination. RNFL, retinal nerve fibre layer.

CRP was completely normal (0.8 mg/L). Thus, the systemic and clinical features do not support GCA.

TREATMENT

Acute management of AION requires systemic corticosteroid therapy in arteritic AION but not in NAION.[1] [1]No systemic corticosteroid therapy was started in our patient.

Vitamin D deficiency was treated with oral supplementation. At cardiological screening, 8 weeks after hospital discharge, a moderate systemic hypertension (150/90) was measured. Valsartan was started with intake in the morning to avoid nocturnal hypotension (80 mg per day) together with aspirin (80 mg per day) as secondary cardiovascular protection.

OUTCOME AND FOLLOW-UP

During 2-month follow-up, the visual acuity remained 20/20 (0.0 logMAR) in both eyes. Optic disc oedema decreased (optical coherence tomography/OCT) (figure 4) and optic disc pallor developed (figure 5). The automatic visual field at 1-month follow-up showed a generalised reduction of light perception threshold in the residual upper hemifield (figure 6). Visual fields remained stable at 2-month follow-up with moderate improvement of mean deviation value (figure 6). Macular ganglion cell layer analysis with OCT showed a progressive decrease in thickness in the right eye at 2-month follow-up (figure 4). Vitamin D was within normal range (22.3 µg/L) at 2-month follow-up.

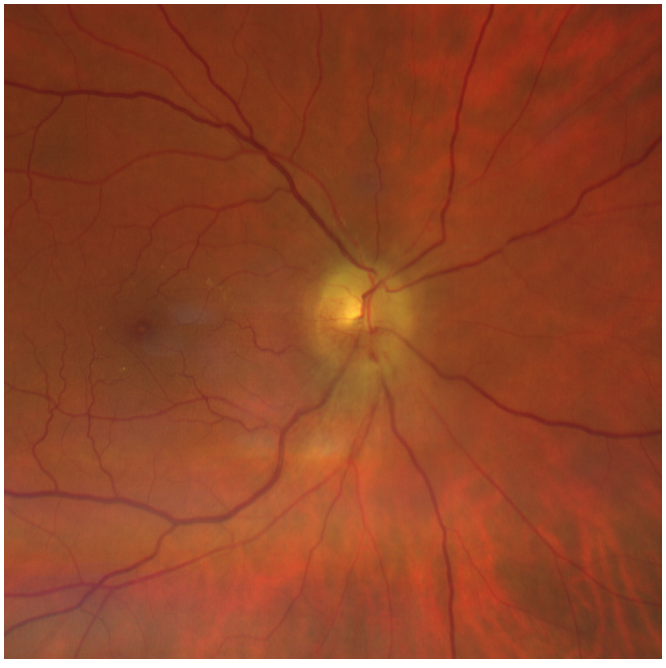

Figure 5 At 2-month follow-up, superior swelling was reduced but inferior part was also involved. This aspect is highly suggestive of papillary oedema in progressive non-arteritic anterior ischaemic optic neuropathy. The macula appears within normal limits with no signs of cilioretinal artery occlusion.

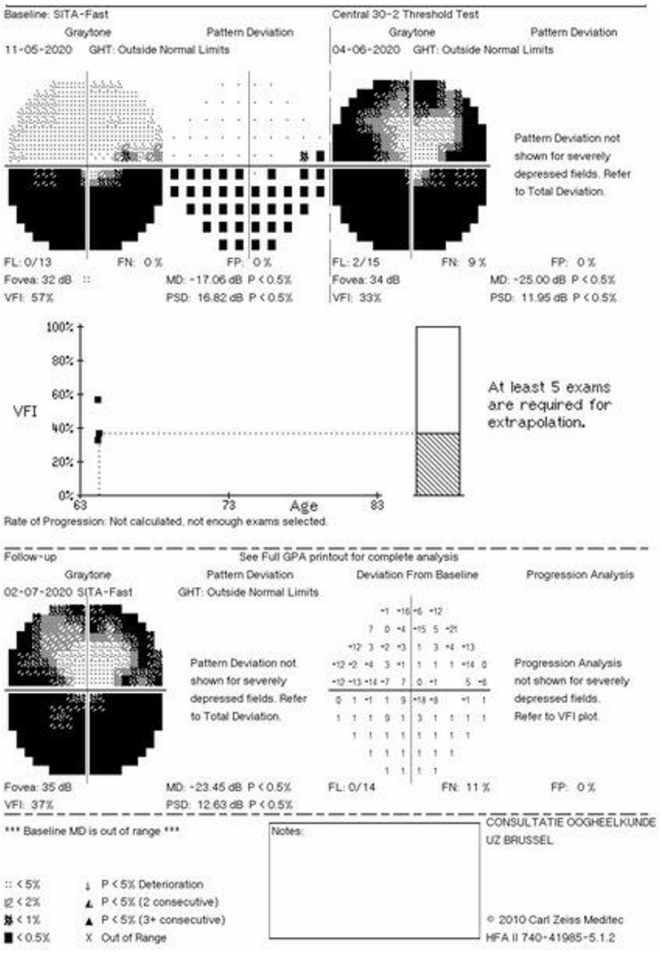

Figure 6 Generalised reduction of light perception threshold in 1-month follow-up with preserved central and paracentral superior visual field area. Moderate improvement in mean deviation parameter in 2-month follow-up examination. MD: mean deviation, PSD: pattern standard deviation, dB: decibel

DISCUSSION

We attribute the ophthalmological condition in our case to SARS-CoV-2 virus-associated endotheliopathy.

Emerging studies over SARS-CoV-2 virus and COVID-19 disease suggest that endotheliopathy is a central feature of its pathophysiology and leads to severe vascular systemic sequelae by loss of vascular compliance[2] including at the level of optic nerve.[3]

Savastano *et al*[3] have recently reported the impact of SARS-CoV-2 infection on the microvascular network of optic nerve head in patients who recovered from COVID-19, 4 weeks after discharge. It results in an impairment in the blood supply to the peripapillary retinal nerve fibre layer characterised by a reduction of radial peripapillary capillary plexus density that has been previously correlated to visual field loss in NAION.[2]

Furthermore, a recent study over lung perfusion abnormalities in patients with COVID-19 proposed possible underlying mechanisms, not only microthrombosis but also perfusion defects caused by vasoconstriction that brings to subsequential SARS-CoV-2-induced vasoplegia.[4] The transient hypoperfusion of optic nerve head circulation is indeed the most common cause of NAION.[1]

Patient's perspective

I was hospitalized with a corona infection from March 30 to April 3. On April 3, my saturation value was 96. I had to stay in quarantine for 14 days at home. On 11 May I got up and immediately noticed that my right eye was malfunctioning. I only had a partial view. I could not make visual observations with the bottom half of my right eye. My left eye was functioning normally. I have not experienced any headaches or pain in my right eye. After the consultation of 4 June 2020, two medicines were prescribed: Valsartan and Aspirin. I have also been following a vitamin D cure since 4 June 2020. The diminished vision in the right eye has stabilized. The left eye is functioning normally. At the consultation on 2 July it was established that vision in the right was slightly improved. However, I was not aware of that improvement.

Learning points

- Endotheliopathy is a central feature of COVID-19 disease.
- SARS-CoV-2 virus can impact the vascular compliance of the optic nerve head with a reduction of radial peripapillary capillary plexus density that can result in non-arteritic anterior ischaemic optic neuropathy.
- Endothelial protection by vitamins D and K_2 should be considered in all patients with COVID-19.
- Intervention studies are needed to assess the effect of the administration of vitamins D and K_2 on reducing the severity and complications of COVID-19 pneumonia.

No treatment is available to restore visual function in NAION.[1] Therefore, prevention is paramount. Endothelial function and integrity can be improved by vitamins D and K_2.[5–9] Moreover, there is support that vitamin D deficiency is particularly common in patients with COVID-19 developing endothelial dysfunction sequels elsewhere.[5 6] Vitamin K_2 status may also be reduced in patients with COVID-19 and related to poor prognosis.[7 8] No test is available to measure vitamin K_2 status, but vitamin D level in our patient was markedly reduced (11.4 µg/L).

Based on the growing understanding of SAR-CoV-2 endotheliopathy, we propose considering endothelial reserve in patients with COVID-19 and initiating prophylactic protection to prevent ophthalmic and other systemic sequelae at the earliest moment of diagnosis.

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