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Anisocoria in an intubated patient with COVID-19

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SUMMARY

The effects of COVID-19 on the eye are still widely unknown. We describe a case of a patient who was intubated and proned in the intensive care unit (ICU) for COVID-19 and developed unilateral anisocoria. CT venogram excluded a cavernous sinus thrombosis. MRI of the head showed microhaemorrhages in the midbrain where the pupil reflex nuclei are located. After the patient was stepped down from ICU, intraocular pressure (IOP) was found to be raised in that eye. A diagnosis of subacute closed angle glaucoma was made. It is important for clinicians to rule out thrombotic causes in patients who develop acute anisocoria. It is also crucial to measure IOP in patients who develop ophthalmic pathology and have been proned for extended periods.

BACKGROUND

The Wuhan Coronavirus 2019 (COVID-19) has rapidly spread across the world and has led to increased morbidity and mortality. The spread of the SARS-CoV-2 virus is due to its incubation period coupled with its infectivity through aerosols. The COVID-19 pandemic has led to the imposition of lockdown across many countries in order to control the spread of the virus and prevent healthcare systems from becoming overwhelmed.

With over 400 000 reported deaths worldwide, COVID-19 associated mortality has been primarily due to acute respiratory distress syndrome.[1] However, as more patients have been affected by this virus, there has been an inundated report of other signs and systemic implications associated with COVID-19. Evidence suggests that COVID-19 can be transmitted through the ocular surface.[2] Clinically, COVID-19 has been associated with multiple ocular manifestations such as conjunctivitis, worsening of ocular manifestations of systemic diseases such as Kawasaki disease, and pathological retinal changes.[3] In neurology, case reports of meningitis-encephalitis, encephalopathy, and olfactory and gustatory disorders have all been reported. However, with the knowledge of COVID-19 stimulated cytokine storm and patients developing a prothrombotic state, there has been an increased number of cerebrovascular events.[4] This risk is amplified by comorbidities such as hypertension, diabetes mellitus and chronic obstructive pulmonary disorder. Moreover, these are the very risk factors that lead to a severe form of the disease, where critical care support will be more likely indicated.[5] This case highlights a patient with COVID-19 who was intubated and developed anisocoria during his time in the intensive care unit (ICU).

CASE PRESENTATION

A 74-year-old man was admitted to the hospital with a 2-week history of cough, fever and progressive shortness of breath. He had a background of hypothyroidism, hypertension and benign prostate hypertrophy. His initial imaging and swab test confirmed COVID-19. The patient was placed on a trial of continuous positive airway pressure to support his deteriorating oxygen saturation. However, after a week of supportive therapy, he was transferred to the ICU and was supported with mechanical ventilation and proning. The proning protocol used involves patients being proned for up to 18 hours a day (figure 1).

While in ICU, the patient's recovery was impacted by a *Klebsiella*-positive pneumonia, and a subsequent CT scan showed multiple pulmonary emboli. This was treated with low molecular weight heparin. During the second week in ICU, the patient's critical care team identified anisocoria. They reported a left relative afferent pupillary defect (RAPD) with no new neurology or squint on gross assessment. There was no significant ocular history prior to this, and the patient's ICU team booked a CT scan of the head and accompanying venogram, which did not highlight any notable pathology and ruled out venous sinus thrombosis.

An ophthalmology review was requested: on bedside examination the patient appeared orthophoric and a ptosis assessment was difficult to assess as the patient was in a sedated state. Pupillary inspection revealed a notable anisocoria; the left pupil was measured at 6 mm and was fixed with no change in light or dark/dim lighting (figure 2). The right pupil was 3 mm in light and 4 mm in dark assessment. Assessment of the left pupillary reflex identified no direct or consensual response and an RAPD. The right pupillary reflex identified a normal direct response, no consensual response and no RAPD. A full ophthalmological examination revealed a normal anterior segment without any signs of inflammation. There was an early cataract in both eyes. There was no inflammation in the vitreous, with normal optic nerve heads, retina and macula. Digital palpation was normal. iCare intraocular pressure (IOP) readings for the right eye were 18 mmHg and in the left eye 22 mmHg, although this was difficult to record accurately due to patient positioning. As IOP readings were relatively normal, we did not think IOP could be a cause of the anisocoria.

Around week 4, the patient underwent a tracheostomy and was eventually decannulated. As he was weaned off his sedation, a clearer assessment of his lids was made and no ptosis was identified. The patient's anisocoria did not change over the course of his admission, and as he was weaned off ventilation he expressed blurred vision.

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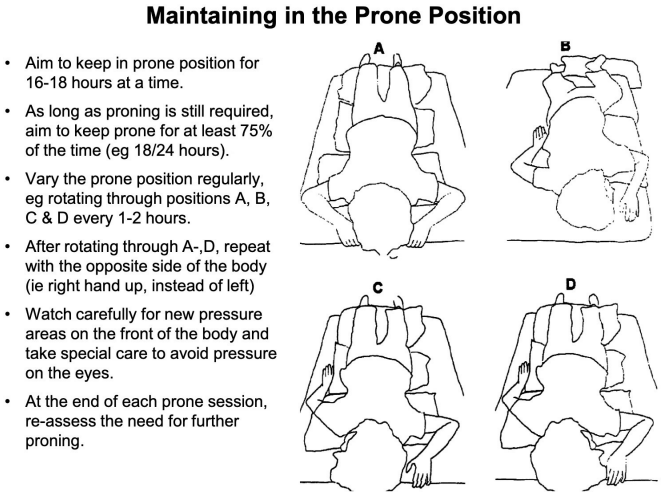

Figure 1 Proning protocol used in the intensive care unit.

He was now able to be safely transferred for an MRI of the head, where the ophthalmic team specifically asked the radiologist to focus on the midbrain. There were scattered intracranial haemorrhages, with a particular concentration of microhaemorrhages in the midbrain.

The patient was brought to ophthalmology clinic when it was safe to do so. Visual acuity in the right eye was 6/6 and in the left eye was 6/30. IOP in the right eye was 13 mmHg and in the left eye was 44 mmHg. Ishihara scores in the right eye were 17/17 and in the left eye 3/17. Diluted pilocarpine or accommodation did not cause constriction of the left pupil. Gonioscopy showed closed angle in the right eye and between 180° and 270° angle closure in the left eye. There was no cupping of the optic disc. Visual fields were normal in the right eye and revealed a glaucomatous visual field defect in the left eye. A diagnosis of subacute closed angle glaucoma was made.

INVESTIGATIONS

The patient had a CT pulmonary angiogram which showed multiple bilateral lobar, segmental and subsegmental pulmonary emboli with evidence of right heart strain. A CT head with venogram showed no intracranial or extracranial haemorrhage and no cavernous sinus thrombosis. An MRI of the head showed multiple microhaemorrhages in the midbrain (figure 3A,B). It showed no evidence of encephalitis or inflammatory demyelinating disease.

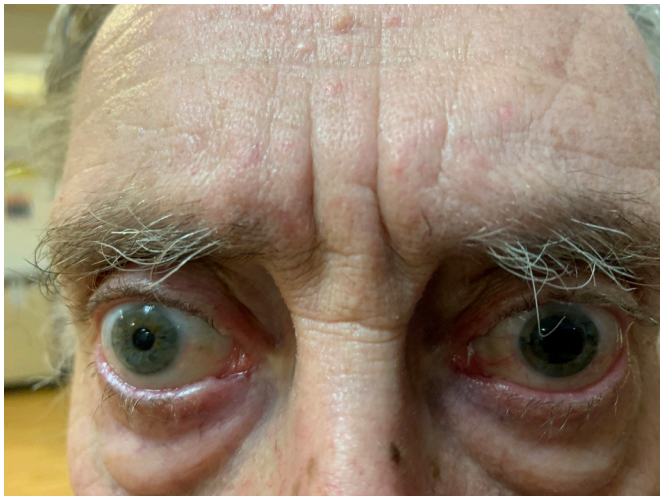

Figure 2 Photograph of the patient's left eye anisocoria.

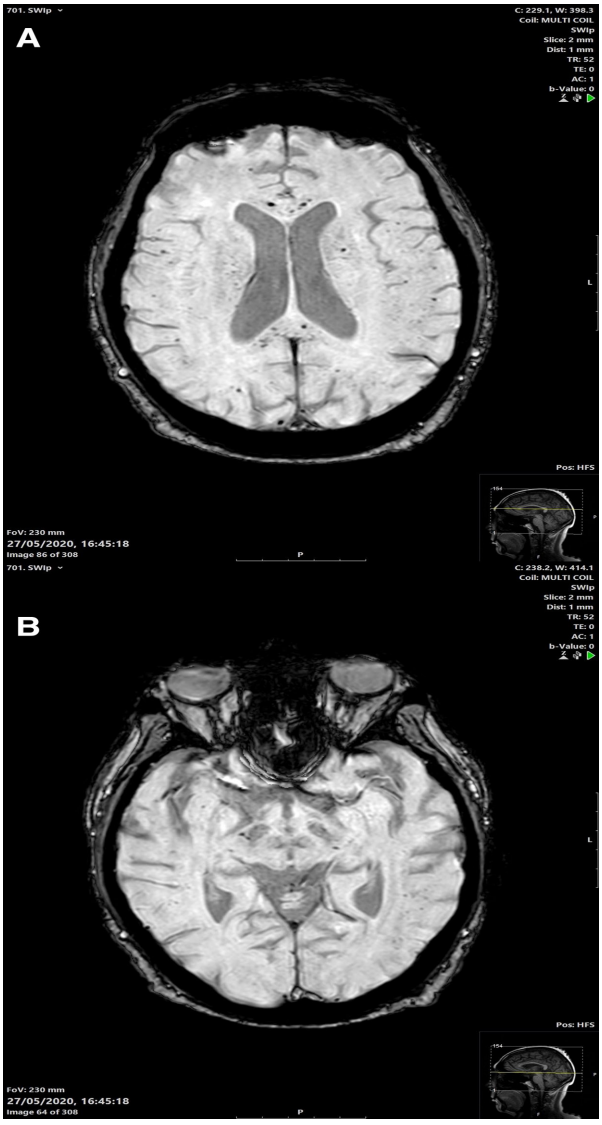

Figure 3 (A) Brain MRI axial T2* gradient echo scan at the level of the body of the lateral ventricles showing low signal microhaemorrhages. (B) Brain MRI axial T2* gradient echo scan at the level of the upper midbrain showing low signal microhaemorrhages.

DIFFERENTIAL DIAGNOSIS

As COVID-19 is known to be prothrombotic, our first differential diagnosis was a cavernous sinus thrombosis. This was disproved after CT venogram. Both the ophthalmology team and the neurology team then thought that a thrombotic or ischaemic event could have happened specifically in the midbrain (as this is where the pupil reflex nuclei are found). Microhaemorrhages on the MRI of the head did provide evidence towards this diagnosis, although the absence of disc swelling made a diagnosis of ischaemic optic neuropathy more difficult.

However, after the patient was stepped down from ICU, IOP measurements were high and the angle was partially closed in the left eye. Therefore, our final diagnosis was subacute closed angle glaucoma.

After reviewing the patient's medication in ICU, none was known to cause an increase in IOP or acute angle closure glaucoma.

An Adie's tonic pupil is also an important differential for anisocoria. An Adie's pupil occurs due to parasympathetic denervation of the ciliary ganglion. There are reports of Adie's pupils occurring in patients with COVID-19.[6 7] It is therefore important to test anisocoria with diluted pilocarpine and examine if there is light-near dissociation to exclude an acute Adie's pupil.

TREATMENT

The patient received IOP-lowering drops: apraclonidine, pilocarpine, travoprost and dexamethasone. He also received acetazolamide orally. The patient also underwent bilateral peripheral iridotomies. The patient also had left eye cataract extraction and intraocular lens implantation.

OUTCOME AND FOLLOW-UP

The patient's vision has now improved to 6/19 in the left eye. The left eye pressure was 17 mmHg after cataract surgery. Unfortunately, pupil size did not change after reduction of IOP. The left eye IOP has continued to be within normal limits on Cosopt and Lumigan . Visual acuity has improved to 6/9.5. There is a possibility that the patient had shallow angles prehospitalisation and therefore had a predisposition to angle closure glaucoma. Unfortunately, the patient has no previous ophthalmic record to confirm this.

DISCUSSION

Anisocoria was found to be present in 5% of patients with stroke in a retrospective study in New York.[8] In an intensive care setting, the incidence was higher, with 19% of patients found to have anisocoria on examination and 68% of these patients had a stroke diagnosis.[9] The mechanism is most likely due to loss of the parasympathetic nucleus of Edinger-Westphal resulting in loss of parasympathetic tonus.[8]

There have been only a few cases described in the literature of patients with COVID-19 having acute anisocoria.[6 7] However, it has been shown in a case series that neurological manifestations of COVID-19 can occur in 36% of patients, although visual symptoms only affected 1.4% of patients.[10]

COVID-19 has been recognised as causing an increase in cytokines that can leave patients in a hypercoagulable state.[11] In a study of 184 ICU patients with COVID-19, 31% suffered from arterial and venous thromboembolism. In the largest cohort study to date, it was found patients with COVID-19 are 7.6 times more likely to develop a stroke compared with patients with influenza.[12] There has been a case report of a patient with COVID-19 developing a cerebral venous sinus thrombosis and then developing limb weakness, slurred speech and expressive dysphasia.[13] However, there are no cases in the literature of a patient with COVID-19 having a cavernous sinus thrombosis, leading to any cranial nerve palsy or anisocoria. Therefore, it is important to rule out a thrombotic event in patients with COVID-19 who develop unusual ophthalmic signs or symptoms, including anisocoria.

Interestingly, our final diagnosis for the cause of the anisocoria was subacute closed angle glaucoma in the left eye. Closed angle glaucoma is predominantly an asymptomatic disease, with individuals often unaware they have the disorder until advanced visual loss has occurred. In less than a third of cases, patients may present with acute closed angle glaucoma, a clinical condition with signs of marked conjunctival hyperaemia, corneal oedema, a mid-dilated unreactive pupil, a shallow anterior chamber and a very high IOP.[14] Subacute closed angle glaucoma is when the patient experiences brief episodes of acute closed angle glaucoma that resolve spontaneously. We believe the subacute category was most likely for this patient given the previous normal IOP measurement and lack of clinical signs of acute closed angle glaucoma.

Studies have shown that a high IOP can cause mydriasis in humans. Rutkowski and Thompson's[15] study showed that when IOP exceeds the systolic ophthalmic artery pressure, an afferent pupillary defect develops due to transient retinal ischaemia. Iris sphincter function is also clearly impaired at high IOP. This is likely due to the loss of contractile ability of the iris sphincter under high IOP.

There is no data in the literature of any link between COVID-19, IOP and glaucoma. However, intubated patients with COVID-19 in ICU are routinely put in prone position to increase ventilation of the lungs. Studies have shown that IOP is significantly raised in patients who are anaesthetised in prone position for spinal surgery.[16] Studies have also shown that non-invasive ventilation can cause increased IOP, which this patient had before being intubated on ICU.[17] A higher IOP can lead to decreased ocular perfusion pressure and reduced blood flow to the optic nerve head. This can lead to ischaemic optic neuropathy and can lead to decreased vision. Cases have also been reported of patients developing unilateral and bilateral acute closed angle glaucoma after proning in spinal surgery.[18 19] The mechanism for this may be due to a gravity-induced forward shift of the lens-iris diaphragm with a relative pupillary block, causing obstruction of the aqueous humour flow from the posterior chamber to the anterior chamber. However, the long-term effect of proning for many weeks as is the case with many patients with COVID-19 in ICU and acute closed angle glaucoma is not known.

Patient's perspective

When I first became conscious, after being on a ventilator and after the tracheostomy, I remember thinking I had got something in my left eye. The vision in the left eye felt like there was dust or muck in that eye. However, the vision in the right eye was completely clear. I think I said something to a nurse but then I quickly realised it was a new permanent state.

If I had to describe what it is like now, it is as if I am looking through tracing paper in the left eye. I get light, colour, shape and form but it is as if there is a sheet between me and the field of vision. I don't quite get double vision but I get blurred vision and there have been times particularly when it is very bright that I feel quite disturbed. I find wearing sunglasses a relief, as it brings light away from the bad eye. I don't get any eye pain however I do get headaches from time to time which I believe is related to my blood pressure.

Learning points

- If a patient with COVID-19 develops anisocoria, it is important to request imaging to rule out cavernous sinus thrombosis and midbrain stroke.
- It may be worthwhile to check intraocular pressure in all patients with COVID-19 who have been proned for extended periods of time in the intensive care unit.
- The effect of proning in patients with COVID-19 and acute closed angle glaucoma is unknown and more studies are needed to investigate this.

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