Primary Angle Closure During Hospitalization for Coronavirus Disease-19 (COVID-19): A Likely Event

Guido Barosco*, Roberta Morbio, Francesca Chemello, Roberto Tosi and Giorgio Marchini

Department of Neurosciences, Biomedicine and Movement Sciences, Eye Clinic, University of Verona, Verona, Italy

Corresponding Author*

Guido Barosco
Department of Neurosciences,
Biomedicine and Movement Sciences,
Eye Clinic, University of Verona,
Verona, Italy
E-mail: guido.barosco@gmail.com

Received 16 July 2021; **Accepted** 30 July 2021; **Published** 06 August 2021

Abstract

This short review evaluates how the therapeutic interventions for Coronavirus Disease-19 (COVID-19) could lead to the development of an Acute Primary Angle Closure (APAC) and Primary Angle Closure Glaucoma (PACG). The 2 recent reports share some important features related to the settings of the pathological ophthalmic conditions. Patients' severe clinical conditions and prolonged systemic therapies could mask their symptoms and delay the diagnosis. Recognition of early signs of Primary Angle Closure (PAC) is crucial to averting its progression to PACG. It is therefore necessary to warn anesthesiologists and intensivist doctors to be aware of the ophthalmic risks of the general therapy against the COVID-19 in the Intensive Care Unit (ICU) in order to promptly detect signs and symptoms on an Acute Primary Angle Closure (APAC).

Keywords: COVID-19 • Primary angle closure glaucoma • Intensive care unit

Introduction

When we refer to Primary Angle Closure (PAC), we must be conscious that we are only describing a pathological phenomenon, but we are neither making a proper diagnosis nor we can establish a therapy based only on this evaluation. PAC differ from secondary forms by the absence of a pre-existing eye condition that causes the anterior chamber angle to close (e.g. lens dislocation, prolonged inflammation, protruding vitreous, etc.) and arises from different conditions: Pupillary block, plateau iris configuration, thick peripheral iris roll and exaggerated lens vault [1]. Primary forms of AC can be classified by its underlying mechanism of onset: (1) pupillary block type; (2) plateau iris type; (3) lens factors (lens-induced glaucoma); and (4) malignant (ciliary block) glaucoma [2]. Besides the different types, all PACs cause a closure of the iridocorneal angle and results in blockage of the trabecular meshwork. Once a PAC is identified, before considering a diagnosis of Primary Angle Closure Glaucoma (PACG) is mandatory to confirm a glaucomatous optic damage supported by the visual field examination and/or the Ocular Coherence Tomography (OCT) evaluation. The necessary condition for the contact between the iris root and the peripheral cornea in PAC is always an anatomical anomaly/predisposition (hyperopia, shorter axial length, thicker lens, shallow anterior chamber) that represents the "first kick". The "second kick" that act as a trigger results from accommodation, pupil dilation, emotional stress, and body position [3-6].

Several therapeutic approaches during the hospitalization for COVID-19 in the ICU play a synergic role for developing a PAC (and PACG). Facedown (prone) position is part of the therapy against severe acute respiratory syndrome coronavirus 2 (SARSCoV2) for patients hospitalized in Intensive Care Unit (ICU). Positioning patient's facedown improves the ventilation/perfusion ratio and increases blood oxygen levels, but it is also responsible (in predisposed eyes) for obstructing the trabecular meshwork by the iris, which is pushed forward by hydrostatic and tissue pressure [7-9]. The use of systemic sympathomimetics drugs (adrenaline, noradrenaline, dopamine, ephedrine, salbutamol, and terbutaline), and anticholinergics (atropine, ipratropium bromide, tricyclic antidepressants, and antihistamine) in the ICU is another stimulus to pupil dilation, and to PAC as a consequence [10]. With these assumptions the risk of PAC, Acute Primary Angle Closure (APAC), and PACG in patient hospitalized for SARSCoV2 represents a real threat for the vision. At the beginning of the Corona Virus disease 19 (COVID-19) pandemic, the American Academy of Ophthalmology as well as a report warned about this event [11, 12]. And, as Thales says: "Time is the wisest of all things that are; for it brings everything to light". With the passing of time, these warnings turned to be a real problem, and 2 reports about this topic were recently published [13, 14].

Literature Review

The 2 recent reports (one of our group) in literature share some interesting features about the adopted medical therapy and clinical characteristics (Table 1). The first remarkable thing is that both of the cases involved simultaneously both eyes of the patients. Our patient experienced a bilateral PAC with a glaucomatous damage (end-stage PACG) only on one eye, while Nerlikar, et al. reported a bilateral acute PACG. Other relevant things concerned the cycle of pronation and the administered systemic drugs. Adrenergic agonists (i.e. norepinephrine) together with prolonged prone position were probably the most influent contributing factors to the origin of the APAC/PAC. In general, several therapeutic approaches during the hospitalization for COVID-19 in the ICU act as synergic factors for developing a PAC (and PACG). The cycles of prone position last several hours (from 8 to 15) and are repeatedly performed during the whole period of intubation. Prone position acts mostly on 3 pathological mechanisms on the eye. Firstly, it shifts the anterior segment structures (lens, ciliary body, and iris) forward, resulting in the approximation of the iris towards the iridocorneal angle and an additional trigger for APAC [8, 15, 16]. Secondly it increases the peritoneal pressure and in turn central venous pressure, peak inspiratory pressure, and IOP [17]. This event could raise the IOP up to approximately 40 mmHg after 320 minutes in the prone position, and it also reduces directly the ocular perfusion.[12] Thirdly, orbital compartment syndrome has been advocated as an adjunctive probable mechanism for IOP rise [18]. Another element to take into account is the systemic therapy administered. To be intubated, patients need to obtain muscle relaxation through muscle relaxant drugs (i.e. rocuronium bromide) and also frequently suffer from hypotension and are therefore treated with adrenergic agonist (i.e. norepinephrine) [10]. Also benzodiazepines (anticholinergic effect) are commonly used to sedate patients during the intubation. All of these drug classes are blamed for dilating the pupils and potentially leading to angle closure via an "angle crowding" mechanism, in which the peripheral iris is pushed against the trabecular meshwork [19]. Furthermore, hypoxia due to obstructive pneumonia and systemic hypotension can additionally contribute to make the optic nerve more vulnerable through multiple mechanisms such as increased oxidative stress, mitochondrial dysfunction, and activation of apoptosis pathways [20, 21]. The type of PAC detected in the 2 cases is different. We diagnose a clear PAC due to plateau iris configuration, whereas Nerlikar, et al. diagnose a pupillary block type. It must be told that, from the anterior segment OCT published by Nerlikar, et al. a mixed type of PAC (plateau iris and pupillary block) seems to be attributed to the genesis of the ocular pathology. To corroborate this assumption an Ultrasound Bio Microscopy (UBM) from Nerlikar, et al. would have been thorough. If this hypothesis would be true, it will leave space to study how prone position interacts with different iris/anterior segment conformation.

In a normal setting, the acute PAC has strongly suggestive signs (high IOP, conjunctival injection, corneal edema, shallow anterior chamber, and fixed mid-dilated pupils) and symptoms (blurred vision, intense pain, nausea, and emesis) and patients usually seek promptly a medical referral. But what happen if symptoms are abolished, and signs are evaluated by a doctor who is not an ophthalmologist? What makes the diagnosis challenging is that patients in ICU are sedated and treated with analgesics and do not perceive

Table 1. General patients' characteristics of the 2 case reports in literature

Case Report	Type of PAC/PACG	Systemic drugs	Side	Systemic Pathologies	Total time of intubation	Total Time of Pronation	No of Cycles of Pronation	Sign/ Symptoms of PAC	Management of the PAC
Barosco G, Morbio R, Chemello F, Tosi R, Marchini G. Bilateral angle-closure during hospitalization for coronavirus disease-19 (COVID-19): A case report. *Eur J Ophthalmol.* 2021Apr 2:11206721211012197.	Plateau Iris configuration	enoxeparin sodium	Bilateral (OD developed PACG; OS developed PAC)	No systemic pathologies	3 days intubated (34 days sedated)	45 hours (each lasting a mean	5	Anisocoric unresponsive pupils; blurred vision	mannitol 20% IV; topical pilocarpine 2%; topical timolol 0.5%; topical brinzolamide 1%; Phacoemulsification with IOL in the bag implantation and goniosynechiolysis
Nerlikar RR, Palsule AC, Vadke S. Bilateral Acute Angle Closure Glaucoma after Prone Position Ventilation for COVID 19 Pneumonia. *J Glaucoma.* 2021 Apr 28.	Pupillary block	dexamethasone, remdesivir; enoxaparin; sulphmethoxazole; trimethoprim, levofloxaxin, meropenem; voriconazole	Bilateral	Diabetes mellitus type II; Hypertension	22 days	*Unknown*	*Un known*	Blurred vision; discomfort; mild conjutical injection; corneal edema; shallow anterior chamber; unresponsive pupils	mannitol 20% IV; oral acetazolamide; topical brizolamide; topical brimonidine; topical fluorometholone; laser iridotomy

the typical symptoms that easily lead the diagnosis. Our group identifies in anisocoric pupils the most suggestive manifestation of APAC (recorded on the chart of the patients by the ICU medical staff). In our particular report, it was erroneously interpreted as a neurological sign and a cranial Computed Tomography (CT) was preformed to further investigate this finding. Nerlikar, et al. reported anisocoric pupils in addition to all the classic APAC's signs (corneal edema, conjunctival injection, and shallow anterior chamber). Space to prevent vision loss stands all in a fast diagnosis and straightforward therapy. It appears clear from both these reports how important is to train the ICU staff to beware of ocular signs such as ocular redness and anisocoria (the most specific) and promptly ask for an ophthalmic consult in case of doubt, because it is all a matter of time. The 2 reports describe different therapeutic approaches to normalize the IOP (Table 1). The reason is attributable to different stages of the pathology, different lens status (cataract versus clear lens) of the patients, and different PAC mechanism (plateau iris configuration versus pupillary block type). However, both reports administered mannitol 20%, the fastest medical treatment to reduce the IOP in case of APAC. In an ICU setting, with mostly bedridden patients, IV mannitol 20%, topical miotics, and anti-glaucomatous drugs appear to be the most manageable and effective measures to rapidly lower the IOP and eventually resolved an APAC. On the other hand, aridity and cataract surgery implicates to physically move the patient from the ICU to the operating room (or to a laser station, at least), this hypothesis is not easily doable if the patient is positive to COVID-19, intubated, and weak. Thus, a medical therapy appears easier and more manageable as a first line treatment against PAC/APAC in an ICU.

Conclusion

As they say, we recognize what we already know. Keeping this as a prerequisite, it is essential to know all the complications secondary to the COVID-19 if we want to be able to look for them, and eventually recognize them. APAC and PAC belong to this category and the altered symptoms (especially in case of the acute PAC) need to be well known to be properly investigated. The first step is sensitizing the ICU staff, secondly routinely examinee corneal Clarity as well as pupil size and reaction as a part of the ICU protocol for prone ventilated patients may result in earlier ophthalmic referral and may help prevent or reduce the risk of potential serious visual consequences. The challenging part of the diagnosis is that it could be based only on ophthalmological signs, since patients are sedated, under analgesia, and unable to refer their symptoms. Last but not least, this complication could be extended as a possible finding also to different situations where prone position, sedation and adrenergic agents are used, such as in case of spinal surgery, breeding the need of sharing a protocol with anesthesiologists and intensivist doctors. It would be also interesting to investigate if any anatomical factor or eye condition makes the subject more susceptible to PAC/APAC triggered by prone position, in order to better prevent this occurrence. We hope that in the future some study will enlighten this topic.

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Cite this article: Barosco G, Morbio R, Chemello F, Tosi R , Marchini G. Primary Angle Closure During Hospitalization for Coronavirus Disease-19 (COVID-19): A Likely Event. Med Rep Case Stud, 2021, 06(5), 221