Systematic Review and Meta-Analysis

Medicine

OPEN

An overview of third, fourth and sixth cranial nerve palsies in the setting of COVID-19

A case report and systematic review

Mostafa Meshref, MD[a], Nour Shaheen, MD[b,*], Sarya Swed, MD[c], Mohamed Ibrahim, MD[d], Mostafa Reda Mostafa, MD[e], Mohamed Osman Algazar, MD[f], Monica Dobs, MD[g], Sarah Ibrahim Elsayed, MD[h], Yara Amro, MD[i], Ahmed Afsa, MD[j], Mostafa Ebraheem Morra, MD[k]

Abstract

Background: Covid-19 has serious sequelae that may be poorly understood, underreported, and, as a result, not diagnosed promptly, such as variations in clinical manifestations of hyperinflammation among people infected with SARS-CoV-2. ophthalmoplegia can be one of these manifestations.

Methods: We are reporting a 55-year-old male patient with unilateral diplopia considering it as a case of multisystem inflammatory syndrome in adults. We also reviewed the literature systematically for the previously reported studies/cases with third, fourth and sixth cranial nerve palsies due to or after Covid-19.

Results: The literature search yielded 17 studies reporting 29 patients. 71.4% of the patients were males with a mean age of 42.23 years. Ophthalmological symptoms took 9.7 days to appear after the respiratory involvement. All patients had diplopia as part of their visual symptoms. 41.4% of the patients had unilateral sixth nerve palsy, 24% had bilateral sixth nerve involvement, 17% had fourth nerve involvement, and 27.6% had third nerve involvement.

Conclusion: Ophthalmoplegia is considered presenting symptom of Covid-19. Further research is needed to detect all neuro-ophthalmological manifestations of Covid-19.

Abbreviations: COVID-19 = coronavirus disease 2019, CT = comptuted tomography, ED = emergency department, ICP = intracranial pressure, MIS = multisystem inflammatory syndrome, MRI = magnetic resonance imaging, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: abducens nerve, COVID-19, cranial nerve palsy, cranial nerves, fourth nerve, oculomotor nerve, sixth nerve, third nerve, trochlear nerve

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection affects multiple organs, mainly the respiratory system, causing multiple manifestations such as fever, dry cough, myalgia, gastrointestinal problems, neurological symptoms, etc. Neurological symptoms were less frequently reported including headache, dizziness, disturbed consciousness, and paralysis in approximately 36% of Covid-19 hospitalized patients.[1] Ophthalmoplegia secondary to Covid-19 infection was frequently reported in the patients due to involvement of the oculomotor, trochlear, or abducent cranial nerves.[2–4] Abducent nerve palsy is the most common cause of isolated ophthalmoplegia due to microvascular disease in adults secondary to viral infections in children most probably Epstein-Barr virus and Enterovirus.[5,6] Viral infections may cause different variants of Guillain-Barré syndrome.[7,8] It has been suggested that eye involvement during a Covid-19 infection is part of the multisystem inflammatory syndrome (MIS) that is associated with Covid-19 with features that resemble Kawasaki disease. This can explain visual manifestations associated with a current or past infection of Covid-19.[9,10]

Written informed consent was obtained from the patients for publication of the included case report.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval is not necessary for the publication of this systematic review.

[a] Al-Azhar University, Cairo, Egypt, [b] Alexandria University, Alexandria Faculty of Medicine, Alexandria, Egypt, [c] Aleppo University, Faculty of Medicine, Aleppo, Syria, [d] Essex Partnership University NHS Foundation Trust, Wickford, UK, [e] Rochester Regional Health/Unity Hospital, Rochester, USA, [f] Resident of Neurology, Alharam Hospital, Giza, Egypt, [g] University of Florida College of Medicine Jacksonville, Jacksonville, USA, [h] Faculty of Medicine, Zagazig University, Zagazig, Egypt, [i] Pharmacist Ministry of Health, Cairo, Egypt, [j] Emergency Department, Pilgrim Hospital, United Lincolnshire NHS Trust, Boston, UK, [k] Gastroenterology Department, Pilgrim Hospital, United Lincolnshire NHS Trust, Boston, UK.

** Correspondence: Nour Shaheen, Alexandria University, Alexandria Faculty of Medicine, Alexandria, Egypt (e-mail: nourshaheen40@gmail.com).*

How to cite this article: Meshref M, Shaheen N, Swed S, Ibrahim M, Mostafa MR, Algazar MO, Dobs M, Elsayed SI, Amro Y, Afsa A, Morra ME. An overview of third, fourth and sixth cranial nerve palsies in the setting of COVID-19: A case report and systematic review. Medicine 2022;101:49(e32023).

Received: 19 October 2022 / Received in final form: 4 November 2022 / Accepted: 4 November 2022

http://dx.doi.org/10.1097/MD.0000000000032023

Herein, we present a case of left abducent nerve palsy presenting with unilateral diplopia 3 weeks after Covid-19 infection. Furthermore, we review the previously reported ophthalmoplegia cases related to SARS-CoV-2 infection.

2. Materials and methods

We searched PubMed, Scopus, Web of Science, and Google Scholar databases using search terms: "((oculomotor OR third cranial nerve OR trochlear OR fourth cranial nerve OR abducens OR abducent OR sixth cranial nerve OR ophthalmoplegia OR ophthalmoparesis OR diplopia) AND (SARS-CoV-2 OR coronavirus OR COVID-19))." The inclusion criteria included all English studies reporting third, fourth, or sixth cranial nerve palsies or paresis in the setting of Covid-19 regardless of their date of publication. We excluded comments, conference abstracts, book chapters, and review studies. The reference list of the finally included studies was manually checked to avoid missing any relevant records.

3. Results

3.1. Case scenario

A 55-year-old male patient with no medical or surgical history or drug allergies presented to the emergency department (ED) with diplopia on looking to the left side for 2 days that increased upon looking to the left and disappeared on the closure of one eye. The patient was positive for SARS-CoV-2 infection 3 weeks backward from this current presentation. Additionally, he reported complete remission and negative SARS-CoV-2 – PCR within the last 2 weeks prior to this diplopia presentation.

The patient had no local eye inflammation, headache, vertigo, unsteadiness, motor symptoms, or sensory symptoms. On examination, the patient exhibited restricted abduction at the left indicating problematic left lateral rectus muscle and left sixth nerve palsy, but the other ophthalmological examination showed no abnormalities including normal fundi, normal other ocular motility and normal pupillary reactions. A point-of-care comptuted tomography (CT) brain was performed at the ED, but it was within normal results (Fig. 1). While chest X-ray revealed evidence of resolved pneumonia (Fig. 2), routine lab investigations (complete blood count, random blood sugar, hemoglobin A1C, thyroid function tests, and serum electrolytes) were within normal ranges. Furthermore, magnetic resonance imaging (MRI) of the brain revealed normal size, shape, and contour of both lateral recti with no significant brain stem lesion (Fig. 3A–D). The patient was admitted and given supportive treatment (acetaminophen, Vit B complexes and self-eye movement training to enhance the eye movement at the affected side via an alternative covering technique) that fulfilled marked recuperation. The patient was discharged home after 4 days of admission. He was vitally stable without any other neurological deficits. On the follow-up visit after 1 month, the ocular motility showed marked improvement.

3.2. A systematic review of the literature

Searching the databases yielded 451 studies. After removing 200 duplicates, 251 studies were considered for title/abstract screening; of which, only 25 studies were eligible for full-text screening. Eventually, 17 case reports including 29 patients -other than our patient- were finally eligible for qualitative analysis Prisma Flow. The mean age of patients was (42.23 ± 20.7) years and 71.4% of them were males (15/21) since the gender of patients was not reported in eight patients. The time from respiratory symptoms to the onset of ophthalmological symptoms ranged from 3 to 30 days as reported in 20 patients with a mean period of 9.7 days Table 1. All patients reported diplopia as part of their visual symptoms. 41.4% of the patients had unilateral sixth nerve palsy (12/29), whereas 7/29 (24%) had bilateral sixth nerve involvement, 5/29 (17%) had fourth nerve involvement, and 8/29 (27.6%) had third nerve involvement. Other neurological manifestations ranged from mild symptoms of headache in 7/29 (33.3%) to severe symptoms of paralysis, paresis, ataxia, and loss of sensation Table 2.

Figure 1. CT brain without contrast: normal brain parenchyma, no bone defects, no intracerebral hemorrhage, CT = comptuted tomography.

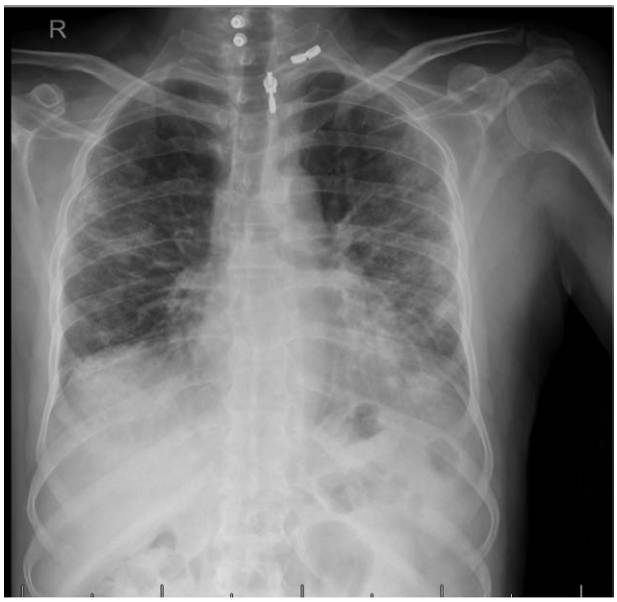

Figure 2. X-ray chest antero-posterior view: showed signs of resolved pneumonia.

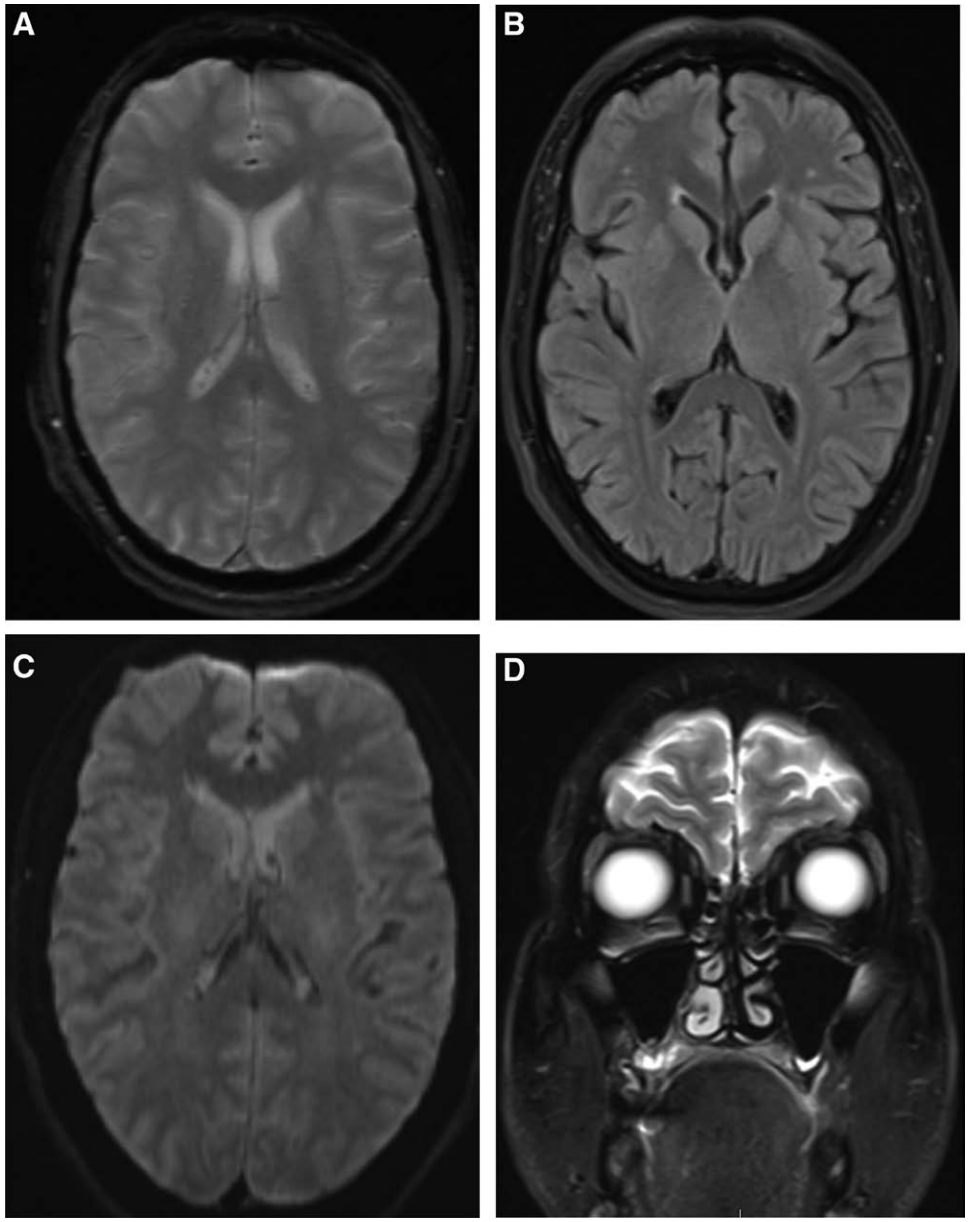

Figure 3. (A) MRI brain with different sequences (T2, flair, diffusion and coronal sequences) showed no cortical structural abnormalities, no vascular lesions in brain stem, no signs of increased intracerebral pressure, no mass lesions, no ocular muscles abnormalities, and no orbital masses. (B) MRI brain with different sequences (T2, flair, diffusion and coronal sequences) showed no cortical structural abnormalities, no vascular lesions in brain stem, no signs of increased intracerebral pressure, no mass lesions, no ocular muscles abnormalities, and no orbital masses. (C) MRI brain with different sequences (T2, flair, diffusion and coronal sequences) showed no cortical structural abnormalities, no vascular lesions in brain stem, no signs of increased intracerebral pressure, no mass lesions, no ocular muscles abnormalities, and no orbital masses. (D) MRI brain with different sequences (T2, flair, diffusion and coronal sequences) showed no cortical structural abnormalities, no vascular lesions in brain stem, no signs of increased intracerebral pressure, no mass lesions, no ocular muscles abnormalities, and no orbital masses. MRI = magnetic resonance imaging.

4. Discussion

We report a post-Covid-19 complication of unilateral diplopia. The cause of diplopia was thoroughly investigated with all potential laboratory and radiological tests in the ED. The neurological examination concluded a 6 cranial nerve palsy, whilst the ophthalmological examination was normal. Miller–Fisher syndrome presents with a triad of ophthalmoplegia, ataxia and areflexia which is confirmed by the detection of an anti-GQ1b antibody.[11] Acute ophthalmoplegia is a cardinal feature of this syndrome, however, the absence of other neurological signs such as areflexia and ataxia makes this diagnosis unlikely. Consequently, it was not unnecessary to do the antibody tests because of the absence of ataxia and areflexia in our patient.[7,8,12] Brain CT and MRI were normal which exclude any potential central nervous system causes of diplopia such as stroke or an increase in intracranial pressure (ICP) causing a stretch of the abducent nerve (Fig. 3A–D). The patient denied any history of chronic illness. However, we carried out some laboratory tests including thyroid function tests and HbA1C which excluded thyroid and diabetes as possible etiologies of ophthalmoplegia.[13,14] The only abnormal investigation was CXR showing resolved pneumonia (Fig. 2) and positive Covid-19 test 3 weeks prior to the onset of ophthalmoplegia. Encephalomyelitis was reported in other cases of Covid-19 presenting with disturbed conscious level and seizures which was not the case in our study. We hypothesized that the onset of ophthalmoplegia is directly related to viral invasion of the neuronal tissue of the abducent

Table 1

Basic and clinical demographic characters of included patients.

Author/ year	Case N.	Gender	Age	Time from respiratory symptoms to ophthalmological symptoms	Ophthalmological symptoms	Region affected	Concomitant neurological symptoms
Dinkin 2020[8]	1	Male	36	4 d	Left ptosis, Diplopia, limited depression and adduction	Partial left oculomotor palsy progressed to bilateral abducent nerve palsy	Bilateral distal leg paresthesia. Lower extremity hyporeflexia and hypesthesia, and gait ataxia
	2	Woman	71	NA	Painless diplopia	Right abduction palsy	NA
Falcone 2020[4]	1	Male	32	3 d	Acute binocular, horizontal diplopia on waking	Complete left abducent nerve palsy	NA
Pascual-Goñi 2020[18]	1	Woman	60	10 d	Diplopia	Right abducent nerve palsy	Right hemi cranial headache
	2	Woman	35	NA	Diplopia	Bilateral abducent nerve palsy	Progressive encephalopathy (decreased arousal, disorientation, and episodic memory deficits) and mild paraparesis with normal reflexes
Oliveira 2020[2]	1	Male	69	11 d	Binocular diplopia	Bilateral paresis of the fourth cranial nerve	Cerebral vasculitis with severe stabbing occipital headache
Greer 2020[27]	1	Woman	43	3 d	Acute painless binocular diplopia, worse in the far gaze and on the left lateral gaze	Left abducent nerve palsy	NA
	2	Male	52	1 wk	Acute horizontal binocular diplopia, worse in the distance and left gaze. Abduction deficit of the left eye as well as decreased saccadic velocity and an esotropia on an alternate cover test self-performed by the patient	Isolated left sixth nerve palsy	NA
Ordás 2020[31]	1	Male	62	3 wk	Binocular vertical diplopia blurred vision and dilated left pupil	Right trochlear nerve palsy	NA
Belghmaidi 2020[24]	1	Woman	24	3 d	Acute onset of diplopia and strabismus of the left eye	Incomplete palsy of the third cranial nerve	NA
Sanayet 2020[33]	1	Woman	55	10 d	Marked diplopia on right lateral gaze, a right-sided convergent squint with restriction of right lateral gaze	Right-sided 6th cranial nerve palsy	Headaches
Pascual-Prieto J, 2020[25]	1	NA	NA	14 d	Diplopia	IV right pair	NA
	2	NA	NA	19 d		VI right pair	
	3	NA	NA	11 d	Diplopia	VI right pair	
	4	NA	NA	30 d	Diplopia	IV right pair	
	5	NA	NA	NA	Diplopia	VI right pair	
	6	NA	NA	NA	Diplopia	III left pair	
	7	NA	NA	NA	Diplopia	III left pair	
	8	NA	NA	15 d	Diplopia	VI pair bilateral (at onset)	
Fitzpatrick 2020[3]	1	Male	67	N/A	Double vision and left ptosis, supraduction, adduction and infraduction deficits and the left pupil was 1mm larger than the right	3rd nerve palsy	NA
Ben-David 2020[19]	1	Male	44	NA	Binocular diplopia and a limitation to abduction in the left eye	Isolated abducent paresis	Headache, Generalized muscle weakness
Oliveira 2020[2]	1	Male	69	11 d	Binocular diplopia	Bilateral paresis of the fourth cranial nerve	Mild then a severe stabbing occipital headache
Consuelo Gutierrez-Ortiz 2020[7]	1	Male	50	5 d	Vertical diplopia, right hypertropia in all fields of gaze, severe limitations to the adduction and downgaze movements of his right eye, and left eye nystagmus on left gaze	Right internuclear ophthalmoparesis and right fascicular oculomotor palsy	Perioral paresthesia, and gait instability, absent deep tendon reflexes in the upper and lower limbs
	2	Male	39	3 d	Acute onset of diplopia, esotropia of 10 prism diopters at distance and 4 prism diopters at near, severe abduction deficits in both eyes, and fixation nystagmus, with the upper gaze more impaired	Bilateral abducent palsy	All deep tendon reflexes were absent
Victor Soto Insuga 2020[28]	1	Male	7	3 d	Convergent strabismus, blurred vision, binocular diplopia and pain with eye movements	Bilateral papilledema and sixth cranial nerve palsy of the left eye	Hypogeusia, and hyposmia

(*Continued*)

Table 1
(*Continued*)

Author/ year	Case N.	Gender	Age	Time from respiratory symptoms to ophthalmological symptoms	Ophthalmological symptoms	Region affected	Concomitant neurological symptoms
Lantos 2020[12]	1	Male	36	4 d	Left eye drooping, blurry vision and diplopia	Partial left third nerve palsy, progressive ophthalmoparesis (including initial left CN III and eventual bilateral CN VI palsies)	Ataxia and reduced sensation and paresthesia in both legs
Baccarella 2020[21]	1	Male	9	7 d	Diplopia	Right abducent palsy without papilledema	Elevated ICP (Headache)
	2	Male	6	NA	Diplopia	Right abducent palsy and bilateral papilledema	Elevated ICP (Headache)
Faucher 2020[26]	1	Male	21		Binocular horizontal diplopia, Oculomotor examination showed strabismus with a constant exotropia of the left eye in primary position, showed vivid and diffused osteotendinous reflexes, with bilateral Hoffmann sign, Hess-Lancaster test evidenced the partial left third cranial nerve palsy)	Partial left third cranial nerve palsy	NA

ICP = intracranial pressure.

nerve. SARS-CoV-2 uses spike protein to gain access to different tissues by attachment to ACE2 receptors expressed on the surface of different cell types including respiratory, gastrointestinal, and neurological cells.[15,16] The patient improved with supportive management which illustrates the transitory state of viral activation in neuronal tissue. These manifestations could be considered in light of neurological complications of the MIS. Adults with MIS are often confused with biphasic acute Covid-19 infections and post-acute sequelae of SARS-CoV-2 infections due to the occurrence of other types of hyperinflammation associated with Covid-19 However, there is also no evidence that multisystem inflammatory syndrome in adults is correlated with SARS-CoV-2 infection and antecedent acute Covid-19 infection.[17]

During our review, we checked all previously reported cases of ophthalmoplegia in the setting of Covid-19. Some cases reported additional neurological manifestations besides ophthalmoplegia such as bilateral distal leg paraesthesia, hyporeflexia and ataxia suggesting Miller–Fisher syndrome.[8] Other cases experienced right hemi-cranial headache or progressive encephalopathy with MRI showing T2 hyperintensity of Abducent nerve and other brain regions including the hypothalamus, tegmentum, mammillary body, thalami and pituitary stalk.[18] Oliveira et al[2] reported a case of severe stabbing occipital headache as a result of vertebrobasilar system vasculitis. Headache was reported in 2 case reports without any signs of increased ICP,[19,20] while it was part of increased ICP manifestation in the other 2 cases.[21] Lightheadedness and vertigo were reported in a 60-year-old male along with the sudden onset of diplopia, vertical gaze palsy and scotoma due to right branch retinal artery occlusion.[22] Finally, one patient experienced coma and quadriplegia due to brainstem lesions on MRI, while another experienced right hemiparesis due to the absence of blood flow in the left internal carotid artery which was explained by the presence of echogenic material at the bifurcation of the common carotid artery.[23]

The affection of the third cranial nerve (oculomotor nerve palsy) was reported in 8 patients,[3,7,8,12,24–26] while affection of the fourth cranial nerve (trochlear nerve palsy) was reported in four patients. Finally, palsy of the sixth cranial nerve (Abducent) was reported in seventeen cases[4,7,8,12,18–21,25,27,28] Abducent nerve affection has the largest number of reported cases. Whether there is a predilection for SARS-CoV-2 infection of the Abducent nerve compared to other oculomotor nerves remains a question to be answered. Some patients experienced ophthalmoplegia due to stroke through affection of the occipital lobe, brainstem[29,30] or right branch retinal occlusion.[22]

The pathology was detected by MRI in most cases while it was unclear in others..[20,24,28,31] In our case, MRI was normal as in (Fig. 3A–D) which may be due to early imaging before pathology became apparent. In other cases, only CT was done because of limited access to facilities during Covid-19 or patient family refusal.[7,19,25]

Management was supportive treatment using hydroxychloroquine or Azithromycin used in some cases.[4,8,12,18,24,26] Corticosteroids were used in the management of other cases.[2,20,30,31]

4.1. Strength and weakness

Currently, this study provides the biggest and most recent data regarding the causal pathogens of Covid-19-induced ophthalmoplegia, its diagnosis, and its etiology. Using a systematic search strategy, a comprehensive search of databases was conducted to identify cases for this review. Despite the stringent inclusion criteria, we cannot exclude the possibility that some important cases might have been missed in larger series, given that some patient data was not available. Another limiting factor is publication bias, as reports of rare or atypical observations are more likely to be published, thereby potentially excluding more common ones.[32]

5. Conclusion

To conclude, physicians should consider Covid-19 as a possible cause of ophthalmoplegia and consider it as a presenting symptom of Covid-19. A high degree of clinical suspicion is needed for diagnosis. Ophthalmoplegia should be investigated with laboratory and radiological tests to determine the pathology and be treated properly in a timely manner to prevent further complications. Usually, the full resolution will occur spontaneously if there is no cause identified. Supportive management and follow-up are suggested in this situation (Fig. 4).

Table 2

The data extracted from previous case reports.

Author/year	Case N.	Imaging studies performed	Imaging results	TTT received (drug regimen)	The time needed for recovery
Dinkin 2020[8]	1	MRI	Revealed enhancement, T2-hyperintensity, and enlargement of the left oculomotor nerve	IV immunoglobulin, 2g/kg, for 3 d – hydroxychloroquine, 600 mg bid for 1 d – then 400 mg QD for 4 d	3 d after admission
	2	MRI	Enhancement of the optic nerve sheaths and posterior Tenon capsules	Hydroxychloroquine, 600 mg bid for 1 d – then 400 mg QD for 4 d	2 wk after discharge
Falcone 2020[4]	1	MRI	Atrophic left lateral rectus muscle which was hyper-intense on T2	Hydroxychloroquine, 5 d	NA
Pascual-Goñi 2020[18]	1	MRI	T2 hyperintensity in right VI cranial nerve nuclei, tegmentum, hypothalamus, mammillary body hypothalamus and the pituitary gland	Hydroxychloroquine and azithromycin	1 mo after admission
	2	MRI	T2 hyperintensity in the VI cranial nerve nuclei, thalami, medial temporal lobes, mammillary bodies, hypothalamus and upper pituitary stalk)	Thiamin and pyridoxine	1 mo
Oliveira 2020[2]	1	MRI	Vasculitis of the vertebrobasilar system, with inflammatory signs in the periaqueductal region, along the topography of the trochlear nuclei	Methylprednisolone	5 d
Greer 2020[27]	1	MRI	NA	NA	NA
	2	NA	NA	NA	(Day 14 of symptoms onset)
Ordás 2020[31]	1	Unrevealing MRI		Oral prednisone, tapering dose, 4 wk	NA
Belghmaidi 2020[24]	1	Unrevealing MRI		Chloroquine, 500 mg, "2 times per day for 10 d" – azithromycin, 500 mg QD for 1 d – Then 250 mg QD for 5 d – vitamin C, 1 g bid, 10 d – Zinc, 90 mg bid, 10 d	5 d
Sanayet 2020[33]	1	Unrevealing MRI		IV Methyl Prednisolone, IV Remdesivir, Subcutaneous Enoxaparin, supplemental Oxygen	1 wk after admission
Pascual-Prieto J, 2020[25]	1 2 3 4 5 6 7 8	Unrevealing CT scans	Imaging tests (computerized tomography) did not reveal findings in the patients	NA	NA
Fitzpatrick 2020[3]	1	Head CTA and brain MRI	MRI (scattered nonspecific T2/FLAIR hyperintensities that could be reflective of microvascular ischemic changes vs inflammatory lesions)	NA	3 mo after discharge
Ben-David 2020[19]	1	Computed tomography of the head		Azithromycin, hydroxychloroquine, 5 d	10 d after discharge
Oliveira 2020[2]	1	MRI with MRI angiography	Signs of vasculitis of the vertebrobasilar system, as well as inflammatory radiologic signs in the periaqueductal region, the topography of the trochlear nuclei	IV methylprednisolone, 5 d	NA
Consuelo Gutierrez-Ortiz 2020[7]	1	CT without contrast		IV immunoglobulin, 0.4 g/kg, 5 d	2 wk after discharge
	2	CT without contrast		Acetaminophen and telemedicine	NA
Victor Soto Insuga 2020[28]	1	Unravelling Magnetic resonance venography – optical coherence tomography (154/151 µm right/left eyes)		Oral azithromycin, 5 d – low molecular weight heparin – IV methylprednisolone, 20 mg/kg/d, 5 d – oral acetazolamide, 20 mg/kg/d	2 d after starting the treatment
Lantos 2020[12]	1	MR imaging of the brain, including high-resolution imaging of the orbits and retro-orbital region	Striking enlargement, prominent enhancement with gadolinium, and T2 hyper-intense signal of the left cranial nerve (CN) III	IV immunoglobulin, hydroxychloroquine	NA
Baccarella 2020[21]	1	MRI and venography	Normal	Lumbar puncture/institution's MIS-C protocol/acetazolamide	2 d after admission

(*Continued*)

Table 2

(*Continued*)

Author/year	Case N.	Imaging studies performed	Imaging results	TTT received (drug regimen)	The time needed for recovery
	2	MRI brain and orbits	Kinking and distention of the bilateral optic nerve sheaths with protrusion of the optic discs into the globes, consistent with increased ICP	Vasopressor support in ICU/our institution's MIS-C protocol/Steroid taper at home	NA
Faucher 2020[26]	1	Brain MRI	Arterial micro-ectasia	For respiratory symptoms: Cefotaxime, Rovamycine and Hydroxychloroquine/ preventive anticoagulation with low molecular weight heparin twice per day in ICU	7 d

CT = comptuted tomography, ICP = intracranial pressure, MIS = multisystem inflammatory syndrome, MRI = magnetic resonance imaging, TTT = time-targeted therapy.

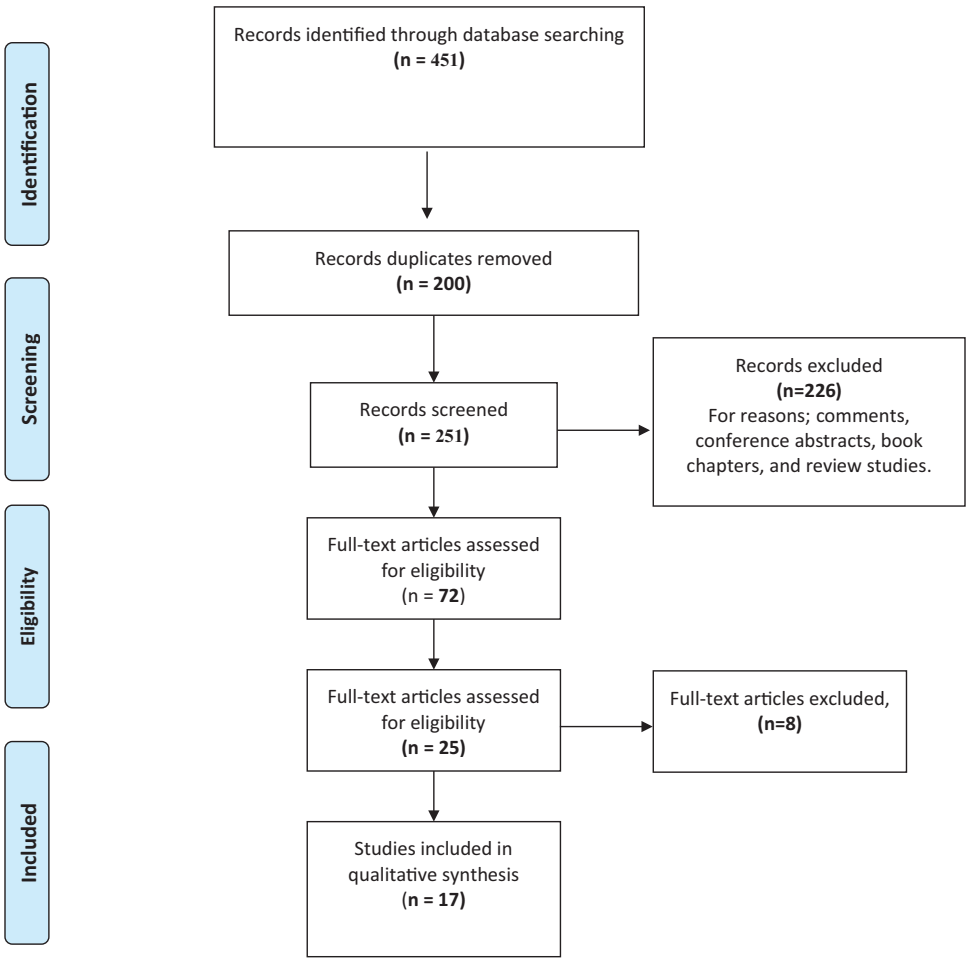

Figure 4. Prisma flow diagram of the included studies.

Author contributions

Conceptualization: Mostafa Meshref, Nour Shaheen.
Methodology: Mostafa Meshref, Nour Shaheen.
Writing – original draft: Mostafa Meshref, Nour Shaheen.
Writing – review & editing: Mostafa Meshref, Nour Shaheen, Sarya Swed, Mohamed Ibrahim, Mostafa Reda Mostafa, Mohamed Osman Algazar, Monica Dobs, Sarah Ibrahim Elsayed, Yara Amro, Ahmed Afsa, Mostafa Ebraheem Morra.

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