

Abducens Nerve Palsy Due to Coronavirus Disease (COVID-19)

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Abstract

The main causes of N.VI paralysis in adults are microvascular disease, vasculopathy, tumors, and inflammatory conditions. However, recent studies suggest that neurotropic viruses may be the etiology of N.VI paralysis. COVID-19 also has neurotropic and neuroinvasive capabilities that make the eye susceptible to bilateral optic neuritis, papilledema, and cranial nerve paralysis, the most common of which is abducens nerve palsy. The aim of this literature review is to review studies that describe the occurrence of abducens nerve palsy in COVID-19 patients. The literature search began in the period April-May 2022 from the Google Scholar database (<https://scholar.google.com/>). This mini review used the AMSTAR (Assessment of Multiple Systemic Review 2, including randomized and nonrandomized studies) checklist and reviewers independently agreed on the selection of eligible studies and reached consensus regarding which studies to include with inclusion criteria. This mini review found that 75% of cases were strongly associated with viral infection and 25% of cases were strongly associated with COVID-19 vaccination. Only 50% of cases report improvement in abducens nerve palsy. This has the implication that with the increasing prevalence of COVID-19 worldwide, ophthalmologists should be aware that abducens nerve palsy may be part of COVID-19.

Keywords: abducens nerve paralysis, corona, COVID-19

Kelumpuhan Saraf Abducens Akibat Penyakit Virus Corona (COVID-19)

Abstrak

Penyebab utama kelumpuhan N.VI pada orang dewasa adalah penyakit mikrovaskular, vaskulopati, tumor, dan kondisi inflamasi. Namun, penelitian terbaru menyatakan bahwa virus neurotropik dapat menjadi etiologi paralisis N.VI. COVID-19 juga memiliki kemampuan neurotropik dan neuroinvasif yang membuat mata menjadi rentan terhadap neuritis optik bilateral, papilledema, dan paralisis saraf kranial, dan yang paling sering terjadi adalah kelumpuhan saraf abducens. Tujuan literature review ini adalah meninjau studi yang menggambarkan terjadinya kelumpuhan saraf abducens pada pasien COVID-19. Pencarian literatur dimulai pada periode April-Mei 2022 dari database Google Scholar (<https://scholar.google.com/>). Mini review ini menggunakan ceklis AMSTAR (Assessment of Multiple Systemic Review 2, including randomized and nonrandomized studies) dan reviewer secara independen menyepakati pemilihan studi yang memenuhi syarat dan mencapai konsensus mengenai studi mana yang akan dimasukkan sesuai kriteria inklusi. Mini review ini menemukan bahwa 75% kasus berhubungan kuat dengan infeksi virus dan 25% kasus berhubungan erat dengan vaksinasi COVID-19. Hanya 50% kasus yang melaporkan perbaikan kelumpuhan saraf abducens. Hal tersebut memiliki implikasi bahwa dengan meningkatnya prevalensi COVID-19 di seluruh dunia, dokter mata harus menyadari bahwa kelumpuhan saraf abducens mungkin merupakan bagian dari COVID-19.

Kata Kunci: Corona, COVID-19, kelumpuhan saraf abducens

How to Cite :

Goenawan, K., Mahayana, I. T. Abducens Nerve Palsy Due to Coronavirus Disease (COVID-19). J Kdkt Meditek, 2023: 29(3), 342-347. Available from: <https://ejournal.ukrida.ac.id/index.php/Meditek/article/view/2805/version/2835> DOI: <https://doi.org/10.36452/jkdoktmeditek.v29i3.2805>

Introduction

The most prevalent isolated cranial nerve palsy is abducens nerve palsy. It is due to its long path as its unique anatomy. There are various etiologies of abducens nerve palsy. To determine the etiology of abducens nerve palsy, it is required to understand the nerve path. Abducens nerve palsy can result from pathologic mechanisms along the nerve's course, including the brainstem, pons, postine cistern, petroclival region, cavernous sinus, or orbital region.¹ Lesions might be isolated^{2,3} or with additional cranial nerve involvement.⁴ Generally, frequent causes of children's abducens nerve palsy are often associated with postviral or postvaccination, idiopathic, trauma, elevated intracranial pressure, neoplasm, or viral infections,⁵⁻⁷ while in adults are microvascular diseases, vasculopathies, tumors, and inflammatory conditions.^{8,9} Ten years cohort study showed the etiologies of old population were presumed to be vascular (56.6%), idiopathic (27.2%), neoplastic (5.6%), and traumatic (4.9%).¹⁰ However, several case report have shown that Coronavirus Disease/COVID-19 (neurotropic virus) or even the vaccine may play a role to the causes.¹¹⁻¹⁸ The aim of this study was to review studies that describing the occurrence of abducens nerve palsy in COVID-19 patients.

Method

Literature search was commenced during the period of April-May 2022 from Google Scholar

database (<https://scholar.google.com/>). Keywords for the review were “covid-19” OR “SARS-CoV-2” OR “vaccination” AND “abducens palsy” OR “sixth cranial nerve palsy”. Paper were examined in terms of palsy linked to the covid-19 or its vaccine. All the case reports were included in this review. Inclusions were include studies with human subjects only, case series or case report study, in English and adhere with the keywords. Exclusions criteria were review, mini review and opinion manuscript. Using AMSTAR (Assessment of Multiple Systematic Review 2, including randomized and nonrandomized studies) checklists. A reviewer independently agreed on selection of eligible studies and achieved consensus on which studies to include.

Result and Discussion

Clinical presentation

Hitherto, there are only a scarce of case reports describing isolated cranial nerve palsies post SARS-CoV-2 infection. Based on the literature search on google scholar using keyword: “covid-19” OR “SARS-CoV-2” OR “vaccination” AND “abducens palsy” OR “sixth cranial nerve palsy”, it showed there were 1840 results (April 2022). After removing the duplicate and looking for covid-19 causes or its vaccines, 15 appropriate case reports has been added to this review (Table 1).

Table 1. Summary Case

No	Author	Age	F/M	Onset	Virus/vaccine	Other symptoms	Laterality	CT Scan/MRI	Therapy	Follow-up	Resolve
1	Anilkumar et al. ¹¹	44	F	0,5	Virus	No	Right	Normal	no	2	Yes
2	Bingöl Kızıltunç et al. ¹²	28	F	10	Virus	No	No data	Normal	no	8	Yes
3	Medeiros et al. ¹³	48	M	18	Virus	No	No data	No data	orthopic + fresnel	32	Yes
4	Pawar et al. ¹⁴	23	M	7	Covishield	No	No data	Normal	no	6	Yes
5	Ben-David et al. ¹⁵	44	M	2	Virus	No	No data	No data	no	No data	No data
6	Veisi et al. ¹⁶	No data	M	7	Sinopharm	No	No data	No data	No data	8	Yes
7	Pereira et al. ¹⁷	65	M	3	AstraZeneca	No	No data	Normal	no	No data	No data
8	Falcone et al. ¹⁸	32	M	3	Virus	No	No data	Abnormal ^d	no	5	No
9	Francis ¹⁹	69	F	8	Virus	Yes ^a	No data	No data	no	6	Yes
10	Pascual-Goñi et al. ²⁰	35	F	21	Virus	Yes ^b	Bilateral	Abnormal ^e	no	4	Yes
11	Pascual-Goñi et al. ²⁰	60	F	10	Virus	No	Right	Abnormal ^f	no	4	No
12	Corrêa et al. ²¹	25	F	6	Virus	Yes ^c	Right	Abnormal ^g	oral prednisone, 60 mg /day, for 7 days	1	Yes
13	Mbchb et al. ²²	62	F	0	Virus	No	Bilateral	No data	No data	No data	No data
14	Manolopoulos et al. ²³	41	F	2	Virus	No	Right	Normal	no	1	Yes
15	Reyes-Capo et al. ²⁴	59	F	2	Pfizer-BioNTech	No	No data	Normal	no	No data	No
16	Voitenkov et al. ²⁵	2	M	1	Virus	No	Bilateral	Normal	No data	No data	No data

^a Anosmia ;^b Neurologic examination showed decreased arousal, disorientation, episodic memory deficits, bilateral abducens nerve palsy, and mild paraparesis with normal reflexes ;^c Vertigo, muscle weakness in the right side of the face, and difficulty in closing the right eye ;^d Sixth nerve atrophy;^e Axial FLAIR demonstrates HI in the tectum of the midbrain and subtle HI in the medial temporal lobes. Coronal FLAIR shows a prominent HI in the periventricular region of the III ventricle and in the mammillary bodies, and subtle HI in the medial temporal lobe ;^f Axial FLAIR shows HI in the tegmentum, involving the right abducens nucleus ;^g a hyperintense focus on T2-weighted imaging, associated with restricted diffusion, in the caudal portion of the pons, medial to the sulcus limitans, in the right abducens nerve nucleus

Fourteen of the case reports showed covid-19^{11-13, 15, 18-23} or the vaccine^{14, 16, 17, 24} affects adults or young adults, and only one case report showed there was 2 years old boy that have bilateral abducens nerve palsy.²⁵ Isolated abducens paralysis^{11-18, 20, 22-25} or with other cranial involvement¹⁹⁻²¹ due to COVID-19 have been reported. Since the affected anatomy is the same, the signs and symptoms of this disease are the same

regardless of the cause, that is including binocular diplopia, unilateral or bilateral diminishing of abduction (there is no laterality predilection), and eso-deviation (eye turned in toward the nose). There is no risk factor of who can attain this palsy as all the patients are in healthy condition and had comorbidities including diabetes mellitus or hypertension. In addition to abducens nerve palsy, vertigo, muscle weakness in the affected side of the

face, difficulty in closing the right eye,²¹ anosmia,¹⁹ decreased arousal, disorientation, episodic memory deficits, and mild paraparesis with normal reflexes²⁰ have been reported.

Physical examination also showed no difference between general abducens nerve or due to post COVID-19 infection. To elaborate, ophthalmologic examination typically shows esodeviation, while movement of the affected eye to temporal is worse. Although there is movement paralysis, it shows good intraocular pressure, unremarkable pupillary reaction, anterior chamber, or fundus exam. Two of the case report normal CT Scan.^{17,25} Ten cases reports did MRI, 6 of it showed unremarkable result,^{11, 12, 14, 23-25} 3 of it showed hyperintense focus on T2,^{20, 21} one case report showed magnetic resonance imaging obtained 5 weeks after the onset of diplopia demonstrated an atrophic left lateral rectus muscle, consistent with denervation.¹⁸

The precise mechanism of the neurological symptoms caused by the coronavirus is remain unknown and still developing. According to research, SARS-CoV-2 infection can lead to a sheer immune response in some people, which can result in inflammatory nerve injury. The hypothesis is pro-inflammatory cytokines (not clear yet) lead to demyelination resulting in slower or may stop the nerve impulses, causing the symptoms.^{24, 26} In vitro study show that the virus has neurotropic and neuroinvasive properties. SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) to enter the host cells. Pathway route of the virus is still unknown (whether hematogenous or other mean), but it is believed that the virus has the abilities to bypass the intrinsic and native defences of the nerve, then bind into surface of host cell which cascade multiplication of the virus inside cell.²⁷ Although the virus has neuroinvasive properties, the way it can produce direct damage (axonal death or denervation) is unclear. On the other hand, some researcher believed direct damage by attached virus may also play a role.^{13, 18}

Treatment

Assuming that the patient acquires the palsy due to virus or vaccine, the prognosis is better than the usual causes (e.g. microvascular disease). Furthermore, without any medication (however,

there is one case report use oral prednisone, 60 mg/day, for 7 days),²¹ the clinical symptom of the COVID-19 gradually improve. Therefore, the main goal of treatment is healing the patient from COVID-19. In other word, treatment for abducens nerve palsy due to COVID-19, would be dealings for COVID-19 infection itself, while ophthalmologist also supporting the symptomatic treatment due to diplopia of strabismus. Yet, three case report showed lack of improvement even after 5 weeks after the onset of symptoms,¹⁸ and no improvement at all.^{20, 24} Author suggest that the causes of non-healing palsy might be denervation or axonal death cell that our body cannot repair due to nature of the cell itself.

Our suggestion for this case is to observe without directly treat the diplopia. The therapy can be gentle and non-confrontational in nature. On the occasion the patient feels uncomfortable due to diplopia, we can suggest for using one eye (one eye closed using blindfold) and wait until the symptom generally disappear after the treatment of COVID-19 itself.

Other modalities for abducens nerve palsy including correction of refractive errors, pharmacological therapy, and extraocular muscle surgery. One case report use orthoptic and Fresnel lens while waiting for the symptom disappear.¹³ As for pharmacological therapy, one case report the usage oral prednisone, 60 mg/day, for 7 days with good result (although it is almost the same without medication).²¹ It is logic to use steroid since the mechanism proposed is patient's immunological reaction. However, further research is needed for the uses, doses, and complication. There was no case report had done the surgery. Surgery might be done for the refractory palsy that the diplopia needs to be corrected after the infection cured.

Conclusion

It was found that 75% of cases associated strongly with the virus infection and 25% cases associated with the COVID-19 vaccination. Only 50% cases reported the improvement of abducens nerve palsy. Because the prevalence of COVID-19 is increasing worldwide, ophthalmologists must recognize that abducens nerve palsy may be part of the disease's neurologic spectrum. The natural course of the disease makes us no need to do immediate treatment. We recommend every ophthalmologist to do COVID-19 screening for

case of unexplained sixth nerve palsy although it is still a minor cause.

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