



Epidemiology, clinical features, and treatment modalities of facial nerve palsy in COVID-19 patients: a systematic review

Aya Turki^{1,2} · Kirellos Said Abbas^{2,3} · Abdelrahman M Makram^{2,4,5} · Mostafa Elfert^{2,6} · Mahmoud Elmarabea^{2,6} · Nahla Ahmed El-Shahat^{2,7} · Hassan Abdalshafy^{1,2} · Akua Sampong^{2,8} · Sirisha Chintalapati^{2,8} · Nguyen Tien Huy^{2,9}

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Abstract

Background Coronavirus disease 2019 (COVID-19) is responsible for a wide variety of multi-system clinical features. Facial nerve palsy (FNP) is identified as one of the neurological complications of the virus. This work aims to systematically review the clinical picture, laboratory/imaging findings, treatment options, and prognostic factors of FNP in COVID-19 patients.

Methods Using six online databases, a search was conducted to include all articles with patients infected with COVID-19 and presenting with unilateral or bilateral FNP. Screening for eligibility and data extraction were done by three and four independent reviewers, respectively. Descriptive analyses and data visualizations were done using Google Sheets. Survival analysis and Kaplan–Meier plotting were done by R software.

Results The data from 22 studies included 32 patients who were infected with COVID-19 and presented with clinical features of FNP. Fourteen patients were male while 18 were female. FNP affected 29 patients unilaterally and 3 patients bilaterally. The imaging findings confirmed that complications of FNP were COVID-19 related. Additionally, antivirals combined with steroids had the lowest median time (21, IQR = 8) to clinical improvement compared to steroid-only (30, IQR = 15) and antiviral-only (33, IQR = 3.5) treatments.

Conclusion This study has shown a potential correlation between the increased incidence of FNP and COVID-19. We have also found that combining antivirals with steroids may have better outcomes in patients with FNP and COVID-19 although the evidence to support this claim is not strong enough. Further studies are required to assess the extent of linkage between the two conditions and how to properly manage FNP when encountered in COVID-19 patients.

Keywords COVID-19 · SARS-CoV-2 · Facial nerve palsy · Cranial nerve VII palsy

Abbreviations

ACE2	Angiotensin-converting enzyme 2
COVID-19	Coronavirus disease 2019
CSF	Cerebrospinal fluid
CT	Computed tomography
EBV	Epstein–Barr virus
FNP	Facial nerve palsy
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IQR	Interquartile range

MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
RNA	Ribonucleic acid

Introduction

Since its outbreak on the 31st December of 2019, coronavirus disease 2019 (COVID-19) has infected more than 66 million people till the end of November 2020 globally [1]. Although the reported number of cases is massive, many disease mappers believe that the actual burden of this pandemic is higher than anticipated [2]. This is because up to

Aya Turki, Kirellos Said Abbas, Abdelrahman M. Makram equally contributed to the work and share first authorship.

✉ Nguyen Tien Huy
tienhuy@nagasaki-u.ac.jp

Extended author information available on the last page of the article

80% of infected cases are asymptomatic, and 20% of them will remain asymptomatic disease propagators [3] till testing negative [4]. Moreover, the high rate of transmission (R naught) makes it hard to contain the viral spread [5–8].

It takes nearly 5.2 days for the virus to start manifesting. Common symptoms include fever, cough with or without sputum production, sore throat, sneezing, headache, and/or diarrhea [5, 7]. Other symptoms that require immediate care and hospitalization include shortness of breath, bluish discoloration of membranes, persistent chest pain, and new confusion [7]. Atypical, non-respiratory manifestations of COVID-19 include a fruitful of central and peripheral nervous system conditions, such as olfaction and gustation dysfunction, encephalitis, Guillain–Barre syndrome, stroke, neuralgia, epilepsy, and ataxia [9]. Based on recent data published, facial nerve palsy (FNP) rates can be correlated to infection with SARS-CoV-2 [10–13]. One study estimated that the incidence increased from 1.3% in 2019 to 3.5% in 2020 [14].

The pathogenesis of idiopathic FNP is not fully understood to this day. Some researchers found some degree of disrupted blood supply to the nerve through the vasa nervorum. This process can be related to the development of microthrombi, idiopathic vasospasms, or edema [15–18]. During the COVID-19 pandemic, there is also a possibility of direct viral invasion or autoimmune reaction (e.g., Guillain–Barré syndrome) to be the triggers of FNP [19, 20]. The direct invasion hypothesis is suitable for SARS-CoV-2 due to its high selectivity to the angiotensin-converting enzyme 2 (ACE2) receptor [20, 21]. This specific receptor is found on different tissue cell membranes, including the vascular endothelial cells [22] and brainstem glial cells [23], making neurological complications of COVID-19 more logical [21].

The true impact of COVID-19 on the incidence of FNP is yet to be discovered. In this paper, we aim to represent the clinical picture, laboratory/imaging findings, treatment options, and prognosis of FNP in cases suffering from concomitant COVID-19.

Methods

Protocol development and registration

Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24], the protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with ID number CRD42021226404 [25]. Online Resource 1 provides the updated results as a PRISMA checklist. As a systematic review, the manuscript does not contain clinical studies or patient data.

Search strategy

In November 2020, we searched six electronic databases for possible inclusion. In PubMed, we used this search term: [(facial nerve) OR (seventh cranial nerve) OR (facial paralysis) OR (bell’s palsy) OR (facial palsy)] AND (SARS OR MERS OR coronavirus OR coronaviruses OR HCoV OR nCoV OR Cov OR Cov2 OR COVID OR COVID19 OR corona OR coronaviridae). The term was edited to suit the other databases (Scopus, Web of Science, Google Scholar, Virtual Health Library VHL, and Ovid). Online Resource 2 provides the search terms used for each database and the yielded number of articles.

Manual search

Before summarizing the data from the included studies, another PubMed search, in 2021, was done to identify newer articles, if available. Additionally, two manual searches were conducted to trace the references and citations of the included studies using PubMed, Google Scholar, and Scopus to identify any other relevant studies.

Eligibility criteria

The inclusion criteria were applied as follows: any study reporting positive COVID-19 and facial nerve palsy regardless of race, age, sex, language, socioeconomic status, ethnicity, geographical area/place, and publication date. Non-extractable data, duplications, unreliable or incomplete reports, conference proceedings, commentaries, editorial, discussions, books, or book chapters were excluded. Overlapped data sets were also excluded after extensive assessment and revisions. Finally, studies reporting FNP as part of a syndrome like Guillain–Barré syndrome and Melkersson–Rosenthal syndrome were not included.

Article selection

Titles and abstracts were firstly screened for inclusion using the above-mentioned criteria by three independent reviewers. Then, the full texts were obtained and screened with the same procedure. Through discussion, any disagreement was resolved. In case the three reviewers did not reach a consensus, a senior reviewer helped in solving the dispute.

Data extraction

Using Google Sheets, a pilot extraction sheet was developed using the two most relevant articles included. The data extraction process was held in a proximate fashion to the

screening steps where four independent authors extracted the data, compared the results at the end, and solved any differences by discussing them. Further conflicts were resolved by a senior researcher. The extracted data included the study referencing form (first author's last name, year of publication, and country of investigation), basic study characteristics (publishing journal, type of study, and peer-review status), and patients' data (age, sex, comorbidities, medical history, COVID-19 status, side of the affected nerve, other nerves affected besides cranial nerve VII, time of symptom resolution, and the follow-up duration). Data about investigations were also extracted and discussed if available; cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), and computerized tomography (CT) scan.

Quality assessment

Quality assessment of all included studies was performed in the same manner as data extraction. The quality of the included studies was weighed using the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports [26].

Statistical analysis

Basic descriptive statistical analyses and data visualizations were done using Google Sheets. The data was presented in crude and relative numbers using percentages. As for the survival analysis and Kaplan–Meier plotting, they were done using R software version 4.1.1 [27] with the help of the “prodlm” package [28]. Survival analysis was presented in median and interquartile range (IQR).

Results

Results of the literature search

The literature search yielded a sum of 274 studies. Using EndNote X8, 96 duplicates were identified and removed. Only 25 articles of 178 were included after screening titles and abstracts for eligibility. After reading the full texts meticulously and obtaining 10 papers by manual search, we included 22 final papers in our qualitative synthesis. The PRISMA flow diagram of the literature search and screening is illustrated in Fig. 1.

Study characteristics

From the 22 included studies, we extracted the data of 32 FNP patients who were infected with COVID-19. Among the patients, 14 were male and 18 were female. Each patient had been diagnosed with COVID-19 and had experienced either unilateral or bilateral FNP. The mean age was 31.9 years.

Two patients were pregnant and primigravida [10, 29]. Three other patients had cranial polyneuropathy [17, 30, 31]. The average number of days for follow-up was 27 ± 9.3 and 26.3 ± 13 (mean \pm standard deviation) for COVID-19 and FNP status, respectively. The baseline characteristics of each patient are summarized in Table 1. Combined patient baseline characteristics are summarized in Table 2.

Clinical features

FNP symptoms appeared at a median of 7 and a half days after the onset of COVID-19 symptoms. 16 patients experienced FNP on the right side, while 13 patients had it on the left side. Three patients experienced facial nerve palsy bilaterally. According to the House–Brackmann grading system reported, facial nerve damage resulted in mild (grade 2) dysfunction in five patients, moderate (grade 3) dysfunction in four patients, moderately severe (grade 4) in two patients, severe (grade 5) in one patient, and total paralysis (grade 6) in one patient. Four patients presented with drooling, fifteen with ophthalmoplegia, four with facial asymmetry at rest, three with facial numbness, one with tingling in the face, one with jaw pain, nine with facial droop, nine with frontalis muscle involvement, one with decreased sensation, nine with labial commissure deviation, seventeen with facial weakness, but none of the patients presented with parotid swelling nor hyperacusis. Tables 3 and 4 summarize the clinical and laboratory features of COVID-19 and FNP, respectively, in the included patients. Fever was the most encountered symptom of COVID-19 in the population, while facial weakness and ophthalmoplegia represented most of the FNP symptomatology. Figures 2 and 3 provide the frequency of the symptoms or signs with which the patients presented.

Investigation findings

Tests of patients' CSF, in addition to serology, brain MRIs, electroneuromyography, and cerebral vascular imaging were conducted. From the CSF, it was concluded that very few patients exhibited high cell counts, protein levels, glucose levels, or pressure. Tests were not positive in any patients for human immunodeficiency virus (HIV) or herpes simplex viruses 1 and 2 (HSV-1 and HSV-2). Brain MRIs showed facial nerve enhancement in 11 patients. Electroneuromyography showed decreased compound muscle action potential in one patient (Table 4). Chest CT also showed ground-glass opacities in five patients.

Treatment and prognosis

Prednisone and prednisolone were administered to 14 and 6 patients, respectively, while the rest of the patients were given either ciclesonide, dexamethasone, betamethasone,

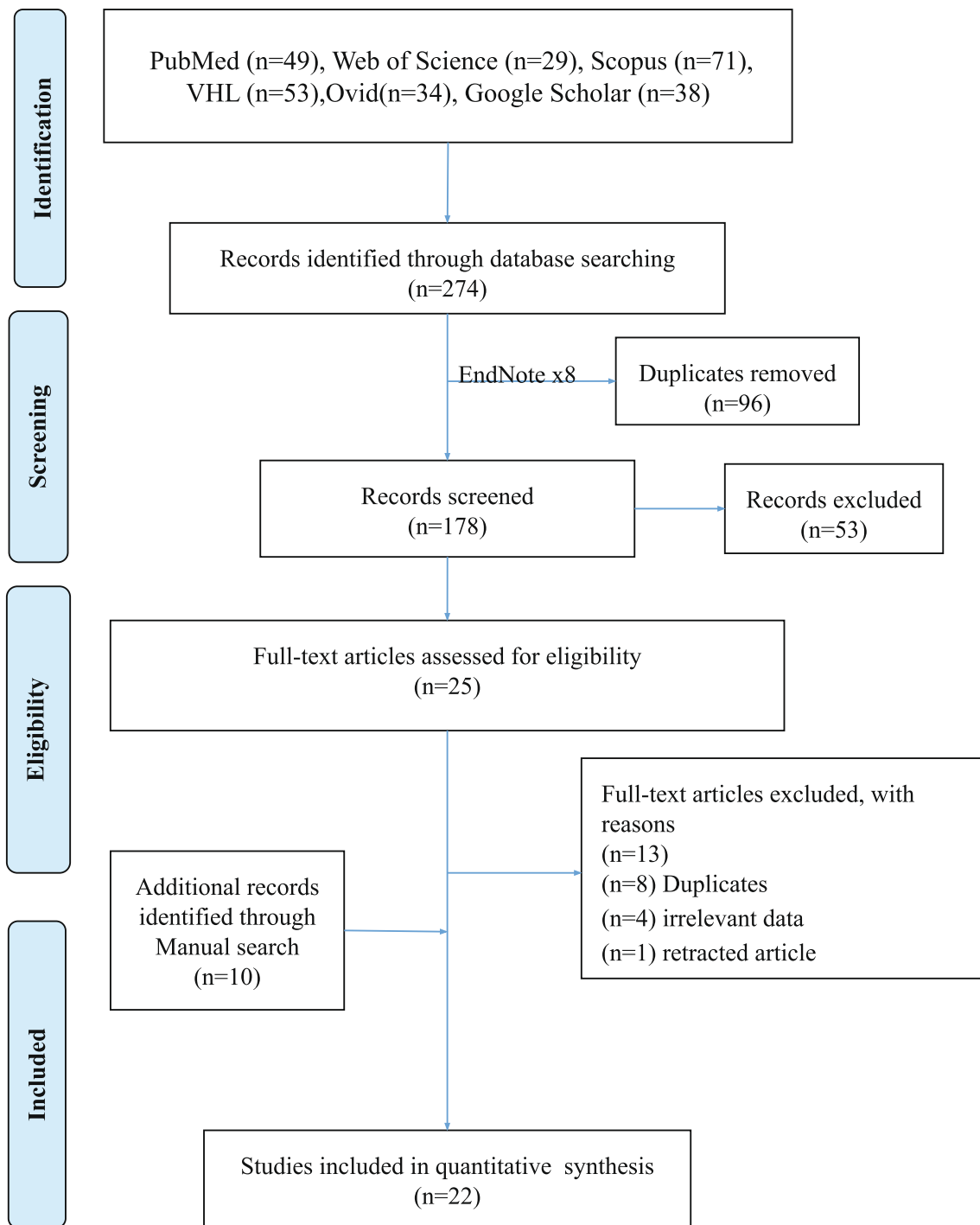


Fig. 1 PRISMA flow diagram of the literature search and screening for eligibility steps

or methylprednisolone. Moreover, only around a third of the patients (37.5%) received antiviral therapy, where acyclovir, valacyclovir, remdesivir, and favipiravir were provided to three, three, two, and one patients, respectively. Only one patient [12] of the patients who received antiviral therapy did not have concomitant corticosteroid administration. For COVID-19, 11 patients recovered

while 1 patient had minimal improvement and 1 patient had definite improvement. Seventeen patients were not reported. For FNP, 20 patients recovered, there was one patient with no improvement and 5 patients who had only minimal improvement with 3 patients for definite improvement. Three patients were not reported (Table 4). Using survival analysis and Kaplan–Meier plotting for the

Table 1 Basic characteristics of the studies and patients included

Reference ID	Patients reported, <i>n</i>	Age, years	Sex	Medical history	COVID-19 diagnosis	COVID-19 outcome	FNP outcome	Follow-up, days
Correa/2021/Brazil [44]	3	25	F	NA	PCR	Recovery	Recovery	NR
		30	F	NA	PCR	Recovery	Recovery	NR
		33	M	NA	PCR	Recovery	Recovery	NR
Lima/2020/Brazil [17]	8	43	F	NA	PCR	NR	Minimal/slight improvement	30
		25	F	NA	PCR	NR	Recovery	30
		33	F	NA	PCR	NR	Minimal/slight improvement	30
		26	F	NA	PCR	NR	Recovery	30
		50	F	NA	PCR	NR	Minimal/slight improvement	30
		38	F	NA	PCR	NR	Recovery	30
		39	F	NA	PCR	NR	Recovery	30
		34	M	NA	PCR	NR	Recovery	30
Ribeiro/2020/Brazil [32]	1	26	M	NA	PCR, chest CT	NR	NR	NR
Mehta/2020/Canada [36]	1	36	M	NA	PCR	NR	NR	NR
Wan/2020/China [12]	1	65	F	NA	PCR, chest CT	NA	Recovery	30
Derollez/2020/France [45]	1	57	F	Overweight (BMI: 27.7 kg/m ²)	PCR	Recovery	Recovery	30
Roussel/2020/France [31]	1	6	F	SCA complicated with cerebral vasculopathy HSCT from a matched-related donor Graft-versus-host disease prophylaxis included CYC and MTX Asymptomatic EBV replication Severe mucositis, aggravated by concomitant HSV-1 reactivation	PCR, chest CT	NR	Definite improvement	NR
Kumar/2021/India [29]	1	28	F	PCOS primigravida (36 weeks of gestation)	PCR	NR	Recovery	14
Karimi-Galou-gahi/2020/Iran [35]	1	60	M	NA	Chest CT	NR	NR	NR
Decio/2020/Italy [41]	1	15 months	F	NA	Serology, clinically	Recovery	Recovery	NR
Homma/2020/Japan [33]	1	35	F	Smoker	PCR, chest CT	Recovery	Recovery	NR

Table 1 (continued)

Reference ID	Patients reported, <i>n</i>	Age, years	Sex	Medical history	COVID-19 diagnosis	COVID-19 outcome	FNP outcome	Follow-up, days
Bastola/2021/Nepal [46]	1	48	M	History of trauma Diabetes mellitus History of vesicular skin lesions, ear discharge, and vision loss Recent exposure to a new vaccine or medication	PCR	Recovery	Definite improvement	45
Dahl/2021/Norway [47]	1	37	M	NA	PCR	Definite improvement	Recovery	NR
Figueiredo/2020/Portugal [10]	1	35	F	Primigravida (39 weeks of gestation)	PCR	Recovery	Minimal/slight improvement	15
Goh/2020/Singapore [11]	1	27	M	NA	PCR, clinically	Minimal/slight improvement	No improvement	7
Neo/2021/Singapore [42]	2	25	M	NA	PCR	NR	Recovery	30
		34	M	NA	Serology	NR	Minimal/slight improvement	30
Cabrera Muras/2020/Spain [34]	1	20	M	NA	PCR, serology	NR	Recovery	21
Casas/2020/Spain [48]	1	32	M	vWD	PCR	Recovery	Recovery	21
García Ochoa-Fernández/2021/Spain [49]	1	6	F	NA	PCR	Recovery	Recovery	49
Gogia/2020/USA [30]	1	58	M	History of trauma COPD Hypertension Non-obstructive CAD	PCR	Recovery	Recovery	21
Theophanous/2020/USA [50]	1	6	M	Asthma Moderate OSA Gastrostomy tube Failure to thrive Chromosomal deletions 17 and 19 Submucosal CP Surgically repaired ASD and VSD Agammaglobulinemia Hyper IgM Hypospadias	PCR	NR	Definite improvement	21

Table 1 (continued)

Reference ID	Patients reported, <i>n</i>	Age, years	Sex	Medical history	COVID-19 diagnosis	COVID-19 outcome	FNP outcome	Follow-up, days
Zain/2021/USA [51]	1	23 months	F	Obesity LGA Resolved MRSA skin infection Erythematous papular rash in the groin area sparing the thighs most consistent with contact dermatitis treated with zinc oxide ointment	PCR	NA	Recovery	21

ASD atrial septal defect, *BMI* body mass index, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CP* cleft palate, *CYC* cyclosporin, *EBV* Epstein–Barr virus, *HSCT* hematopoietic stem cell transplantation, *HSV-1* herpes simplex virus-1, *LGA* large for gestational age, *MRSA* methicillin-resistant staphylococcus aureus, *MTX* methotrexate, *NA* not applicable, *NM* not mentioned, *OSA* obstructive sleep apnea, *PCOS* polycystic ovarian syndrome, *VSD* ventricular septal defect, *vWD* Von Willebrand disease

Table 2 Baseline demographic and geographic features of the included patients

	Number (%)
Total number of patients	32
Age: years, mean (range)	31.9 (1.25–65)
Gender: males/females	14 (43.8)/18 (56.3)
Country	
Brazil	12 (37.5)
Canada	1 (3.1)
China	1 (3.1)
France	2 (6.3)
India	1 (3.1)
Iran	1 (3.1)
Italy	1 (3.1)
Japan	1 (3.1)
Nepal	1 (3.1)
Norway	1 (3.1)
Portugal	1 (3.1)
Singapore	3 (9.4)
Spain	3 (9.4)
USA	3 (9.4)

Table 3 COVID-19 clinical and laboratory features of the included patients

	Number (%)
Diagnostic RT-PCR	
SARS-CoV-2 PCR, positive/negative	30 (93.8)/1 (6.3)
SARS-CoV-2 PCR testing swab type ^a	
Nasopharyngeal swab	16 (50)
Nasal swab	10 (31.3)
Oropharyngeal swab	8 (25)
Tracheal swab	1 (3.1)
Throat swab	1 (3.1)
Outcome and follow-up	
Duration of follow-up in days: mean \pm SD	27 \pm 9.3
Not reported	17 (53.1)
Not applicable ^b	6 (18.8)
Hospital admission	15 (46.9)
Received oxygen support	5 (15.6)
ICU admission	2 (6.3)
Minimal or slight improvement from COVID-19	1 (3.1)
Definite improvement from COVID-19	1 (3.1)
Complete recovery from COVID-19	11 (34.4)
Death	0 (0)

^aSome patients received more than one type of swab for the diagnosis of COVID-19

^bThese patients were asymptomatic for typical COVID-19 symptoms

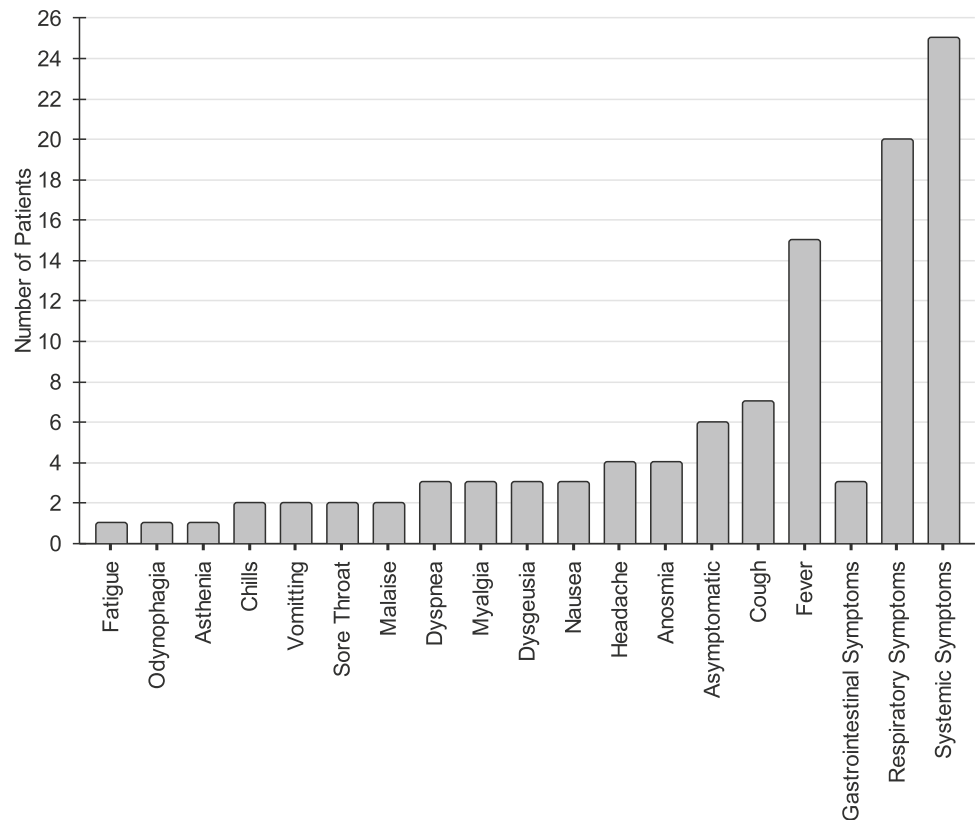
treatment modalities, the median days for improvement for the combination (antiviral + steroids), steroid-only, and antiviral-only were (21, IQR = 8), 30 (IQR = 15), 33 (IQR = 3.5), respectively (Fig. 4).

Table 4 FNP clinical and laboratory features of the included patients

	Number (%)
Diagnosis of FNP	
Bell's palsy	15 (46.9)
FNP showing <i>before</i> COVID-19	13 (40.6)
FNP showing <i>after</i> COVID-19	19 (59.4)
Number of days till onset of FNP after onset of COVID-19 symptoms: median (IQR), (range)	7.5 (4.25–14), (1–28)
Number of days after the onset of FNP till hospital visit: mean \pm SD	4.4 \pm 3.6
Laterality	
Right	16 (50)
Left	13 (40.6)
Bilateral	3 (9.4)
Investigations	
Brain MRI	21 (65.6)
Normal	10 (31.3)
Facial nerve enhancement	11 (34.4)
Right	5 (45.5)
Left	3 (27.3)
Bilateral	3 (27.3)
¹⁸ FDG-PET/CT	1 (3.1)
Normal	1 (100)
Cerebral vascular imaging	1 (3.1)
Normal	1 (100)
Electroneuromyography	1 (3.1)
Decreased compound muscle action potential	1 (100)
Treatment	21 (80.8)
Corticosteroid therapy	23 (71.9)
Prednisone	14 (43.8)
Prednisolone	6 (18.8)
Others (ciclesonide, dexamethasone, betamethasone, methylprednisolone)	4 (12.5)
Duration: days, mean \pm SD	7.5 \pm 1.9
Antivirals	12 (37.5)
Acyclovir	3 (9.4)
Valacyclovir	3 (9.4)
Remdesivir	2 (6.3)
Favipiravir	1 (3.1)
Combined antiviral and corticosteroid therapy	11 (34.4)
Antibiotics	2 (6.3)
Supportive therapy for ocular protection	10 (31.3)
Outcome and follow-up	
Number of days till the outcome after hospital visit: mean \pm SD	26.3 \pm 13
Not reported	3 (9.4)
No improvement	1 (3.1)
Minimal or slight improvement from FNP	5 (15.6)
Definite improvement from FNP	3 (9.4)
Complete recovery from FNP	20 (62.5)

¹⁸FDG-PET/CT (2-fluoro-2-deoxy-D-glucose–positron emission tomography)

Fig. 2 The reported frequency of COVID-19 symptoms in the included studies



Quality assessment

In terms of quality assessment, 7 were good, 14 were fair, and one was poor. Online Resource 3 provides the quality assessment of all the included studies.

Discussion

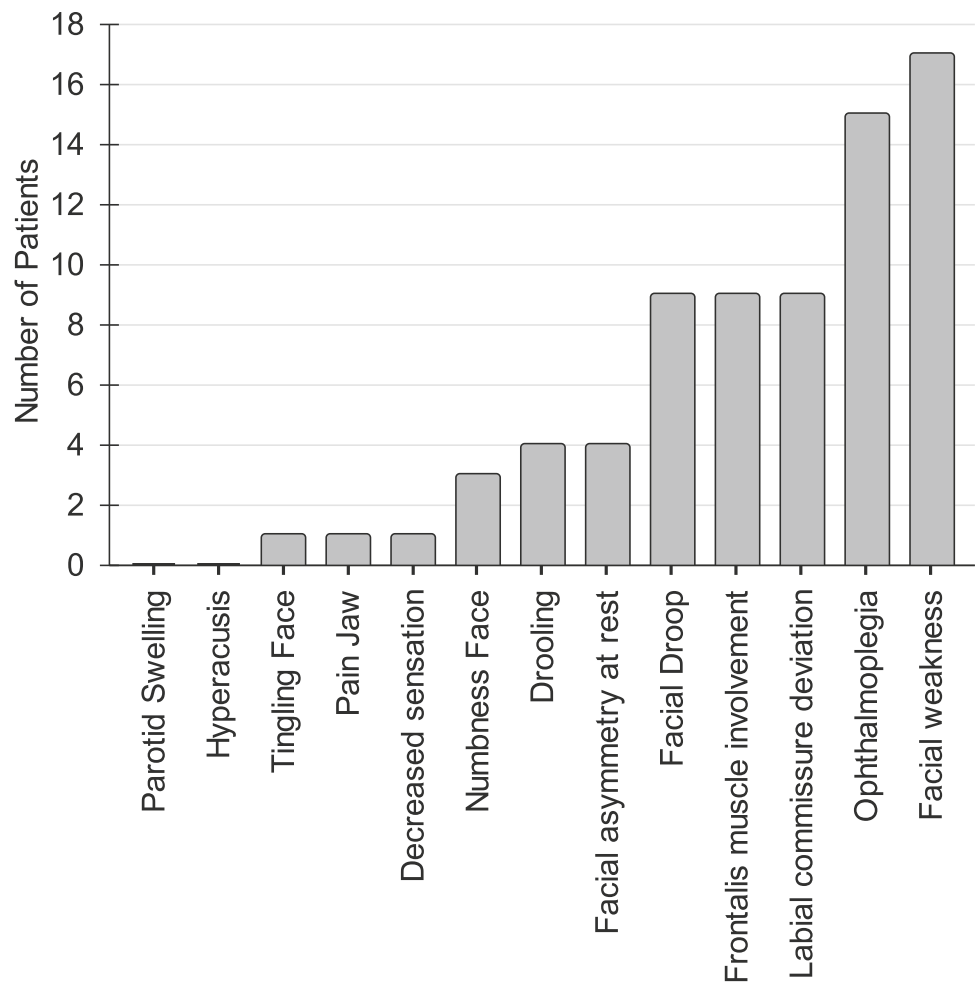
By systematically reviewing the literature for patients suffering from FNP and COVID-19, we were able to identify a potential correlation between the occurrence of FNP and COVID-19. From 22 studies, we were able to extract data from 32 patients.

As FNP pathogenesis can be linked to microthrombi formation, direct viral invasion, or autoimmune reactions [15–18], the hypercoagulability or direct neural invasion of SARS-CoV-2 can be blamed for this increased incidence of FNP. Multiple studies have indicated that patients with COVID-19 had an absence of SARS-CoV-2 viral ribonucleic acid (RNA) in their CSF analyses [17]. Due to the absence of the viral RNA in the CSF, it is possible to rule out direct viral neurotropism as a cause for neurological manifestations [32]. Instead, there is more evidence to suggest that the FNP can be a result of the activation of the angiotensin-converting enzyme (ACE2) receptors in the nervous system. Once SARS-CoV-2 binds to the ACE2 receptors

within the central nervous system, it will induce a release of cytokines that can cause negative effects. The SARS-CoV-2 can enter the central nervous system via mucosa or viremia. This can cause peripheral neuropathies in the facial nerve and olfactory nerve, leading to FNP and anosmia [33]. The cytokine release can lead to immune-mediated inflammatory responses such as ischemia of vasa nervorum and demyelination at the site of the facial nerve [17]. Further research is required to confirm the pathogenesis between FNP and COVID-19.

Regarding diagnostics, there were a high number of patients with COVID-19 presenting with neurological manifestations. Other than these neurological issues, these patients were asymptomatic for COVID-19. Since the patients presented asymptotically, physicians need to be aware of the possible strong correlation between FNP and COVID-19. In the CSF polymerase chain reaction (PCR) analysis of the patients, the cell count and protein levels were normal. There was no CSF evidence of SARS-CoV-2 or any other infections such as Epstein–Barr virus (EBV) and HSV. In one case report, the patient presented with serological evidence of coinfection with EBV and SARS-CoV-2 but lacked evidence of these infections in the CSF PCR [31]. EBV can lead to bilateral nerve palsy and in this case, there is a possibility that this can be linked to COVID-19 [34]. The effect of coinfections and FNP is an avenue for future evaluation.

Fig. 3 The reported frequency of FNP symptoms in the included studies



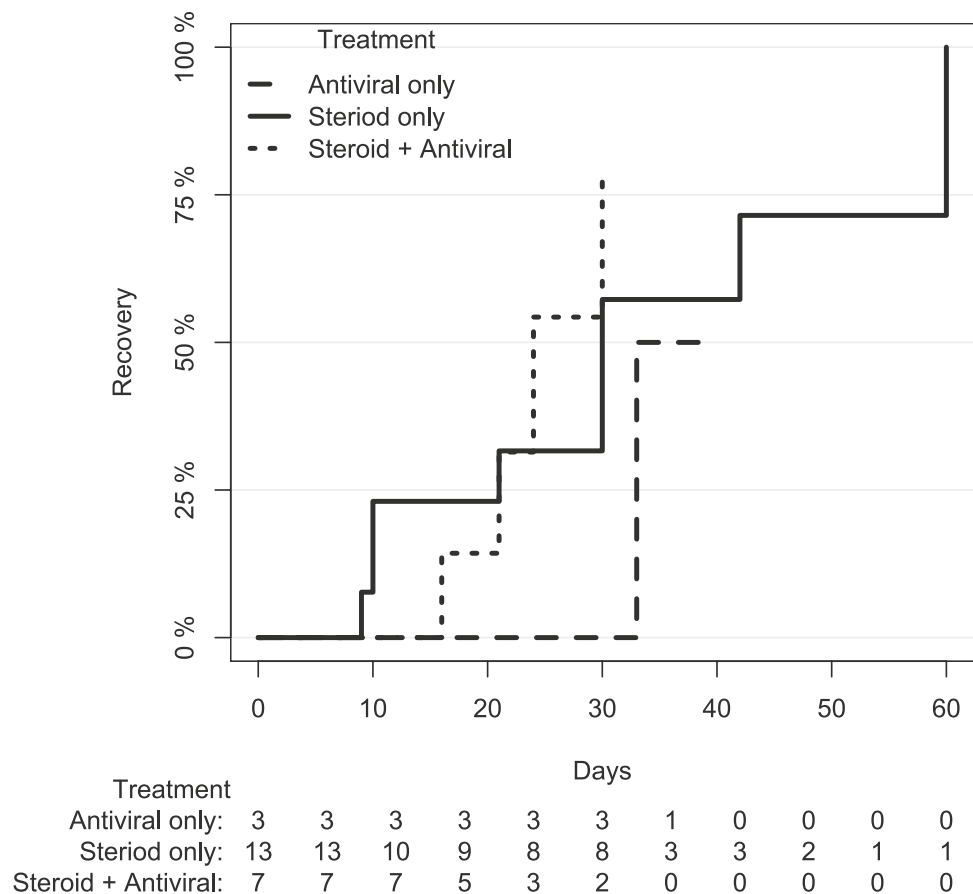
Twenty-three patients out of the 32 included in the review received different steroids as a controlling measure of FNP. Although the exact correlation between steroid usage and FNP is unknown, there were some improvements in FNP when steroids were used. The steroids used include prednisone, methylprednisolone, prednisolone, ciclesonide, dexamethasone, or betamethasone. Using these medications, 20 patients had clinical improvement or recovered completely from FNP, while 1 patient failed to show any recovery [11]. Additionally, three people were not reported [32, 35, 36]. Specifically, glucocorticoids were recommended for the treatment of Bell's palsy, but glucocorticoids can be contraindicated in COVID-19. For short-term COVID-19 cases, glucocorticoids can help decrease inflammation and a reduction in the need for mechanical ventilation. Despite the benefits, glucocorticoid usage can lead to delayed viral clearance and an increased risk of secondary infections [37]. Additionally, in our paper, we found that combining steroids with antivirals can decrease the time till the improvement of FNP using a Kaplan–Meier plot. Since COVID-19 is relatively new, further research is required to understand the correlation between different treatment options such as

corticosteroids. Once that correlation has been established, continuing research must be conducted to analyze effective FNP treatments in concordance with COVID-19 treatments.

COVID-19 has been reported to have caused multiple, devastating non-respiratory complications in the infected population [4, 5, 8, 13]. The incidence of different nervous system inflammatory conditions, whether central or peripheral, has been widely reported in the literature to be increasing in the era of COVID-19 [14]. For instance, patients are more likely to experience anosmia or hyposmia when infected by SARS-CoV-2 than other pathogens belonging to the coronavirus family [2, 19]. Therefore, it is of importance for physicians to suspect COVID-19 when encountering etiologically unexplained neurological manifestations.

This paper encourages physicians to pay close attention to patients presenting with sole FNP, since the etiology of this morbidity may be related to an asymptomatic infection with COVID-19. However, the authors could not identify a way of analyzing the probable incidence of FNP caused by the virus. Another limitation of this study is that the included papers were essentially descriptive of the patients included within. Due to the urgent need for information about the

Fig. 4 Survival analysis with Kaplan–Meier plot showing the performance of steroid-only, antiviral-only, and combined therapy in improvement of FNP symptoms



virus, physicians are unable to conduct analytical studies, which are required to detect dissimilarities in the prevalence of FNP in infected and non-infected cohorts. Also, some papers with ethical issues may pass unnoticed. We have included the study published by Elkhoully and Kaplan at first [38] but excluded it once it got retracted, and we removed it from the qualitative synthesis once we saw the retraction notice [39]. Besides, 25 patients can be considered an insufficient sample size required to confirm precise correlations between COVID-19 and FNP. The insufficient sample size could be related to the low incidence of FNP and COVID-19 due to asymptomatic patients. For example, a study in Italy noted that there was a marked increase in the incidence of FNP from 2019 (before COVID-19) to 2020 (once COVID-19 began) [40]. Since patients with different defining characteristics such as age or gender were compared, this can be another potential limitation. This can cause a false sense of precision due to the unknown effects of the defining characteristics on the potential correlation between FNP and COVID-19. Finally, some papers have based the COVID-19 diagnosis on only the clinical findings, serological testing, and/or CT scan findings without the confirmation of a PCR test [35, 41, 42]. This was widely exercised at the beginning of the pandemic due to the scarcity of PCR tests,

the overwhelming number of new cases, or the high cost of a PCR test, especially in low-to-middle income countries [43]. This systematic review is one of the first reviews performed to establish an important correlation between FNP and COVID-19. Due to the small sample size, the different types of antivirals used, and the insufficient details about the treatment (e.g., when the medications were started), this systematic review does not provide comparative data regarding the treatment modalities that can be used in managing FNP. In future studies, increasing the sample size and conducting a methodical analytical investigation can confirm the correlation between COVID-19 and FNP.

Conclusion

COVID-19 has been linked to an unlimited number of neurological symptoms. In this study, we performed an online literature search of 6 databases, yielding 22 studies reporting 32 patients who suffered from FNP and COVID-19 simultaneously. After comparing various case studies and reports, it is safe to assume that there is a potential correlation between the occurrence of FNP and COVID-19. Moreover, starting a combined antiviral-steroid treatment regimen may decrease

the time needed for improvement although the evidence is not strong enough. However, further studies are warranted to measure the correlation between FNP and COVID-19 and to examine the best treatment modality of FNP in the context of COVID-19.

Clinical correlation

As the pandemic continues, it is crucial to test for and promptly treat SARS-CoV-2 when addressing a patient presenting with FNP. Starting with a combined regimen of antivirals and steroids may improve the clinical manifestations more rapidly.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s13760-022-02026-8>.

Author contributions KSA developed the idea. KSA and AT performed the literature search. KSA, HA, KSA, MEF, and MEM contributed to eligibility screening. MEF, MEM, NA, HA, and AT contributed to data extraction. All members checked for more articles to include via manual search. AMM, AS, and SC contributed to data analysis, manuscript writing, and the formation of tables and figures. All authors approved the final version under the supervision of NTH.

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Availability of data and material The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

References

- World Health Organization: WHO Coronavirus Disease (COVID-19) Dashboard (2020). <https://covid19.who.int/table>. Accessed 28 Nov 2020
- Meng H, Xiong R, He R, Lin W, Hao B, Zhang L et al (2020) CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan. *J Infect* 81(1):e33–e39. <https://doi.org/10.1016/j.jinf.2020.04.004>
- Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C et al (2020) Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 382(10):970–971. <https://doi.org/10.1056/NEJMc2001468>
- Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM et al (2020) Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. *PLoS Med* 17(9):e1003346. <https://doi.org/10.1371/journal.pmed.1003346>
- Giwa AL, Desai A, Duca A (2020) Novel 2019 coronavirus SARS-CoV-2 (COVID-19): an updated overview for emergency clinicians. *Emerg Med Pract* 22(5):1–28
- Lopez-Villegas A, Maroto-Martin S, Baena-Lopez MA, Garzon-Mirallas A, Bautista-Mesa RJ, Peiro S et al (2020) Telemedicine in times of the pandemic produced by COVID-19: implementation of a teleconsultation protocol in a hospital emergency department. *Healthcare (Basel)* 8(4):357. <https://doi.org/10.3390/healthcare8040357>
- Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 109:102433. <https://doi.org/10.1016/j.jaut.2020.102433>
- Wu JT, Leung K, Leung GM (2020) Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet* 395(10225):689–697. [https://doi.org/10.1016/S0140-6736\(20\)30260-9](https://doi.org/10.1016/S0140-6736(20)30260-9)
- Abobaker A, Raba AA, Alzwi A (2020) Extrapulmonary and atypical clinical presentations of COVID-19. *J Med Virol* 92(11):2458–2464. <https://doi.org/10.1002/jmv.26157>
- Figueiredo R, Falcao V, Pinto MJ, Ramalho C (2020) Peripheral facial paralysis as presenting symptom of COVID-19 in a pregnant woman. *BMJ Case Rep* 13(8):e237146. <https://doi.org/10.1136/bcr-2020-237146>
- Goh Y, Beh DLL, Makmur A, Somani J, Chan ACY (2020) Pearls & Oysters: facial nerve palsy in COVID-19 infection. *Neurology* 95(8):364–367. <https://doi.org/10.1212/WNL.00000000000009863>
- Wan Y, Cao S, Fang Q, Wang M, Huang Y (2020) Coronavirus disease 2019 complicated with Bell's palsy: a case report. *Research Square, Durham*. <https://doi.org/10.21203/rs.3.rs-23216/v1>
- Whittaker A, Anson M, Harky A (2020) Neurological manifestations of COVID-19: a systematic review and current update. *Acta Neurol Scand* 142(1):14–22. <https://doi.org/10.1111/ane.13266>
- Zammit M, Markey A, Webb CA (2020) A rise in facial nerve palsies during the coronavirus disease 2019 pandemic. *J Laryngol Otol*. <https://doi.org/10.1017/S0022215120002121>
- Duarte-Neto AN, Monteiro RAA, da Silva LFF, Malheiros D, de Oliveira EP, Theodoro-Filho J et al (2020) Pulmonary and systemic involvement in COVID-19 patients assessed with ultrasound-guided minimally invasive autopsy. *Histopathology* 77(2):186–197. <https://doi.org/10.1111/his.14160>
- Gussen R (1977) Pathogenesis of Bell's palsy. Retrograde epineurial edema and postedematous fibrous compression neuropathy of the facial nerve. *Ann Otol Rhinol Laryngol* 86(4):549–558. <https://doi.org/10.1177/000348947708600416>
- Lima MA, Silva MTT, Soares CN, Coutinho R, Oliveira HS, Afonso L et al (2020) Peripheral facial nerve palsy associated with COVID-19. *J Neurovirol* 26(6):941–944. <https://doi.org/10.1007/s13365-020-00912-6>
- Zhang W, Xu L, Luo T, Wu F, Zhao B, Li X (2020) The etiology of Bell's palsy: a review. *J Neurol* 267(7):1896–1905. <https://doi.org/10.1007/s00415-019-09282-4>
- Berlit P, Bosel J, Gahn G, Isenmann S, Meuth SG, Nolte CH et al (2020) "Neurological manifestations of COVID-19" - guideline of the German society of neurology. *Neurol Res Pract* 2(1):51. <https://doi.org/10.1186/s42466-020-00097-7>
- Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S et al (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181(2):271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>

21. Alomari SO, Abou-Mrad Z, Bydon A (2020) COVID-19 and the central nervous system. *Clin Neurol Neurosurg* 198:106116. <https://doi.org/10.1016/j.clineuro.2020.106116>
22. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 203(2):631–637. <https://doi.org/10.1002/path.1570>
23. Xia H, Lazartigues E (2010) Angiotensin-converting enzyme 2: central regulator for cardiovascular function. *Curr Hypertens Rep* 12(3):170–175. <https://doi.org/10.1007/s11906-010-0105-7>
24. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6(7):e1000097. <https://doi.org/10.1371/journal.pmed.1000097>
25. Turki A, Abbas KS, Makram AM, Elmarabea M, Elfert M, Abdalshafy H, et al. (2021) Facial palsy in COVID-19 patients: a systematic review. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021226404.
26. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. (2017) Chapter 7: systematic reviews of etiology and risk. Joanna Briggs institute reviewer's manual. The Joanna Briggs Institute, Adelaide p 5
27. R Core Team (2020) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna
28. Gerds TA. (2019) prodlm: Product-Limit Estimation for Censored Event History Analysis. R package version 2019.11.13
29. Kumar V, Narayanan P, Shetty S, Mohammed AP (2021) Lower motor neuron facial palsy in a postnatal mother with COVID-19. *BMJ Case Rep* 14(3):e240267. <https://doi.org/10.1136/bcr-2020-240267>
30. Gogia B, Gil Guevara A, Rai PK, Fang X (2020) A case of COVID-19 with multiple cranial neuropathies. *Int J Neurosci*. <https://doi.org/10.1080/00207454.2020.1869001>
31. Roussel A, Germanaud D, Bouchoucha Y, Ouldali N, Vedrenne-Cloquet M, Castelle M et al (2021) Cranial polyneuropathy as the first manifestation of a severe COVID-19 in a child. *Pediatr Blood Cancer* 68(3):e28707. <https://doi.org/10.1002/pbc.28707>
32. Ribeiro BNF, Marchiori E (2020) Facial palsy as a neurological complication of SARS-CoV-2. *Arq Neuropsiquiatr* 78(10):667. <https://doi.org/10.1590/0004-282X20200127>
33. Homma Y, Watanabe M, Inoue K, Moritaka T (2020) Coronavirus disease-19 pneumonia with facial nerve palsy and olfactory disturbance. *Intern Med* 59(14):1773–1775. <https://doi.org/10.2169/internalmedicine.5014-20>
34. Cabrera Muras A, Carmona-Abellan MM, Colliá Fernandez A, Uterga Valiente JM, Anton Mendez L, Garcia-Monco JC (2021) Bilateral facial nerve palsy associated with COVID-19 and Epstein-Barr virus co-infection. *Eur J Neurol* 28(1):358–360. <https://doi.org/10.1111/ene.14561>
35. Karimi-Galougahi M, Yousefi-Koma A, Raygani N, Bakhsh-ayeshkaram M, Haseli S (2021) ¹⁸FDG-PET/CT assessment of COVID-19-induced Bell's palsy. *Acad Radiol* 28(1):144–145. <https://doi.org/10.1016/j.acra.2020.11.001>
36. Mehta S, Mackinnon D, Gupta S (2020) Severe acute respiratory syndrome coronavirus 2 as an atypical cause of Bell's palsy in a patient experiencing homelessness. *CJEM* 22(5):608–610. <https://doi.org/10.1017/cem.2020.418>
37. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM (2020) Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Crit Care* 24(1):696. <https://doi.org/10.1186/s13054-020-03400-9>
38. Elkhoully A, Kaplan AC (2020) Noteworthy neurological manifestations associated with COVID-19 infection. *Cureus* 12(7):e8992. <https://doi.org/10.7759/cureus.8992>
39. Elkhoully A, Kaplan AC (2021) Retraction: noteworthy neurological manifestations associated With COVID-19 infection. *Cureus* 13(3):r26. <https://doi.org/10.7759/cureus.r26>
40. Codeluppi L, Venturelli F, Rossi J, Fasano A, Toschi G, Pacillo F et al (2021) Facial palsy during the COVID-19 pandemic. *Brain and behavior* 11(1):e01939. <https://doi.org/10.1002/brb3.1939>
41. Decio A, Mazza A, Quadri V, Ronconi MS, Brusadelli C, Ruggeri M et al (2021) Neurological manifestations of COVID-19 in children: a case of facial nerve palsy. *Pediatr Neurol* 116:59. <https://doi.org/10.1016/j.pediatrneuro.2020.12.006>
42. Neo WL, Ng JCF, Iyer NG (2021) The great pretender-Bell's palsy secondary to SARS-CoV-2? *Clin Case Rep* 9(3):1175–1177. <https://doi.org/10.1002/ccr3.3716>
43. da Silva SJR, Silva C, Guarines KM, Mendes RPG, Pardee K, Kohl A et al (2020) Clinical and laboratory diagnosis of SARS-CoV-2, the virus causing COVID-19. *ACS Infect Dis* 6(9):2319–2336. <https://doi.org/10.1021/acsinfectdis.0c00274>
44. Correa DG, da Hygino Cruz Jr LC, Lopes FCR, Rangel CC, de Araujo Henriques Tassarollo AL, Coelho KCG et al (2021) Magnetic resonance imaging features of COVID-19-related cranial nerve lesions. *J Neuroviro* 27(1):171–177. <https://doi.org/10.1007/s13365-020-00934-0>
45. Derollez C, Alberto T, Leroi I, Mackowiak MA, Chen Y (2020) Facial nerve palsy: an atypical clinical manifestation of COVID-19 infection in a family cluster. *Eur J Neurol* 27(12):2670–2672. <https://doi.org/10.1111/ene.14493>
46. Bastola A, Sah R, Nepal G, Gajurel BP, Rajbhandari SK, Chalise BS et al (2021) Bell's palsy as a possible neurological complication of COVID-19: a case report. *Clin Case Rep* 9(2):747–750. <https://doi.org/10.1002/ccr3.3631>
47. Dahl EH, Mosevoll KA, Cramariuc D, Vedeler CA, Blomberg B (2021) COVID-19 myocarditis and postinfection Bell's palsy. *BMJ Case Rep* 14(1):240095. <https://doi.org/10.1136/bcr-2020-240095>
48. Casas E, Barbosa A, Rubio-García E, Cebrian J, Diaz-Perez C, de la Fuente E et al (2020) Isolated peripheral facial paralysis in a patient with COVID-19. *Rev Neurol* 71(1):40–41. <https://doi.org/10.33588/rn.7101.2020229>
49. Garcia Ochoa-Fernandez E, Villora-Morcillo N, Taboas-Pereira MA (2021) Peripheral facial palsy in a paediatric patient with no risk factors within the context of infection by SARS-CoV-2. *Rev Neurol* 72(5):177–178. <https://doi.org/10.33588/rn.7205.2020629>
50. Theophanous C, Santoro JD, Itani R (2021) Bell's palsy in a pediatric patient with hyper IgM syndrome and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Brain Dev* 43(2):357–359. <https://doi.org/10.1016/j.braindev.2020.08.017>
51. Zain S, Petropoulou K, Mirchia K, Hussien A, Mirchia K (2021) COVID-19 as a rare cause of facial nerve neuritis in a pediatric patient. *Radiol Case Rep* 16(6):1400–1404. <https://doi.org/10.1016/j.radcr.2021.03.063>

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Authors and Affiliations

Aya Turki^{1,2}  · Kirellos Said Abbas^{2,3}  · Abdelrahman M Makram^{2,4,5}  · Mostafa Elfert^{2,6}  ·
Mahmoud Elmarabea^{2,6}  · Nahla Ahmed El-Shahat^{2,7}  · Hassan Abdalshafy^{1,2}  · Akua Sampong^{2,8}  ·
Sirisha Chintalapati^{2,8}  · Nguyen Tien Huy^{2,9} 

Aya Turki
aya-m-turki@students.kasralainy.edu.eg

Kirellos Said Abbas
kirellossaid98@gmail.com

Abdelrahman M Makram
abd-makram@hotmail.com;
abdelrahman.elsayid21@imperial.ac.uk

Mostafa Elfert
mostafa_elfert@hotmail.com

Mahmoud Elmarabea
mahmoud.elmarabea@gmail.com

Nahla Ahmed El-Shahat
nahlaahmed752@gmail.com

Hassan Abdalshafy
hassanabdalshafy000000@gmail.com

Akua Sampong
akuasampong@students.aucmed.edu

Sirisha Chintalapati
sirishachintalapati@students.aucmed.edu

¹ Faculty of Medicine, Cairo University, Cairo, Egypt

² Online Research Club (<https://www.onlineresearchclub.org/>),
Nagasaki, Japan

³ Faculty of Medicine, Alexandria University, Alexandria,
Egypt

⁴ School of Public Health, Imperial College London, London,
UK

⁵ Faculty of Medicine, October 6 University, Giza, Egypt

⁶ Faculty of Medicine, Tanta University, Tanta, Egypt

⁷ Faculty of Medicine for Girls, Al-Azher University, Cairo,
Egypt

⁸ American University of the Caribbean School of Medicine,
Cupecoy, St. Maarten

⁹ School of Tropical Medicine and Global Health, Nagasaki
University, Nagasaki 852-8523, Japan