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Is facial nerve palsy an early manifestation of COVID-19?
A literature review

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ABSTRACT
The primary target of SARS-CoV-2 is the respiratory tract; nevertheless, the virus can invade extrapulmonary organs, such as the nervous system. Peripheral facial nerve palsy has been reported in COVID-19 cases as isolated, unilateral, or bilateral in the context of Guillain-Barré syndrome (GBS). In the present study, online databases, including PubMed and Google Scholar, were searched. Studies without focusing on isolated peripheral facial nerve palsy and SARS-CoV-2 were excluded. Finally, 36 patients with facial nerve palsy were included in our study using reverse transcriptase–polymerase chain reaction (RT-PCR) or antibody SARS-CoV-2 positive test. Interestingly, 23 (63.8%) of these patients had no typical history of COVID-19, and facial nerve palsy was their first clinical manifestation. The present study concludes that there is enough evidence to suggest that SARS-CoV-2 infection may present with facial nerve palsy as the initial clinical manifestation.

Key Indexing Terms: COVID-19; Facial nerve palsy; Peripheral facial nerve palsy; Cranial nerve palsies; SARS-CoV-2.

INTRODUCTION
The COVID-19 epidemic emerged in December 2019 in Wuhan, China, which has rapidly spread worldwide.1 Besides respiratory symptoms, COVID-19 can cause a variety of symptoms. Although lung inflammation and respiratory failure are of vital importance, various manifestations have been increasingly described in the last few months, including asymptomatic renal and cardiac abnormalities or nervous system involvement.2 Neurological symptoms can be the first manifestation of COVID-19 or concomitant of respiratory symptoms, including headaches, hyposmia, hypogeusia, dizziness, confusion, cerebrovascular diseases, Guillain-Barré syndrome (GBS), and encephalopathies. Neurological manifestations were seen in up to 36% of COVID-19 patients, especially in those who suffer from severe respiratory tract infections.3

Based on previous studies, COVID-19 could lead to peripheral facial nerve palsy via angiotensin-converting enzyme 2 (ACE2) receptors, blood circulation, or invading the olfactory nerves; however, the mechanism is unknown.4,5 Combined facial and trigeminal nerve palsy can potentially occur after SARS-CoV-2 infection.6 Numerous cases of facial nerve palsies associated with SARS-CoV-2 infection were reported as the first presentation.7 The COVID-19 pandemic has attracted the attention of physicians as facial nerve palsy cases were increased after the COVID-19 pandemic compared to previous years.8 Therefore, the present literature review aimed to summarize current studies and case series to suggest facial nerve palsy as the initial clinical presentation of COVID-19.

LITERATURE SEARCHES AND FINDINGS
Online databases, including PubMed and Google Scholar, were searched from January 2020 to July 2020. The following keywords were used: “SARS-CoV-2,” “COVID-19,” “facial nerve palsy,” and “facial paralysis.” Cohort studies, case series, and case reports of facial nerve palsy with COVID-19 infection were included. Restrictions were imposed to exclude studies without focusing on isolated peripheral facial nerve palsy and SARS-CoV-2. Nineteen studies are listed in Table 1.
| Author            | Study type | Age | Gender | First symptom | Clinical manifestation (House-Brackmann scale) | Covid test | CSF study | Neuroradiology & nerve studies | Relevant blood investigations | Treatment | Outcome       |
|-------------------|------------|-----|--------|---------------|------------------------------------------------|------------|----------|--------------------------------|--------------------------------|-----------|---------------|
| Dahl et al.       | CR         | 37y | M      | NO            | Right side                                      | PCR+       | NL CT    | NL MRI                        | GD1b IgG +                   | doxycycline | Complete resolution |
| Zain et al.       | CR         | 23M | F      | Yes           | Right side                                      | PCR+       | NA       | NA                            | mild leukopenia, hypochromic anemia, hyperkalemia, elevated alkaline phosphatase, and elevated AST, Respiratory pathogen panel - | Eye hydration | Complete resolution |
| Figueiredo et al. | CR         | 35y | F      | Pregnant (39w) | Left side                                       | PCR+       | NA       | NA                            | mild leukocytosis (1.25 x 10^9 cells/L), lymphopenia (15.2%; 1.92 x 10^9 cells/L), neutrophilia (73.3%; 9.19 x 10^9 cells/L),increased C-reactive protein level (61 mg/dL), | Prednisolone | Complete resolution |
| RIBEIRO et al.    | CR         | 26y | M      | NO            | Right side                                      | PCR+       | increase in proteins (53 mg/dL), NL cell and glucose | Brain MRI (enhancement of the right facial nerve) | NA                          | Prednisolone and valacyclovir | Complete resolution |
| Kumar et al.      | CR         | 28y | F      | Pregnant (36w) | NO Right side                                   | PCR+       | NA       | NA                            | HIV-                          | Valacyclovir | Complete resolution |
| Asafara et al.    | CR         | 36y | F pregnant (37w) | NO | bilateral (4) | PCR+ (positive 6 weeks before refer) raised protein levels (80), normal cell counts and glucose, PCR for viruses, including SARS-CoV-2, Cryptococcus, Mycobacterium tuberculosis, Listeria, Escherichia coli, was negative, Brain and spinal cord MRI explorations were normal, nerve conduction studies showed demyelinating pattern of GBS | Brain and spinal cord MRI explorations were normal, nerve conduction studies showed demyelinating pattern of GBS | Serology of Campylobacter jejuni, Epstein - Barr virus, Cytomegalovirus, TPHA-VDRL, and Borrelia was neg, serology of SARS-CoV-2 IgM - and IgG +. Testing by (IVG) therapy was started at a dose of 0.4 g/kg for 5 days associated with Intravenous steroids (1mg/Kg) for 10 days | Complete resolution of the right facial palsy but still had left facial palsy at 2 weeks' follow-up |

(continued on next page)
| Author          | Study type | Age | Gender | First symptom | Clinical manifestation (House-brackmann scale) | Covid test | CSF study | Neuroradiology & nerve studies | Relevant blood investigations | Treatment          | Outcome     |
|-----------------|------------|-----|--------|---------------|-----------------------------------------------|------------|-----------|---------------------------------|-----------------------------|-----------------------|-------------|
| Muras et al.54  | CR         | 20Y | M      | NO            | Bilateral                                     | PCR+       |           | brain MRI (severe neuropathy of the facial nerve bilaterally) | SARS-CoV2 IgM +& IgG+, positive EBV, Antiganglioside antibodies (IgM and IgG) were negative in serum and CSF | prednisolone | Complete resolution |
| Derollez et al.55 | CR       | 57Y | F      | Yes           | Left side                                     | PCR+       |           | NL Brain MRI | Negative serology for HIV, HVA, HVB, HVC, Lyme, Ganglioside antibodies, nuclear antibodies panel, VDRL, Campylobacter jejuni/ NL Rheumatoid factor, NL/ acquired immunity for CMV, EBV, VZV | NA | NA |
| Caamaño et al.56 | CR       | 61Y | M      | NO            | Bilateral                                     | PCR+       |           | mildly elevated levels of proteins (44 mg/dL), absent leukocytes and a negative RT-PCR for SARS-CoV-2 on CSF. | NL CT and MRI, NA GBS studies | prednisone | Complete resolution |
| Decio et al.57  | CR         | 19M | F      | YES           | Right                                         | PCR+       | NA        | MRI (enhancement of the intra-auricular tract of the right facial nerve) | Neg Serological tests for HSV1, HSV2, varicella zoster virus, EBV, CMV, Mycoplasma pneumonia, Borrelia burgdorferi, positive covid IgG antibodies | Six days followed by tapering | Complete resolution |
| Lima et al.58   | CS         | 43Y | F      | YES           | Right(3)                                      | PCR+       | NA        | NL CT | NA | Oral steroids | Oral steroids + acyclovir | Partial resolution |
| Lima et al.58   | CS         | 25Y | F      | YES           | Right(2)                                      | PCR+       | 5 cell count/mm³, 29 pro mg/dL, | NL MRI | NA |                     |            | Complete resolution |

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Table 1. (continued)

| Author       | Study type | Age | Gender | First symptom | Clinical manifestation (House-brackmann scale) | Covid test | CSF study | Neuroradiology & nerve studies | Relevant blood investigations | Treatment                      | Outcome                      |
|--------------|------------|-----|--------|----------------|-----------------------------------------------|------------|-----------|--------------------------------|-------------------------------|-------------------------------|-----------------------------|
| Lima et al.  | CS         | 33Y | F      | YES            | Right(3)                                      | PCR+       | NA        | NA                              | NA                            | Oral steroids + acyclovir    | Partial resolution            |
| Lima et al.  | CS         | 26Y | F      | NO             | Left(2)                                       | PCR+       | 4 cellcount/mm³; 31pro mg/dl, 55 mg/dl, SARS-Cov-2 PCR neg | MRI: left facial nerve enhancement | NA                            | Oral steroids                | Complete resolution           |
| Lima et al.  | CS         | 50Y | F      | NO             | Left(3)                                       | PCR+       | 3 cellcount/mm³; 50pro mg/dl, 56 mg/dl, SARS-Cov-2 PCR neg | NL CT                               | NA                            | Oral steroids                | Partial resolution            |
| Lima et al.  | CS         | 38Y | F      | NO             | Left(2)                                       | PCR+       | 1 cellcount/mm³; 28pro mg/dl, 51 mg/dl, SARS-Cov-2 PCR neg | NL MRI                              | NA                            | Supportive                   | Complete resolution           |
| Lima et al.  | CS         | 39Y | F      | NO             | Right(2)                                      | PCR+       | 1 cellcount/mm³; 32pro mg/dl, 38 mg/dl, SARS-Cov-2 PCR neg | NL MRI                              | NA                            | Oral steroids                | Complete resolution           |
| Lima et al.  | CS         | 34Y | F      | NO             | Left(2)                                       | PCR+       | 2 cellcount/mm³; 33pro mg/dl, 91 mg/dl, SARS-Cov-2 PCR neg | NL MRI                              | NA                            | Intravenous steroids         | Complete resolution           |
| Neo et al.   | CR         | 25Y | M      | YES            | Left(5)                                       | PCR+       | NA        | NL findings                     | Neg SARS-CoV-2 IgG             | Oral corticosteroids, valaciclovir, and given eye care | Complete resolution           |
| Neo et al.   | CR         | 34Y | M      | YES            | Right(6)                                      | PCR+ / Pos SARS-CoV-2 IgG                    | NL findings                     | Pos SARS-CoV-2 IgG             | Oral corticosteroids, valaciclovir, and given eye care | Partial resolution (3-4)       |
| Goh et al.   | CR         | 27Y | M      | NO             | Left                                          | PCR+       | CSF PCR for herpes simplex virus, varicella zoster virus, Epstein-Barr virus and cytomegalovirus, and RT-PCR for SARS-CoV-2 were negative / CSF analysis did not show any pleocytosis, and glucose and protein levels were normal | MRI: enhancement of the left facial nerve, HIV screen was negative, | prednisone and valaciclovir | Partial resolution            |

(continued on next page)
| Author            | Study type     | Age | Gender | First symptom | Clinical manifestation (House-brackmann scale) | Covid test | CSF study | Neuroradiology & nerve studies | Relevant blood investigations | Treatment                      | Outcome |
|-------------------|----------------|-----|--------|---------------|-----------------------------------------------|------------|-----------|--------------------------------|--------------------------------|-------------------------------|---------|
| Homma et al.       | CR             | 35Y | F      | YES           | Right                                         | PCR+       | NA        | NA                                            | Rapid tests for influenza and streptococci yielded negative results. / . Blood tests showed a blood cell count of 3,320/mL (neutrophils 72%, lymphocytes 18.4%, basophils 0.3%, eosinophils 2.1%, and monocytes 7.2%) | Inhalation of ciclesonide/ favipiravir/ Japanese Kampo medicine | NA |
| Mehta et al.       | CR             | 36Y | M      | NO            | Right                                         | PCR+       | NA        | (CT) angiogram of the head and neck showed no acute abnormalities | Laboratory findings were non-contributory with white blood cells 3.83, neutrophils 1.5, and lymphocytes 1.4. | Oral prednisone as well as eye lubrication | NA |
| Wan et al.         | CR             | 65Y | F      | YES           | Left                                          | PCR+       | NA        | (MRI) showed no abnormality | Influenza virus antigens (including influenza A virus, influenza B virus, parainfluenza virus, adenovirus, Coxsackie virus, respiratory syncytial virus and herpesvirus) were tested negative/ The blood routine test and C-reactive protein level were both normal | Antiviral treatment with arbidol and ribavirin | Complete resolution |
| Theophanous et al. | CR             | 6Y  | M      | YES           | Right(4)                                      | PCR+       | NA        | NA                                            | Herpes Simplex Virus (HSV-1, HSV-2) and Varicella-Zoster Virus (VZV) PCR were negative, prednisolone and acyclovir and his scheduled dose of IVIG infusion | Complete resolution (1) | |
| Islamoglu et al.   | prospective cross-sectional (10 patients) | NA  | NA     | YES           | NA(unilateral)                                | Pos SARS-CoV-2 IgG + IgM /PCR negative | NA        | 70% had facial enhancement in the MRI scan; 20% had normal, and 10% had no MRI scan | NA | Prednisolone and acyclovir and his scheduled dose of IVIG infusion | NA |

Table 1. (continued)
| Author       | Study type | Age | Gender | First symptom | Clinical manifestation (House-brackmann scale) | Covid test | CSF study | Neuroradiology & nerve studies | Relevant blood investigations | Treatment | Outcome |
|--------------|------------|-----|--------|---------------|------------------------------------------------|------------|-----------|--------------------------------|---------------------------------|-----------|---------|
| Kerstens et al. | CR         | 27Y | M      | YES           | Bilateral (Right (5), Left (3))                     | PCR+       | acellular cerebrospinal fluid with normal glucose and protein levels, a slightly elevated IgG (46 mg/L, normal values 10–30) and IgG-index (0.62, normal values 0.30–0.60) and identical oligoclonal bands in serum and cerebrospinal fluid | Brain MRI on day 2 of hospitalization (7 days after symptom onset) showed bilateral contrast enhancement of the facial nerves without other abnormalities, nerve conduction studies of extremities were normal without evidence for GBS | serology for human immunodeficiency virus, syphilis, and Borrelia were all either normal or negative. Epstein-Barr virus (EBV) EBNA-IgG, herpes simplex virus (HSV) IgG, and varicella zoster virus (VZV) IgG all were positive with negative IgM, consistent with previous infections | 10-day of oral methylprednisolone and artificial tears | A five-day course of valaciclovir was added to his treatment | two months later, he had almost completely recovered to bilateral HB grade I |

1 Gender: F female, M male.
2 Facial palsy as first COVID-19 symptom/signal.
3 Cerebrospinal fluid analysis: cell count/mm³—protein level mg/dl—glucose level mg/dl.
4 Case report.
5 normal.
6 Not available (data not provided in the original publications).
7 Case series.
CRANIAL NERVE PALSY PRESENTATION IN COVID-19 PATIENTS

SARS-CoV-2 infection is typically marked by fever and respiratory symptoms, although neurologic manifestations were described. Among large-scale observational studies in the setting of COVID-19 patients, 36.4% had neurologic findings, including cerebrovascular events, cranial nerve abnormalities, and muscle injuries. Recent studies have reported that SARS-CoV-2-related infection may present with cranial neuropathies, including oculomotor, abducens, and peripheral facial nerve palsies. Moreover, peripheral facial nerve palsy was described in SARS-CoV-2-positive patients as isolated and unilateral or bilateral in the context of GBS. Wei et al. reported acute unilateral isolated oculomotor nerve palsy in an adult patient with COVID-19 pneumonia. There was no identifying data of the structural cause of oculomotor nerve injury, suggesting that COVID-19 infection might cause acute oculomotor nerve palsy in this case. Oliveira et al. presented an asymptomatic positive SARS-CoV-2 in a 2-year-old child with acute-onset oculomotor nerve palsy. Studies have shown that young patients with COVID-19 present isolated abducens nerve palsy despite having normal brain imaging, and no clear etiology has been determined to explain those abducens nerve palsies, which may suggest or emphasize the role of SARS-CoV-2. Thus, ophthalmologists need to be aware that abducens or oculomotor nerve palsies may represent part of the neurologic spectrum of COVID-19. During the pandemic, global independent centers have observed an increased load of facial peripheral nerve palsy.

According to Table 1, 36 patients with facial nerve palsy were included using reverse transcriptase–polymerase chain reaction (RT-PCR) or antibody SARS-CoV-2 positive test. The patients’ average age was 32.5 years, except for 10 patients who were excluded due to lack of information. As younger patients might have more potent immune systems, facial palsy might be more common in the younger population of COVID-19 patients. Further, 16 (44.4%) were female, of whom 3 were pregnant, 10 (27.7%) were male, and in 10 (27.7%) cases, gender was not mentioned.

Nine (25%) patients had left-sided, 13 (36.1%) had right-sided, and 4 (11.1%) had bilateral facial paralysis; in 10 (27.7%) patients, the involvement site was not mentioned. They were followed up with the diagnosis of Bell’s palsy, according to not finding an etiology of their paralysis. Tests for SARS-CoV-2 RT-PCR were positive in 24 (66.6%) patients and for IgM or IgG antibodies in 14 (38%) patients. Cerebrospinal fluid (CSF) tests revealed that only 1 patient had the SARS-CoV-2 IgG antibody positive test and no positive SARS-CoV-2 RT-PCR test. Interestingly, 23 (63.8%) patients had no history of fever, malaise, cough, or any shortness of breath sign, and facial nerve palsy was their first clinical manifestation.

Zammit et al. reported that the facial nerve palsy rate was 2.7% higher than last year. They conducted a retrospective review of facial nerve palsies from January to June 2020; they compared their findings to the previous year’s Liverpool population. During the first phase of the COVID-19 pandemic in Italy (27 February to 3 May 2020), the incidence of individuals presenting with facial palsy was compared in 6 emergency rooms to the same period in 2019; it was found that cases were younger than those of the previous year and showed a prolonged delay between the onset of facial palsy and seeking medical treatment. This could be attributed to a systemic inflammatory response that predisposes COVID-19 patients to neurological abnormalities.

Neurologic manifestations without typical COVID-19 symptoms became a challenge amid the pandemic. Not only do patients not follow isolation and social distancing in the absence of common symptoms, but medical staff may also underestimate the risk of those patients. Finssterer et al. also reported that facial nerve palsy could be a manifestation of GBS. Regarding the potential risk of transmission in missed diagnosed cases during the pandemic, differential diagnosis of facial nerve palsies should include COVID-19. As initial neurologic manifestations of COVID-19, cranial neuropathies have hitherto been unclear. The number of patients in the literature is limited; thus, the RT-PCR test on the first admission and larger patient groups may help clarify the etiology.

MECHANISMS OF NEUROLOGIC MANIFESTATIONS IN COVID-19 PATIENTS

The SARS-CoV-2 genome sequence has 89.1% similarity combined to SARS-like coronaviruses. SARS-CoV-1 has been detected in the CSF and brain tissue of patients, which is the most closely similar to human coronavirus, and also SARS-CoV-2 detection in CSF has been reported. Up to now, shreds of evidence of the neurotropic effect of SARS-CoV-2 have been provided, for instance, involving the cranial nerves (hypoguesia, Bell’s palsy, hyposmia, and abducens nerve palsy) or neurological manifestations (headache, dizziness, and impaired consciousness). Many viruses, including influenza, herpes, or human immunodeficiency virus (HIV), can cause neurological diseases by invading the nervous system. Since the neurotropic mechanisms of SARS-CoV-2 have not yet been established, SARS-CoV-1 and other viruses could play a reference role for SARS-CoV-2.

It has been unclear whether cranial neuropathies, as early neurologic manifestations of COVID-19 infection, arise from the direct viral infiltration of the nervous system or an autoimmune response. Several hypotheses were documented for nervous system involvement in the setting of COVID-19 patients, which can be divided into 2 tenable underlying mechanisms, the first mechanism includes synaptic propagation and the ACE2 receptor virus entranceway. Based on previous studies, coronavi-
ruses can invade CNS by the cribriform plate of the ethmoid, and subsequent invasion of the olfactory neuroepithelium could cause neural death in mice.21

Coronavirus can permeate via synapses from olfactory nerve neurons to the cardiorespiratory center, named the “theory of synaptic propagation.” SARS-CoV-2 may implicate respiratory failures based on this theory.22 SARS-CoV-2 could directly penetrate sensory nerve endings as other coronaviruses.23 The trigeminal nerve is thought to serve as an entry point for viruses in several reported cases of conjunctivitis.24 However, the ACE2 primary entrance receptor view has been accepted in direct neuroinvasion contrasts. ACE2 is widely expressed in the human body, specifically in neurons and some non-neuron cells, mainly astrocytes, oligodendrocytes, and endothelial cells.5,25,26

SARS-CoV-2 enters host cells via binding to the ACE2 receptor with viral surface spike (S) proteins, similar to the SARS-CoV-1 entrance.27−29 Furthermore, it can infect macrophages to migrate via the blood-brain barrier (BBB).30 SARS-CoV-2 affinity to the receptor is almost 20-fold more than SARS-CoV-1,31 which would explain many neurological manifestations such as headache, nausea, and vomiting in COVID-19 patients.32

“Cytokine storm” may be the second mechanism regarding endothelial cell involvement.33,34,35 Intracranial cytokine storms could lead to the BBB breakdown, which could be the leading cause of encephalopathy or GBS.36,37 An ample body of evidence on patients with COVID-19 has documented severe systemic manifestations, including cytokine storm and coagulopathy.38 This systemic inflammatory response could be attributed to various factors, particularly infections.39 It is unassailable that our learnings about SARS-CoV-2 are limited, especially about neurological manifestations. In this regard, neuronal tissue exploration and detailed neurological examination may facilitate our understanding.5

MANAGEMENT OF FACIAL NERVE PALSY AMID THE COVID-19 PANDEMIC

It is challenging to manage facial nerve palsy during the COVID-19 pandemic due to the potential exposure, probability requirement of isolation, and limited healthcare resources. Since the absence of common symptoms of COVID-19 has been reported in patients with facial nerve palsy, it is recommended that all protective measures should be taken until the status of COVID-19 is clarified in these patients. Taking a detailed patient’s medical history and performing a neurological examination may ultimately lead to a Bell’s palsy diagnosis following the elimination of other differential diagnoses and conditions that require immediate treatment.40

COVID-19 patients with facial nerve palsy should undergo a complete diagnostic work-up. In all patients who suddenly manifest peripheral facial paralysis, lumbar puncture is considered a diagnostic procedure. The inflammatory responses of infectious pathogens can be rapidly detected in CSF. The CSF detection of oligoclonal bands, CSF anti-myelin oligodendrocyte glycoprotein (MOG) antibody, CSF anti-neuromyelitis optica (NMO), or ACE level should be considered. Plasma and CSF antibody levels could be measured due to viral (varicella-zoster, herpes simplex, cytomegalovirus, adenovirus, and Epstein-Barr) or Borrelia burgdorferi infections.41

In some specific cases, human immunodeficiency virus serologic tests may be considerably raised. Magnetic resonance imaging (MRI) of the brain may particularly delineate the brainstem, posterior fossa, or petrous bone.42,43 Suggested therapeutic regimes are corticosteroids and antiviral agents and symptom therapy. Steroid edema and swelling reduction may lead to facial nerve decompression, therefore attracting more attention among other regimes.44 Early treatment immediately after the onset of symptoms (<72 h) could improve patients’ outcomes and reduce auricular pain and nerve damage.45

The authors recommend a 1 mg/kg/day course of prednisolone and then tapered for 5−10 days.43,46 Pain with vesicles in the ear canal could be manifested by zoster infection; in this setting, the combination of antivirals and steroids might be beneficial.43 Clinical trials that have been performed to date to answer this question are relatively heterogeneous.37 Available drugs are acyclovir (5−10 mg/kg BW IV tid or 800 mg PO 5 ×/d), valacyclovir (1000 mg PO tid), brivudine (125 mg PO QD), and famciclovir (250−500 mg PO tid).

Patients’ eyes should receive special attention since they are unprotected and dry as a result of incomplete lid closure. Artificial tears and dexamethasone ointment are prescribed, as well as a nocturnal moisture-retaining eye shield.43 Treatment is often supplemented with exercises, either under the direction of a physiotherapist or with self-observation in a mirror.48

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None.

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STATEMENT
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