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Systematic Review / Meta-analysis

Development of facial palsy following COVID-19 vaccination: A systematic review



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ABSTRACT

Objective: Reports of facial palsy occurring after the receipt of COVID-19 vaccines have raised concerns but are rare. The purpose of this study is to systematically assess the association between COVID-19 vaccination and facial palsy.

Methods: Our systematic review followed the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) checklist and compiled all the reported cases of facial palsy post-COVID-19 vaccination. We discussed the probable pathophysiology behind facial palsy as a consequence of COVID-19 vaccination and measures to be taken for future reference. Furthermore, we conducted a detailed assessment of characteristics, clinical courses, treatment, and recovery of patients with facial palsy after receiving a COVID-19 vaccine.

Results: We included 37 studies providing data on 58 individuals in our review. Over half (51.72%) of the patients complained of facial paralysis following the Oxford-AstraZeneca vaccination. Out of 51 cases, most (88.24%) occurred after the 1st dose. The majority (53.45%) of cases had bilateral facial palsy. Intravenous immunoglobin (IVIg), corticosteroids, and plasmapheresis were the first line of treatment with 75.93% of patients partially recovered, including those undergoing treatment or a lack of follow-up till the end while 22.22% had complete symptomatic recovery.

Conclusions: Our review shows that Bell's palsy can be a plausible non-serious adverse effect of COVID-19 vaccination. However, the association observed between COVID-19 vaccination and Bell's palsy is less threatening than the COVID-19 infection. Hence, vaccination should be encouraged because facial palsy, if it occurs, has shown favourable outcomes with treatment.

1. Introduction

Bell's palsy, commonly known as idiopathic facial paralysis (IFP) is a non-progressive neurological disorder occurring in almost 40,000 individuals each year in the United States of America (USA) [1]. The condition involves inflammation of the seventh cranial nerve (facial nerve) supplying the muscles of the face and parasympathetic innervation of lacrimal and salivary glands and limited sensory fibres to the anterior two-thirds of the tongue. Hence, patients with this disorder usually present with facial stiffness, inability to control facial expressions, failure to close the eye (lagophthalmos), drooling, tearing up, and loss of sense of taste in the anterior two-thirds of the tongue (ageusia). The disease has no predilection for gender or either side of the face, however, rarely bilateral Bell's palsy (facial palsy) is also noted [2]. It is believed that inflammation at the level of the geniculate ganglion is the culprit pathology. This increases pressure in the fallopian canal leading to compression, ischemia, and possibly demyelination of the nerve. In most cases, facial paralysis is temporary and resolves after treatment with steroids and antivirals but up to 30% of patients can develop long-term complications while 5% can have a high degree of

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sequelae like permanent facial paralysis or synkinesis [3]. Classically, the cause of facial nerve inflammation is still unknown, however, some association has been described with Herpes Simplex Virus Type I (HSV-1), Lyme Disease, Guillain-Barre Syndrome, autoimmune conditions like sarcoidosis, and influenza vaccine. Recently, various cases of facial palsy after the COVID-19 vaccination have also been reported [4–7].

COVID-19 is an acute respiratory illness caused by SARS-CoV-2. Since its intimation, this deadly pandemic has infected approximately 505,035,185 individuals and caused 6,210,719 deaths worldwide [8]. To curb the rapid spread of this disease research was initiated on diagnosis, prevention, and treatment modalities for coronavirus. Drugs like hydroxychloroquine, remdesivir, favipiravir, and tocilizumab were explored for their safety and efficacy, however, there was no definitive treatment. The game changed when the Pfizer-BioNTech (BNT162b2) mRNA vaccine was authorized for emergency use by the US Food and Drug Administration (FDA) in December 2020 [9]. Currently, approved vaccines for COVID-19 include Comirnaty (BNT162b2), Spikevax (mRNA-1273), Oxford-AstraZeneca COVID-19 Vaccine (AZD1222), Sputnik V, Johnson & Johnson/Janssen COVID-19 Vaccine (JNJ-78436735; Ad26.COV2. S), CoronaVac, Covaxin (BBV152) and 23 others [10]. Due to the emergency, vaccines were granted approval based on only the initial phases of clinical trials without completion of all the phases of a clinical trial [11,12]. Thus, it is important to monitor adverse events reported post-COVID-19 vaccination. The Pfizer-BioNTech and Moderna vaccine trials revealed seven cases of Bell's palsy in comparison with just one in the control groups [13,14]. The 7 (P = 0.07) rate ratio suggests a possible link between the COVID-19 vaccination and Bell's palsy. Additionally, Ozonoff et al. reported that the incidence of Bell's palsy in the mRNA vaccines was 3.5-7 times higher than in the general population [15]. A Hong Kong study reported an increased overall risk of Bell's palsy after CoronaVac, an inactivated vaccine [16]. Dutta et al. also reported 19,529 neurological adverse events after COVID-19 vaccination, including facial paralysis [17].

On the other hand, a recent disproportionality analysis of the World Health Organization (WHO) pharmacovigilance database by Renoud et al. indicated that the rate of facial paralysis reported after mRNA COVID-19 vaccination is not higher than the observed rate with influenza and other viral vaccines [18]. However, this does not completely rule out a possible association and that study does not have a risk estimation as the population exposed to the vaccine is unknown. Similarly, a hospital-based study suggested no connection between the Pfizer BNT162b2 vaccine and Bell's palsy [19].

In light of the existing data, it is clear that the association between Bell's palsy and COVID-19 vaccination is disputed while the literature is sparse. Furthermore, available evidence has not been studied or summarised to portray a potential relationship between the two. It is imperative to review the present resources on this neurological disorder to better understand and prevent its future incidence. Moreover, data from the U.S. Census Bureau's Household Pulse Survey (HPS) on hesitancy rates for COVID-19 vaccination showed hesitancy rates ranging from 2.69% to 26.7% across the US [20]. To reduce reluctance and ensure maximum vaccination of COVID-19, we need to thoroughly study reported adverse events, their severity, and how to tackle them. In this study, we systematically reviewed all reported cases of facial palsy after the COVID-19 vaccination. We also discussed the plausible pathophysiology behind facial palsy as a result of COVID-19 vaccination and what this implies for the future. Furthermore, we conducted a detailed analysis of characteristics, clinical courses, treatment, and recovery of patients affected with facial palsy after vaccination for COVID-19.

2. Methods

2.1. Literature search

Our study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (Supplementary File 1) [21]. We searched for relevant articles on PubMed and Google Scholar databases from the onset of the COVID-19 pandemic till April 22, 2022. Boolean operators and keywords/subject headings synonymous with facial palsy (e.g., facial paralysis OR facial paresis OR Bell's palsy OR facial weakness) AND COVID-19 vaccine (e.g., COVID-19 Vaccines OR SARS-CoV-2 Vaccines OR Coronavirus Disease 2019 Vaccines OR 2019-nCoV Vaccine OR SARS Coronavirus 2 Vaccines) were used for literature search on respective databases. The references of selected studies were also verified to ensure the completeness of the search. The complete search strategy is given in Supplementary File 3. Furthermore, our study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) bearing registration number: CRD42022328860 [22].

2.2. Inclusion and exclusion criteria

We included all the studies which recorded patient-level data of individuals who developed facial palsy post- COVID-19 vaccination. Reviews, meta-analyses, and literature with aggregate-level data were excluded. Moreover, studies were excluded if they had insufficient data on the clinical progression of the condition. Additionally, there was no language restriction, and all published literature was reviewed irrespective of its language. Two authors (HA and IA) screened the title, abstract and full texts of studies in duplicate. Any conflict in the study selection was, thereafter, resolved by a senior author (MK).

2.3. Data extraction

Selected studies were transferred to an Excel sheet where after, tables were formed after the removal of duplicate studies. Extracted data came under the headings of author name, study type, history/comorbidities, age, gender, Guillain Barre present (yes/no), affected side of the face, COVID-19 vaccine name/type, dose number preceding facial palsy (dose 1 or 2), the onset of facial symptoms following last vaccination (days), clinical features of facial palsy, other complaints, examination results (physical and neurological exams), findings in cerebrospinal fluid (CSF) analysis findings (protein level and cell count), investigations, treatment provided and treatment outcome. Additionally, the sole findings of two imaging techniques, magnetic resonance imaging (MRI) and computed tomography (CT), were chosen for inclusion in our tables. The selected studies varied in quality and no set criteria for assessment or reporting of the condition was devised. Consequently, inconsistencies were noted in their reporting methods.

2.4. Quality assessment

Joanna Brigg's Institute Critical Appraisal Checklist for Case Reports and Case Series was used for the quality assessment of included studies [23,24]. For quality assessment, the seven included LTEs were also treated as either case reports or case series based on the number of cases reported. Each qualitative answer was converted into a numeric score. Quality assessment was conducted independently by two reviewers (IA and HG) and the final score was given after resolving disagreements. Different tools were used based on the study type of every included study. Case reports and case series had 8 and 10 questions, respectively. Included case series (n = 7) had a mean score of 8.86 ± 0.64 with scores ranging from 8 to 10 [25–31]. Meanwhile, the 30 case reports had scores ranging from 5 to 8 with a mean score of 6.57 ± 0.76 [4–7,32–57]. A detailed quality assessment is provided in Supplementary File 3. Furthermore, we also used the A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) checklist to assess the quality of our systematic review which came out to be "moderate" (Supplementary File 2) [58].

2.5. Statistical analysis

Our study provided comprehensive data on individuals who experienced facial paralysis following COVID-19 vaccination. This included information on study type, patient characteristics, both facial palsy and non-facial palsy-related complaints, diagnostic test results, treatment regimen, and outcome of the treatment regimen (Table 1). Means and standard deviations (SD) of age were calculated while other variables were expressed as a percentage of their total number of responses.

3. Results

Out of the 317 articles obtained through our database search, 231 were retrieved from Google Scholar while PubMed provided 86 results. 3 studies were extracted from other sources. After resolving any disagreements regarding study selection, studies were entered in an Excel sheet where 174 duplicate articles were removed. Subsequently, 146 articles were screened. 85 articles were rejected after perusing their titles and abstracts. In the final phase of selection, full-text versions of 61 studies were read for clarity. Articles were turned down for reporting aggregate-level data (n = 12), incomplete data on clinical progression (n = 8) and for being meta-analysis or systematic reviews (n = 4). Adhering to our rigorous criteria, 37 studies were finally chosen for inclusion in our systematic review. The detailed study selection procedure is given in a PRISMA flow chart in Supplementary File 3.

3.1. Patient characteristics

Our systematic review collated data from 58 individuals, from 37 studies, inflicted with facial palsy following COVID-19 vaccination. This data was obtained from 25 case reports, 5 case series and 7 LTEs. A higher occurrence of facial palsy was observed amongst the male gender in comparison to females. The ratio of male (n = 36) to female patients (n = 22) was 18:11. The mean age was 49.93 (SD: 14.16) years, ranging from 20 years to 79 years. Studies recorded data on comorbidities for only 39 individuals. Amongst those, 11 respondents (28.21%) had no known comorbidities. Hypertension (n = 8), Dyslipidaemia (n = 4), cardiac issues (n = 4) and Type 2 Diabetes Mellitus (T2DM) (n = 3) were, however, common comorbidities amongst those reported. It is also noteworthy that 10.26% of patients (n = 4) had a history of Bell's palsy or Guillain-Barré syndrome (GBS).

3.2. Symptom presentation

Table 1 displays the results of 58 patients who presented with facial palsy following their inoculation against COVID-19. Over half (51.72%) of the patients complained of facial paralysis following the Oxford-AstraZeneca vaccination. 15.52% had facial complaints after a Pfizer dose, whilst Moderna, Sputnik V and J&J/Janssen COVID-19 vaccine each had 8.62% of patients reporting the same. One patient each reported facial symptoms after Sinovac (1.72%) and Covaxine (1.72%). Thirty-two studies, bearing data from 51 patients, mentioned the vaccine dose which led to facial palsy. In 45 of these patients (88.24%), the onset of symptoms after 1st dose, whereas only 5 (9.80%) had similar symptoms after the 2nd dose. Interestingly, one patient (1.72%) had the emergence of facial palsy after both his first and second vaccine jab. A majority (53.45%) had bilateral facial complaints. 18.97% and 17.24% had isolated left-sided and right-sided faces affected, respectively. Four patients had initial left (6.90%) and 1 patient (1.72%) had

initial right-sided facial palsy which progressed to bilateral involvement over a course of time. The time of onset of facial palsy symptoms varied greatly, ranging from 3 h to 2 months after vaccination. Facial symptoms also varied in intensity per individual. From slight dysfunction to complete facial paralysis, patients experienced a myriad of symptoms. Common facial presenting complaints included lagophthalmos, dysgeusia, dysarthria, facial droop, loss of facial wrinkling, facial numbness, paraesthesia, otalgia, and tearing of eyes. Other complaints consisted of body ache (mainly chest and back region), limb paraesthesia and numbness (mainly hands and feet), fever, fatigue, headache, nausea, and ataxia.

3.3. Investigation and diagnostic results

CSF, MRI and CT Scan Brain and/or Spine were frequent investigations conducted by physicians. CSF analysis results were documented for 36 patients (62.07%). Albuminocytological dissociation was confirmed in approximately 2/3rd of patients (63.89%). Studies did not report the results of CT and MRI for 22 patients (37.93%). Amongst the remaining 36, enhancement of CN 7 was detected in the MRI Brain of 8 patients (22.22%). GBS was diagnosed in 67.24% of patients.

3.4. Treatment plan and its outcome

Intravenous immunoglobin (IVIg) (n = 27), corticosteroids (prednisolone, prednisone and methylprednisone) (n = 20) and Plasmapheresis (n = 8), were the first line of treatments. Antivirals (valacyclovir and acyclovir) (n = 5), eye care (eye drops and artificial tears) (n = 7)and rehabilitation measures (facial and physical) (n = 3) were oftentimes part of the treatment plan to foster faster recuperation. The outcome of the aforementioned treatment plan was documented for 54 patients across 34 studies. 75.93% patients (n = 41) partially recovered (PR)in the duration of the follow-up while 22.22% (n = 12) completely recovered (CR). 1 patient showed full improvement after his first onset of facial palsy following the 1st dose, but partial recovery after a recurrence of facial paralysis, after the 2nd dose. Partially recovered patients were either undergoing rehabilitation or continued the empiric treatment. It is also noteworthy that the follow-up period was insufficient, thus partially recovered patients should not be categorised as a failure in the treatment plan. Considering the rate of recovery in each patient, PR should instead be deemed as a favourable treatment outcome.

3.5. Pathophysiology

A temporal association between the COVID-19 vaccine and Bell's palsy has been accepted by numerous authors, but the pathogenesis is unclear. Genetic predisposition notwithstanding, viral infections, especially of the upper respiratory tract, are classically associated with demyelinating polyneuropathies. Damage may occur directly (autoimmune) or indirectly, compromising the blood supply; the vasa nervum (ischemia) or by degeneration of the myelin sheath (inflammation) [52].

Vaccines containing the viral vector, imitate the infection to trigger an exaggerated autoimmune response [59]. Antibodies generated against the virus protein, cross-react with the peripheral nerve proteins, causing demyelination. According to multiple speculations, this host antibody-antigen reaction may occur due to molecular mimicry. Similar vaccine epitopes, present in the myelin and axons, may spread by inflammation or superantigens. Vaccines also show an adjuvant effect, enhancing antigen presentation. Additionally, bystander activation of dormant self-antigens stimulates autoreactive T cells. Thus, causing an increased cell-mediated response [28,59]. Ozonoff et al. presented a valid discussion between the FDA Vaccines, Related Biologic Products Advisory Committee and Pfizer on the vaccines' likelihood to activate the body's innate immunity by the combination of mRNA and lipids. Hence, the interferons produced, interrupt the peripheral tolerance,

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Table 1

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| Characteristics of incl | luded studie | es. |
|-------------------------|--------------|-----|
|-------------------------|--------------|-----|

| S | # Author | Study type | y No o case | of Patien s S# | tt Past History/ comorbids | Age/sex | GBS Present | Affected ? side of face | COVID-19 vaccine name/ type | Which dose led to a symptom? | onset of facial symptom after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatment outcome |
|---|---------------------------|------------------|----------------|-------------------|-------------------------------|---------|----------------|----------------------------|------------------------------------|---------------------------------------|--|---|---|---|-------------------------------------|--|---|----------------------|
| 1 | Colella et al. | LTE | 1 | 1 | None | 37/M | No | Left | Pfizer- BioNTech | 1 | 5 days | left facial droop, lagophthalmos and mild labial hypomobility with flattening of forehead's skin and pacelobial fold | Malaise, fatigue, headache, left latero-cervical pain and monolateral muscular weakness | N/A | N/A | N/A | prednisone, eye drops and night time eye dressing | PR |
| 2 | Finsterer et al. | Case repor | 1 rt | 1 | GBS | 32/M | Yes | Right | vector-based vaccine | 1 | 8 days | dysphagia | peripheral limb paraesthesia, muscle weakness and headache | Neurologic: Right peripheral facial palsy affecting orbicularis oris muscle, motor: B/L muscle weakness and DTR reduced | Protein: elevated | MRI brain and cervical spine: B/L few nonspecific T2- hyperintensities in the white matter | IVIg and plasmapheresis | PR |
| 3 | Repajic et al. | Case repor | 1 rt | 1 | Bell's palsy and HTN | 57/F | No | Left | Pfizer- BioNTech | 2 | 1 day | left facial droop and lagophthalmos, left ear otalgia and aguesia | jaw pain | Neurologic: consistent with CN7 palsy; motor, sensory, gait and cerebellar examination normal. | N/A | N/A | prednisone and antivirals | CR |
| 4 | Nishizawa et a | l. Case repor | 1 rt | 1 | T2DM, HTN and hyperlipidemia | 62/F | No | Right | J&J/Janssen COVID-19 vaccine | N/A | 20 days | Right facial paralysis, lagophthalmos HB grade VI | None | Physical: consistent with facial palsy; motor, sensory, gait and cerebellar examination normal. | N/A | Head CT and brain MRI: unremarkable | N/A | N/A |
| 5 | Martin-Villares et al. | 5 LTE | 1 | 1 | Bell's palsy | 34/F | No | Right | Moderna COVID-19 vaccine | 1 | 2 days | right facial pain, facial palsy HB grade III | None | N/A | N/A | MRI: unremarkable | Deflazacort, eye support, facial rehabilitation | CR |
| 6 | Maramattom et al. | Case series | 7 s | 1 | None | 43/F | Yes | B/L | Oxford- Astrazeneca | 1 | after 20 days | facial diplegia | upper back pain, areflexic quadriparesis and respiratory failure | sensory: normal; motor strength: severely weakened muscle power and areflexia | Albuminocytological dissociation | N/A | IVIg and MV | CR |
| | | | | 2 | N/A | 67/F | Yes | B/L | same | 1 | 16 days | facial diplegia and dysphagia | distal paraesthesia, limb weakness and respiratory failure | CN: Right abducens palsy, facial diplegia, and bulbar palsy Sensory: abnormal; motor strength: severely weakened muscle power and areflexia | Albuminocytological dissociation | MRI Brain: unremarkable | MV, IVIg and plasmapheresis | PR |
| | | | | 3 | N/A | 53/F | Yes | Right | same | 1 | 12 days | facial and tongue numbness | B/L LL numbness, weakness, back pain and Respiratory failure | CN: Right facial and tongue numbness, facial diplegia. Sensory - B/L LL distal sensory impairment (pinprick and | Albuminocytological dissociation | MRI Brain: unremarkable | MV and IVIg | PR n next page) |

S # Author Study No of Patient Past History/ Age/sex GBS Affected COVID-19 Which onset of Clinical features Other Examination CSF analysis results Investigation Treatment Treatment type cases S# comorbids Present? side of face vaccine name/ dose facial of facial palsy complaints results outcome type led to a symptom symptom? after last vaccination vibration), right trigeminal V2-V3 sensory impairment (touch, pinprick). Areflexia N/A 68/F Yes B/L 18 days B/L facial B/L UL and LL CN: facial diplegia, Albuminocytological MV and IVIg PR 4 same 1 numbness, LMN numbness, bulbar palsy, B/L dissociation MRI Brain: facial weakness weakness. facial unremarkable and dysphagia areflexic flaccid numbnessSensory: quadriplegia and B/L distal UL and LL numbness, respiratory failure (distal LL pinprick impairment), B/L sensory impairment to touch in all 3 divisions of the trigeminal nerve, areflexia 5 N/A 11 days facial diplegia, B/L distal UL and CN: facial diplegia, N/A N/A MV and IVIg PR 70/M Yes B/L same 1 B/L facial LL numbness and bulbar numbness and respiratory palsySensory: B/L distal UL and LL bulbar palsy failure numbness, no objective sensory impairment and areflexia 6 N/A 12 days facial diplegia B/L distal UL and CN: facial diplegia, N/A PR 69/F Yes B/L 1 N/A IVIg and same and bulbar palsy LL numbness, bulbar palsy, Plasmapheresis complete complete ophthalmoplegia ophthalmoplegia, leading to left Sensory: B/L UL Abducens nerve and LL distal numbness, no palsy objective sensory impairment and areflexia 7 CN: facial diplegia, albuminocytological N/A PR N/A 69/F Yes B/L same 1 13 days facial diplegia B/L UL and LL MV and IVIg and bulbar palsy numbness and bulbar dissociation palsySensory: B/L respiratory UL and LL failure numbness, no objective sensory impairment and areflexia 7 Allen et al. 16 days DTR normal, no cell count: elevated; MRI brain: oral Prednisolone PR Case 4 1 None 54/M Yes B/L Oxford-1 bifacial distal series Astrazeneca weakness dysesthesia in objective Protein: elevated unremarkable feet and hands sensorimotor signs. Cerebellar, bulbar, extraocular movement and respiratory function normal.

No dysautonomia

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Table 1 (continued)

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| S # Author | Study type | No of cases | Patient S# | Past History/ comorbids | Age/sex | GBS Present? | Affected side of face | COVID-19 vaccine name/ type | Which dose led to a symptom? | onset of facial symptom after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatment outcome |
|--------------------|----------------|----------------|---------------|---|---------|-----------------|--------------------------|-----------------------------------|---------------------------------------|--|---|--|---|--|---|---|----------------------|
| | | | 2 | ulcerative colitis | 20/M | Yes | B/L | same | 1 | 26 days | Bifacial weakness | occipital headache, dysesthesia in distal LL | General exam: unremarkable neck movement uncomfortable, remainder of the neurological examination normal. DTR normal, no objective sensorimotor signs. Cerebellar, bulbar, extraocular movement and respiratory function normal. No dysautonomia General exam: | cell count: elevated; Protein: elevated | MRI Brain: unremarkable | oral Prednisolone | PR |
| | | | 3 | asthma and osteoarthritis with B/L knee replacement | 57/M | Yes | B/L | same | 1 | 21 days | bifacial weakness, dysarthria | lumbar back pain that radiated to flanks, distal dysesthesia in feet, proximal leg weakness | unremarkable subjective diplopia on extreme left gaze, normal extraocular eye movements. Symmetric weakness proximally in legs. DTR absent at the knees but normal alsowbare | cell count: elevated; Protein: elevated | Noncontrast MRI brain: unremarkable | IVIg | PR |
| | | | 4 | HTN | 55/M | Yes | B/L | same | 1 | 29 days | facial diplegia | B/L thigh paresthesias, sacral and lumbar numbness | N/A | albuminocytological dissociation | MRI brain and whole spine with contrast: enhancement of the facial nerve | None | CR |
| 8 Iftikhar et al. | Case report | 1 | 1 | None | 36/M | No | Left | Moderna COVID-19 vaccine | 2 | 1 day | facial weakness | left deltoid weakness, difficulty in speaking and eating, mild numbness and tingling of left arm, left subjective UL weakness | N/A | N/A | CT and MRI brain: unremarkable | oral Prednisolone and artificial tears | PR |
| 9 Bonifacio et al. | LTE | 5 | 1 | N/A | 66/M | Yes | B/L | Oxford- Astrazeneca | 1 | 17 days | facial weakness, tongue and mouth numbness | paraesthesia of hands and feet | marked B/L LMN facial weakness. Tone, power and reflexes normal, but absent right ankle jerk. Light touch and pinprick sensation reduced symmetrically in B/L LL, gait ataxia | albuminocytological dissociation | MRI: unremarkable except for B/L smooth contrast enhancement along whole facial nerve | IVIg | PR |

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| S # Author | Stud <u>y</u> type | y No c case | of Patien s S# | t Past History/ comorbids | Age/sex | GBS Present | Affected side of face | COVID-19 vaccine name/ type | Which dose led to a symptom? | onset of facial symptom after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatment outcome |
|--------------------|-----------------------|----------------|-------------------|-------------------------------------|---------|----------------|-------------------------------|-----------------------------------|---------------------------------------|--|---|---|--|--|---|----------------------------|----------------------|
| | | | 2 | N/A | 43/M | Yes | B/L | same | 1 | 17 days | severe facial weakness, dysphagia, dysguesia, tongue paraesthesia | myalgia, pins and needles in extremities, severe neck pain, urinary retention | severe B/L LMN facial weakness. Limb tone normal, mild weakness in right hip flexion. Reflexes were later lost. Flexor planter responses, Patchy, asymmetrical glove and stocking reduction in pinprick sensation, sensory ataxia. | cell count: elevated; Protein: elevated | MRI: unremarkable except for B/L smooth contrast enhancement along whole facial nerve | IVIg | PR |
| | | | 3 | N/A | 51/M | Yes | Right, progessed to B/L | same | N/A | 14 days | facial weakness | severe cramping leg pain, feet and hands numbness, spread to ankles | complete B/L LMN facial weakness. Tone, power and reflexes normal. Sensation impaired in all limbs, sensory ataxia. | albuminocytological dissociation | MRI: unremarkable except B/L smooth contrast enhancement along whole facial nerve | None | PR |
| | | | 4 | COVID-19 infection 5 weeks prior | 71/F | Yes | B/L | same | N/A | 15 days | facial weakness and dysguesia | lower back and abdominal pain, mild proximal leg weakness. | severe B/L LMN facial weakness, slight B/L weakness in hip flexion. Absent knee and left ankle reflexes, normal sensory | albuminocytological dissociation | MRI: unremarkable | None | PR |
| | | | 5 | N/A | 53/M | Yes | B/L | same | N/A | 14 days | facial and perioral paraesthesia progressing to severe simultaneous B/ L facial weakness | lower back discomfort, radicular pain, LL parasthesia | severe LMN B/L facial weakness, normal power elsewhere. UL reflexes depressed; LL normal. Mild distal LL sensory loss to vibration and ninprick | Albuminocytological dissociation | CT: unremarkable | None | PR |
| 10 Nasuelli et al. | Case repor | 1 rt | 1 | HTN and hyperuricemia | 59/M | Yes | B/L | Oxford- Astrazeneca | 1 | 10 days | facial diplegia, progressed to HB grade V | four limb distal paraesthesia, postural instability | physical exam: gait ataxia, global areflexia, distal UL and LL paraesthesia. No CN, vegetative, or sphincter involvement No spine sensory level | albuminocytological dissociation | Brain and cervical MRI: unremarkable | IVIg and rehabilitation | PR |
| 11 Burrows et al. | Case repoi | 1 rt | 1 | T2DM, HTN and hyperlipidemia | 61/M | No | Right | Pfizer- BioNTech | 1 | 5 h | right facial weakness | N/A | Right LMN facial palsy, lagophthalmos, no forehead movement | N/A | N/A | Prednisolone | CR |
| | | | | | | | | | | | | | | | | (continued | on next page) |

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| S # Author | Study type | No of cases | Patient S# | t Past History/ comorbids | Age/sex | GBS Present | Affected ? side of face | COVID-19 vaccine name/ type | Which dose led to a symptom? | onset of facial symptom after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatment |
|-------------------|----------------|----------------|---------------|--|---------|----------------|-------------------------------|------------------------------------|---------------------------------------|--|---|---|---|--|---|---|-----------|
| | | | | | | | Left | | 2 | 2 days | Severe left facial nerve palsy, dribbling and dysphagia | N/A | severe left facial nerve palsy HB grade IV, left lagophthalmos, SB grade 13, remainder of neurological exam and gait normal | N/A | N/A | Prednisolone | PR |
| 2 Obermann et al. | Case report | 1 | 1 | N/A | 21/F | No | Right | Pfizer- BioNTech | 1 | 2 days | facial muscle paralysis | minimal muscle tenderness at injection site | N/A | unremarkable | MRI: unremarkable | oral Prednisolone, face muscle training, eye Protecting ointment and overnight eye patch. | PR |
| 3 McKean et al. | Case report | 1 | 1 | dyslipidaemia | 48/M | Yes | Left, progressed to B/L | Oxford- Astrazeneca | 1 | 10 days | LMN facial weakness, initially HB grade III, progressed to grade V | severe mid- thoracic back pain | Progressive ascending paraesthesia, B/L LL weakness with foot drop, inability to bear weight, hand weakness and LL areflexia, impaired sensation to pain | cell count: elevated; Protein: elevated | MRI and CT brain: normal | IVIg, oral Prednisolone and physiotherapy | PR |
| ‡ Rossetti et al. | Case report | 1 | 1 | anxiety, depression, drinker and drug addict | 38/M | Yes | B/L | J&J/Janssen COVID-19 vaccine | 1 | 14 days | facial weakness, tongue and lips numbness and tingling, dysarthria, difficulty drinking from a straw and controlling his lips, cheeks, and tongue while eating | B/L hand and foot paresthesias | general exam: headaches, mild gait unsteadiness, generalized fatigue, exertional dyspneadysarthria, B/L LMN facial weakness, mild lagophthalmos B/ L, inability to smile or puff cheeks against resistance. DTR reduced | albuminocytological dissociation | MRI brain: focal enhancement of the B/L internal auditory canal fundi and B/L cisternal segments of the trigeminal nerves | IVIg | PR |
| 5 Čenščák et al. | Case report | 1 | 1 | bronchial asthma | 42/M | Yes | Right | Pfizer- BioNTech | 1 | 25 days | lagopthalmos | hands and feet paraesthesia, unsteady gait, weak knees, lumbalgia | right mimic muscle weakening and lagophthalmos up to 2 mm, handgrip and right arm elevation weak reflexes C5-8 minimal,L2-S2 absent, slow movement in lower limbs, hypoesthesia 10 cm above the wrist, B/L vibration sense mildly weak takes 3–4 steps by leaning, knees buckling and etavia | albuminocytological dissociation | MRI LS spine with post- contrast: increased roots of cauda equina | IVIg and rehabilitation | PR |

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| * * Autur Spice your performance Appendix performance Spice your performance <t< th=""><th>C # Auth</th><th>04 1</th><th>N</th><th>Deci</th><th>Dent History</th><th>A - 1 /</th><th>- CPC</th><th>A 66 1</th><th>001/ID 10</th><th>TATL: 1</th><th></th><th></th><th>Other</th><th>Provide of 1</th><th>COT and a state</th><th>T</th><th>Turatura</th><th>Trans</th></t<> | C # Auth | 04 1 | N | Deci | Dent History | A - 1 / | - CPC | A 66 1 | 001/ID 10 | TATL: 1 | | | Other | Provide of 1 | COT and a state | T | Turatura | Trans |
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| 10 Pander is 10 Pander is 11 Pander is 11 Pander is | S # Author | Study type | No of cases | S# | t Past History/ comorbids | Age/sex | GBS Present | Affected ? side of face | COVID-19 vaccine name/ type | Which dose led to a symptom? | onset of facial symptom after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatmer outcome |
| 2 Chatchesses See 1 3 Zabbit and blackses Yao Yao No. No. No. No. No. Sees Sees Sees Main | 16 Prasad et al. | Case report | 1 | 1 | morbidly obese | 41/M | Yes | B/L | J&J/Janssen COVID-19 vaccine | 1 | 15 days | left facial droop, difficulty eating, right facial weakness | subjective weakness, distal paraesthesia, limb areflexia | CN: B/L LMN facial nerve palsy, more prominent on the left. B/L DTR absent at the patella and Achilles, mute plantar responses | albuminocytological dissociation | CT and MRI brain: colloid cyst MRI LS with contrast: thickening of cauda equina | IVIg and rehabilitation | PR |
| 18 Rutkove is port Case is port I None SM Yes No. Add/Amase is port No. 14 sty Relative is port No. Beak is port No. Busine is port Busin | 17 Christensen et al. | Case report | 1 | 1 | T2DM and Diabetic foot | 73/M | Yes | B/L | Moderna COVID-19 vaccine | N/A | 7 days | tingling in tip of tongue and around mouth, progressive B/L facial paresis and dysarthria | B/L sensory disturbances in LL, tingling in fingertips and dorsum of hands, left thoracic back pain radiating to the neck and jaw, could not walk | reflexes weakened, sensory ataxia in lower extremities. | unremarkable | MRI: unremarkable | None | PR |
| 19 Mason et al. Case 1 1 migraine badcheshes 35/7 Yes Right, Moderna N/A 28 days facial weakers occipici oculal not as albuminecytological contrait MRI IV IPR 8 No eport alcohe): 3 dinuks per week output angoptabalano, alcoheshes, mile sociation Angiography, a | 18 Rutkove et al. | Case report | 1 | 1 | None | 58/M | Yes | B/L | J&J/Janssen COVID-19 vaccine | N/A | 14 days | facial weakness | modest appendicular weakness, small subarachnoid hemorrhages | N/A | albuminocytological dissociation | N/A | N/A | N/A |
| 20 Corrèa et al. Case 1 1 None 1 7 days left otalgia, None N/A unremarkable Brain MRI with oral Prednisone CR report - | 19 Mason et al. | Case report | 1 | 1 | migraine headaches alcohol: 3 drinks per week | 35/F | Yes | Right, progessed to B/L | Moderna COVID-19 vaccine | N/A | 28 days | facial weakness and asymmetry, dysarthria, dysphagia, lagophthalmos | occipital headaches, mild right arm weakness | could not raise eyebrows, B/L lagophthalmos, unable to frown or smile. B/1 N/ Asolabial fold flattening, right handgrip weak CRanial nerves, touch, vibration, reflexes normal | albuminocytological dissociation | contrast MRI Brain and CT Angiography: unremarkable | IV methylprednisolone and acyclovir | PR |
| 21 Oo et al. Case 2 1 NSTEMI and seasonal 51/M Yes B/L Oxford-1 14 days diplopia, lower back pain, diplopia, bifacial albuminocytologic N/A IVIg, MV and PR series influenza Astrazeneca dysphagia and Respiratory weakness, dissociation plasmapheresis bifacial failure, LL motor moderate neck weakness, and progressive deficit, weakness, and series influenza plasmapheresis influenza | 20 Corrêa et al. | Case report | 1 | 1 | None | 42/M | Yes | Left | Oxford- Astrazeneca | 1 | 7 days | left otalgia, facial muscles weakness, forehead muscles paralysis, lagophthalmos and labial hypomobility | None | N/A | unremarkable | Brain MRI with gadolinium: enhanced canalicular and labyrinthine portions of the left facial nerve and left geniculate exanelion | oral Prednisone | CR |
| | 21 Oo et al. | Case series | 2 | 1 | NSTEMI and seasonal influenza | 51/M | Yes | B/L | Oxford- Astrazeneca | 1 | 14 days | diplopia, dysphagia and bifacial weakness | lower back pain, Respiratory failure, LL motor deficit, progressive ascending LL sensorimotor deficit and areflexia | diplopia, bifacial weakness, moderate neck weakness, and flaccid areflexic quadriparesis with prominent proximal LL weakness. Pinprick sensation was distally reduced on the right LL | albuminocytologic dissociation | Ň/Ă | IVIg, MV and plasmapheresis | PR |

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| S # Author | Study type | No of cases | Patien S# | t Past History/ comorbids | Age/sex | GBS Present? | Affected side of face | COVID-19 vaccine name/ type | Which dose led to a symptom? | onset of facial symptom ? after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatment outcome |
|-------------------|----------------|----------------|--------------|---|---------|-----------------|-------------------------------|---------------------------------------|---------------------------------------|--|---|--|--|--|---|---|----------------------|
| | | | 2 | Renal Cell Carcinoma Atrial Fibrillation Hypercholesterolemia | 66/M | Yes | Right | Oxford- Astrazeneca | 1 | 21 days | NA | lower back pain, progressive ascending sensorimotor involvement -proximal LL weakness | Peoximal paraparesis, prominent right facial LMN weakness, and areflexia | Albuminocytologic dissociation | N/A | IVIg and rehabilitation | PR |
| 22 Yu et al. | Case report | 1 | 1 | left Bell's palsy | 36/F | No | Right | Sinovac | 1 | 2 days | facial weakness and droop, eye discomfort, disappeared forehead wrinkles, lagophthalmos | None | CN: HB grade III isolated right CN 7 palsy motor, sensory, and cerebellar examinations normal. | N/A | CT Brain: unremarkable | Prednisone, artificial tears, fluorometholone eye drops and acupuncture therapy | PR |
| 23 Caro et al. | LTE | 1 | 1 | N/A | 50/M | No | left | Pfizer- BioNTech | 1 | 9 days | facial droop and effacement of left Nasolabial fold | tenderness at injection site. | complete left facial paralysis, lagopthalmos, unable to raise eye brow or left labial fissure. | N/A | MRI: intra cranial space occupying lesions and ischemic changes | Prednisone and articial tears. | |
| 24 Ish et al. | LTE | 1 | 1 | None | 50/M | No | Right | Covaxine | 2 | 7 days | right lagopthalmos with redness and watering | None | Lagopthalmos with lower lid ectropion temporally. Drooping of angle of mouth, loss of nasolabial fold and wrinkiling of forehead. | N/A | N/A | topical antibiotics, lubricating eye drops and oral prednisone | |
| 25 Karimi et al. | Case series | 5 | 1 | None | 38/M | Yes | Right, progessed to B/L | Sputnik V | 2 | 14 days | B/L facial numbness and weakness | numbness and parasthesias in distal UL | B/L Facial palsy HB grade IV | cell count: elevated; Protein: elevated | MRI: unremarkable | plasmapheresis | |
| | | | 2 | None | 38/M | Yes | B/L | Sputnik V | 1 | 6 days | B/L facial paralysis | LL weakness, decreased B/L sensation up to ankles and areflexia with flexor plantar responses. | B/L facial palsy HB grade IV and mild decreased LL light touch sensation and proprioception, distal to the ankle joints. Absent DTR | cell count: elevated; Protein: elevated | MRI brain and CS: few nonspecific B/L T2- hyperintensities viewed in the white matter | plasmapheresis | |
| | | | 3 | HTN | 48/F | Yes | B/L | Sputnik V | 1 | 17 days | B/L facial paralysis | generalized weakness with bulbar symptoms, dyspnea, and autonomic disorder. | Absent DTR. | N/A | N/A | Plasmapheresis and IVIg | |
| | | | 4 | HTN | 44/M | Yes | B/L | Oxford- | 1 | 14 days | B/L facial | LL parasthesia | flaccid tetraparesis | cell count: elevated | N/A | IVIg | |
| | | | 5 | HTN/CABG | 79/M | Yes | B/L | Astrazeneca Oxford- Astrazeneca | 1 | 7 days | B/L facial paralysis | UL and LL parasthesia and weakness | B/L Facial palsy HB grade IV with UL and LL weakness and DTR absent. | N/A | N/A | Plasmapheresis | |
| 26 Kanabar et al. | Case | 2 | 1 | MS | 61/F | Yes | B/L left > | Oxford- | 1 | 10 days | B/L LMN facial | LL weakness, | N/A | N/A | N/A | IVIg | |
| | series | | | | | | right. | Astrazeneca | | | weakness (HB | decreased B/L | | | | (continued of | n next page) |

| 5 # Author | Study type | No of Patient cases S# | t Past History/ comorbids | Age/sex | GBS Present? | Affected side of face | COVID-19 vaccine name/ type | Which dose led to a symptom? | onset of facial symptom after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatment outcome |
|-------------------|----------------|---------------------------|------------------------------|---------|-----------------|--------------------------|-----------------------------------|---------------------------------------|--|---|---|--|--|---|---|----------------------|
| | | 2 | N/A | 56/M | Yes | B/L | Oxford- Astrazeneca | 1 | 7 days | grade IV on the left and grade III on the right) B/L facial paralysis | sensation up to ankles severe back and LL radicular pain, LL numbness | B/L LMN facial weakness (HB grade IV on the left and grade III on the right) and decreased vibration sensation at the ankles. Areflexic plantar | N/A | N/A | IVIg | |
| 7 Cellina et al. | Case report | 1 1 | N/A | 35/F | No | left | Moderna COVID-19 | 1 | 12 h | facial droop, dysphagia and | None | response. slight asymmetry of the left corner of the mouth | N/A | MRI: enhancement of loft facial portu- | oral Prednisone | |
| 3 Walter et al. | LTE | 1 1 | None | 30/F | No | left | vaccine Pfizer- BioNTech | 2 | 2 months | left facial paralysis | ataxia | left facial paralysis, discreet right CN XII paralysis and massive ataxia of all extremities | Albuminocytological dissociation | MRI brain: weak flair hyperintensity of the brainstem, mesencephalon and cerebellar around the fourth ventricle without contrast. MRI of cervical and thoracic spine: unremarkable | IV cortisone with methylprednisolone | |
| ≀ Li Dang et al. | case report | 1 1 | N/A | 63/M | Yes | B/L | Oxford- Astrazeneca | 1 | 14 days | severe B/L facial weakness | sensory ataxia, facial diplegia involving forehead, proximal LL weakness | profound sensory ataxia, facial diplegia involving the forehead, proximal LL weakness, B/L LL areflexia and impaired distal LL proprioception, inability to walk without assistance and B/L lagophtalmos | albuminocytoloigcal dissociation | MRI contrast: B/ L enhancement of CN III and CN VII, consistent with facial diplegia and partial B/L CN III palsy | IVIg | |
| 0 Kharoubi et al. | Case report | 1 1 | Smoker | 42/M | No | Right | Recommbinant vaccine | 1 | 2 days | right facial assymtery | None | peripheral facial paralysis (Charles- Bell positive) HB grade III | N/A | N/A | Prednisone with eye care | |
| . Badoiu et al. | LTE | 1 1 | N/A | 53/F | Yes | B/L | Oxford- Astrazeneca | 1 | 13 days | Asymmetric facial diplegia | tetrameric distal paraesthesia, progressive limb weakness. | mini mental motor deficit, hypopalasthesia, areflexia all 4 limbs, minimal ataxic gait. B/L | albumino- cytological dissociation | MRI: unremarkable. | plasmapheresis | |

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| S | # Author | Study type | No o cases | f Patient S# | : Past History/ comorbids | Age/sex | x GBS Present | Affected ? side of face | COVID-19 vaccine name/ type | Which dose led to a symptom? | onset of facial symptom after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatment outcome |
|---|-----------------------------|----------------|---------------|-----------------|------------------------------|---------|------------------|-------------------------------|-----------------------------------|---------------------------------------|--|--|---|--|-----------------------------------|---|-------------------------------------|----------------------|
| 3 | 2 Kulsirichawaroj et al. | Case report | 1 | 1 | None | 16/F | No | Right, progessed to B/L | Pfizer- BioNTech | 1 | 3 h | right facial numbness and drooling, right lagophthalmous, aguesia and difficulty furrowing right evebrow | None | right facial hypoesthesia, complete right facial palsy, reduced taste in anterior 2/3rd of mouth and absent right gag reflex | N/A | MRI brain and CN: abnormal enhancement of right CN VII | IVIg | |
| 3 | 3 Kim et al. | Case report | 1 | 1 | N/A | 48/F | No | Left | Oxford- Astrazeneca | 1 | 14 days | left facial paresis | band like pain in chest. | left facial paresis | N/A | N/A | IVIg and Prednisolone | |
| 3 | 4 Mirmosayyeb et al. | Case series | 2 | 1 | N/A | 27/F | No | Left | Sputnik V | 1 | 5 days | left lagophthalmous, rightward deviation of left upper lip and unable to drink with straw | Pain at injection site and malaise. | facial nerve hemiparalysis | N/A | N/A | Prednisolone with valcyclovir | |
| | | | | 2 | N/A | 58/M | No | Left | Sputnik V | 1 | 10 days | sudden left facial weakness and lagophthalmos, left mouth droop, drooling, aguesia, slurring of speech, tearing, inability to chew, smile, and move the left evebrow | hyperthermia, myalgia, and pain in the injection site. | left facial paresis and lagopthalmos | N/A | N/A | Prednisolone and valacyclovir | |
| 3 | 5 Mussatto et al. | case report | 1 | 1 | HIV and CKD | 60/M | No | Left | Pfizer- BioNTech | 1 | 42hrs | left facial droop and left lagophthalmos | NA | left facial weakness with forehead involved, inability to raise left eyebrow, sensation and strength intact in B/L UL and LL, mild exposure keratopathy, 5 mm Jagonhthalmos | N/A | N/A | oral Prednisone and valacyclovir | |
| 3 | 6 Andreozzi et al. | Case series | 2 | 1 | Hashimoto thyroiditis | 59/M | No | B/L | Oxford- Astrazeneca | 1 | 15 days | B/L facial numbness | acute spontaneous burning pain of lower back, LL paraesthesia | complete facial diplegia and lagophtalmos: B/L loss of frontal forehead creases, could not raise eyebrows, and could not whistle or smile, mild wsarthria. | albuminocytologic dissociation | CT: unremarkable | IVIg | |
| | | | | 2 | Atrial fibrillation | 43/M | Yes | B/L | Oxford- Astrazeneca | 1 | 7days | subacute facial pain and numbness with lagophthalmos | None | left prevalent facial diplegia; symmetrical weakness MRC grade 4+ in distal UL and LL muscles | albuminocytologic dissociation | N/A | IVIg | |
| | | | | | | | | | | | | | | | | | (continued o | n next page) |

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| atient Pa # co | st History/ morbids | Age/sex GBS Pres | Affected sent? side of face | COVID-19 e vaccine name/ type | Which dose led to a symptom? | onset of facial symptom after last vaccination | Clinical features of facial palsy | Other complaints | Examination results | CSF analysis results | Investigation | Treatment | Treatment outcome |
|-------------------|------------------------|---------------------|--------------------------------|-------------------------------------|---------------------------------------|--|--|---|---|--|--|-----------|----------------------|
| 1 | graine | 60/F Yes | B/L | J&J/Janssen COVID-19 vaccine | 1 | 18 days | B/L facial weakness and numbness | back and leg pain, headache, nausea, vomiting, and diplopia | Left eye esotropia, B/L ocular abduction deficit, areflexia and LL weakness | cell count: elevated; Protein: elevated | MRI LS: enhancement ol cauda equina; Brain MRI: normal | IVIg | |

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T2DM, Type 2 Insulin Independent Diabetes Mellitus; MRI, Magnetic Resonance Imaging; CT, Computed Tomography; LS, Lumbar Spine; CS, Cervical Spine; IVIg, Intravenous Immunoglobulin; IV, Intravenous; MV, Mechanical Ventilation; HB, House-Brackmann grading system; SB, Sunnybrook Facial Grading System; UL, Upper Limb; LL, Lower Limb; CN, Cranial Nerve; CN III, Occulomotor Nerve; CN VII, Facial Nerve, CN XII, Hypoglossal Nerve; LMN, Lower Motor Neuron; MS, Multiple Sclerosis; NSTEMI, Non ST Elevation Myocardial Infarction; CABG, Coronary Artery Bypass Graft; HIV, Human Immunodeficiency Virus; CKD, Chronic Kidney Disease; DTR, Deep Tendon Reflexes; J&J, Johnson & Johnson; MRC, Medical Research Council Annals of Medicine and Surgery 82 (2022) 104758

causing neuropathy [15].

For non mRNA vaccines like Oxford-AstraZeneca and Janssen vaccine, the chimpanzee adenovirus vector directly attacks the culprit; SARS-CoV-2 spike protein, prompting more T cells activation. A crossreaction follows, destroying the peripheral nerve upon sufficient exposure to the neuronal tissue. Elevated cytokines (IL-1, IL-6) and tumour necrosis factor (TNF a) were found in the patients with Bell's Palsy in comparison to a control group. Hence, proving the incidence of an aggravated cell-mediated response [31]. Sputnik V, a recombinant vector-based vaccine that uses adenovirus 26 (Ad26) and adenovirus 5 (Ad5) for molecular hijacking and expression also causes a similar immune-mediated reaction [30]. However, with immunogenetics specific to the individual, the HLA haplotype profile must not be disregarded in precipitating autoimmune neurological disorders [26].

Despite the inconclusive hypotheses, numerous patients found quick relief from IVIg therapy. Consequently, this directs us towards underlying immune-mediated pathogenesis holding the greatest probability [54].

4. Discussion

We reviewed the complete clinical course of 58 patients with symptomatic facial palsy following the COVID-19 vaccination. Besides the chief clinical features, patients often presented with accompanying body aches, fatigue, paraesthesia, and ataxia. These were also noted as major adverse events post-COVID-19 vaccination, in a study by Dutta et al. [17]. Of the reviewed cases, the majority were inoculated by the Oxford-AstraZeneca, a non-mRNA chimpanzee adenovirus vector vaccine, followed by 15% with Pfizer, an mRNA vaccine. Furthermore, these two vaccines have been linked to 15,538 (Pfizer) and 2751 (Oxford-Astra Zeneca) neurological adverse events, including facial palsy [17]. During phase 3 trials, 4 volunteers, who received the Pfizer vaccine, developed facial palsy as compared to zero in the control group [14]. However, this numerical imbalance was not reported with Oxford-AstraZeneca. Regardless, the numerous cases in our study, involving Oxford-AstraZeneca, warrant further exploration of the safety and efficacy of this vaccine.

Over half, 53.45%, of our recorded patients had bilateral facial palsy. Bell's Palsy is usually unilateral with an idiopathic aetiology whereas, bilateral is exceedingly rare, and secondary to systemic diseases like GBS [42]. This association must be credited as 67.24% of our patients were primarily diagnosed with GBS. Post-vaccination GBS has been analysed by several authors. The SARS-CoV 2 spike protein, in the vaccine, increases its transmission by binding to sialic acid-containing glycoprotein and gangliosides present on the neuronal cells' surface. After adequate exposure to the nerve components, antiganglioside antibodies are generated, ensuing in an autoimmune reaction. Thus, demyelination occurs after inflammatory changes, presenting with the afore-mentioned polyradiculopathy [26,27]. This could include the Facial Nerve (CN VII) of both sides, defining bilateral Bell's Palsy. Furthermore, CSF analysis shows albuminocytologic disassociation which can distinctively identify the acute inflammatory phase. An elevated protein level (normal is 0.55 g/L) in two-thirds of the patients, echoes nerve roots' inflammation [60].

In our sampled data, most patients complained of facial palsy after the first dose of vaccination (88%). While there is insufficient literature to explain the tapering rates of facial palsy in consecutive doses, several patients completed their vaccination after recovery. According to the demographic distribution, facial palsy affects people of all ages, with a peak incidence in patients in their 40s, similar to the observed mean age in our review (49.93 \pm 14.16 years) [2]. The prevalence of Bell's palsy after immunization in this age group can be attributed to the higher reactogenicity of the COVID-19 vaccine among individuals between 18 and 65 years of age [17]. The reduced reactogenicity in patients above 65 years of age can be rationalized by immunosenescence; a series of age-linked changes in the soluble molecules that direct the maintenance

and function of the immune system, the lymphoid organs that coordinate the maintenance of lymphocytes; and the initiation of immune responses [61] Ten per cent of patients also reported a recurrence of facial palsy; theoretically, because vaccination triggers a speedy shift from a subclinical to a symptomatic condition [59]. Other minor factors like a Human Immunodeficiency Virus (HIV) infection can also increase the risk of facial palsy [56]. Similarly, a history of facial palsy during 1st pregnancy and existing VZV-IgG antibodies can also manifest a potential reoccurrence [36].

Based on prior studies, about 5% of current patients are at high-risk for sequelae, especially synkinesis, incomplete or abnormal regeneration of the damaged facial nerve [3]. The most threatening consequence is permanent paralysis. Additionally, the malformation of nerve openings into different glands and ducts causes functional impairment.

Nonetheless, recovery is generally spontaneous from this adverse event following immunisation (AEFI). Maximally, 9 months have been observed for complete recuperation given an early and compliant corticosteroids course [16]. Oral corticosteroids, primarily prednisone, and IVIg therapy, have shown greater success than surgical management [1]. Corticosteroids are anti-inflammatory drugs, so the provided relief supports the inflammatory mechanism highlighted above. A favourable response to IVIg and Plasmapheresis indicated the cell's autoimmunity at play. Additionally, for lagophthalmos, treatment included eye drops, artificial tears, and temporary eye patches, to protect the vulnerable eye. Interestingly, a cohort study reported 16 more patients with acute bell's palsy during the pandemic in 2020 than in 2019, with a history of current or recent symptomatic COVID-19 infection [62]. Moreover, Tamaki et al. found an increased risk of Bell's palsy by 6.8% in individuals with COVID-19 infection versus those who were COVID-19 vaccinated [63]. Principally, SARS-CoV-2 has proved that its neurotropism is just one of the many strikes on multiple organ systems. Meanwhile, various authors emphasise that Bell's palsy has a high frequency of positive outcomes. The majority of our reviewed patients had partially recovered with hopes of full remission. The lack of follow-up in the reports hindered in providing an accurate analysis of the prognosis as many were undergoing treatment or within the expected duration noted for a complete symptomatic recovery.

5. Limitations

There were some limitations in the scope of our study, as case reports and series only assess a small number of patients. A total of 58 patients was insufficient to reach an accurate conclusion. A greater pool of patients with standardized reporting of clinical courses is needed for a definitive correlation between facial palsy and the COVID-19 vaccine. Larger, more robust studies must be analysed to assess the neurological side effects of the vaccines, particularly Oxford-AstraZeneca and Pfizer, with proper follow-up of the treatment course. This would reduce the reporting bias in the results and give better insight into the severity and prognosis of the condition. Nevertheless, a relationship between COVID-19 vaccines and the risk of facial palsy cannot be discounted.

6. Conclusions

Our review summarised all reported cases of facial palsy secondary to COVID-19 vaccination since the beginning of the pandemic. Oxford-AstraZeneca, a non-mRNA vaccine, was observed to account for most of the cases of facial palsy. A majority of patients were diagnosed with GBS, a demyelinating polyneuropathy, commonly presenting with bilateral facial palsy. Thus, any adverse event following immunisation must be explored and the possibility of such life-threatening disorders cannot be overlooked in clinical practice. Linking the relevant signs and symptoms to a COVID-19 vaccination history can ensure a prompt diagnosis and early management of facial palsy. Fortunately, facial palsy was seen to be a temporary disorder with extremely low chances of incidence in a larger sample size that could accurately reflect a population. With most individuals achieving complete recovery after appropriate therapy, we recommend that patients complete their vaccination after the condition has been resolved.

Ethics approval

No ethical approval was required for this study.

Funding

No financial support was received for this study.

Authors' contributions

Study conception and design: MK, IA, HA, HG. Study conduct and acquisition of data: AK, IU, HAC, AS. Data analysis: MK, IA, HA. Data interpretation: HG, IU, HAC. Drafting of the manuscript: AS, MYE, AK, MK, IA. Critical revision of the manuscript: IU, AS, HAC, MYE, MK. Final approval of the version to be published: All authors. All authors agree to be accountable for all aspects of the work.

Consent

No consent was required for this study.

Availability of data

The data that support the findings of this study are available from the corresponding author, HAC, upon reasonable request.

Registration of research studies

Name of the registry: PROSPERO.

Unique Identifying number or registration ID: CRD42022328860. Hyperlink to your specific registration: https://www.crd.york.ac. uk/PROSPERO/display_record.php?RecordID=328860.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Guarantor

I, Mohammad Yasir Essar, the corresponding author for this review accept my role as the Guarantor for this research.

Declaration of competing interest

The authors declare that they have no conflicts of interest and no financial interests related to the material of this manuscript.

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N/A.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104758.

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