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Trigeminal Neuralgia in COVID-19: A meta-analysis

Neuralgia del Trigémino en COVID-19: Un Metanálisis

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ABSTRACT: The trigeminal nerve is the fifth cranial nerve, which transmits facial sensations, and is divided into the ophthalmic, maxillary, and mandibular branches. Damage to this nerve can cause trigeminal neuralgia, a clinical condition that can also present in patients with coronavirus disease 2019 (COVID-19). This meta-analysis reviews the clinical cases of trigeminal neuralgia reported in patients with COVID-19 from 2019 to 2022, describes the anatomical mechanism of pain and its radiation and identifies other associated symptoms. We performed a literature search to identify reports of patients with COVID-19 who developed trigeminal neuralgia and examined these cases for prevalence and any identified source of associated ocular pain. Of the relevant studies identified, 638 patients with COVID-19 developed trigeminal neuralgia out of 7561 total COVID-19 cases (8.4 %). Of the 638 cases, 590 (7.8 %) had known causes of ocular pain, while the cause of ocular pain was unknown in 48 cases (0.6 %). Trigeminal neuralgia developed infrequently in patients with COVID-19, and cases with known causes of ocular pain were more common than cases with unknown causes. Understanding the link between COVID-19 and trigeminal neuralgia may lead to preventing further complications and mortality in these patients, as well as improving care for patients with these conditions in the future. Additionally, understanding these new clinical issues can prepare many types of physicians to protect themselves better in the event of a COVID-19 outbreak among medical staff in different departments of hospitals, such as clinics, wards, emergency rooms, and operating theatres.

KEY WORDS: COVID-19; Trigeminal neuralgia; Trigeminal nerve; Ophthalmic pain; Thrombosis.

INTRODUCTION

Trigeminal neuralgia is a painful chronic condition involving the trigeminal nerve, and its development has been linked to COVID-19. Trigeminal neuralgia is characterised by chronic and sharp neuropathic pain (sometimes described as similar to an electric shock) on one side of the face, resulting from spontaneous excitation of one or more of the trigeminal nerve branches (Bendtsen *et al*., 2019). Radiating pain in trigeminal neuralgia can be aggravated by non-radiating pain or stimuli from a region that is not innervated by the trigeminal nerve, and the unilateral effect can last between one second and two minutes (Headache Classification Committee of theInternational Headache Society (IHS), 2018) which assists clinicians in diagnosis. The diagnosis is based on the prevalence of causes. The lifetime prevalence of trigeminal neuralgia in population-based studies is between 0.16 % and 0.3 % (Mueller *et al*.,2011). The annual incidence rate of trigeminal neuralgia is between 0.0004 and 0.0013 %, and incidence increases with age (Yadav *et al*., 2017), potentially reaching as high as 0.07 % over 50 years (Headache Classification Committee of the International Headache Society (IHS), 2018; Jones *et al*., 2019).

The trigeminal nerve is the fifth paired cranial nerve that originates from the pons or the middle part of the brainstem. It travels lateral to the cavernous sinus and carries facial sensations to three sensory nuclei

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(mesencephalic, principal sensory, and spinal nuclei) that extend through the brainstem and into the high cervical spinal cord. Additionally, one associated motor nucleus extends into the brainstem to control mastication muscles (masseter, temporalis, and lateral and medial pterygoids, in addition to the tensor veli palatini, mylohyoid, tensor tympani, and anterior belly of digastric muscles). The trigeminal nerve divides into ophthalmic, maxillary, and mandibular branches, located in the skull via the superior orbital fissure, foramen rotundum, and foramen ovale, respectively (Huff *et al*., 2020). Therefore, ophthalmic neuralgia is a part of trigeminal neuralgia.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was originally discovered in Wuhan, China in 2019 (Veritti *et al*., 2020). The resulting condition was named coronavirus disease 2019 (COVID-19), and a global pandemic was declared on March 11, 2020 (Khalili *et al*., 2020). By December 31, 2022, 665,000,000 people had contracted SARS-CoV-2, over 6,700,000 of whom passed away from COVID-19 or its adverse health consequences (Worldometer, 2020). Case studies of trigeminal neuralgia in COVID-19 patients have been reported (Narasimhalu *et al*., 2021; Santovito & Pinna, 2021; Kaya & Kaya, 2022; Onoda *et al*., 2022), but "the link between trigeminal neuralgia and COVID-19 is not yet well understood". This meta-analysis highlights the different clinical features of trigeminal neuralgia that are present in patients with COVID-19, and it describes the neuroanatomical mechanisms of associated and radiating pain.

MATERIAL AND METHOD

The current study is a meta-analysis study that does not require ethical approval. Studies concerning trigeminal nerve involvement in COVID-19 were obtained from the PubMed and Google Scholar databases, yielding 252 and 607 articles, respectively. Almost 900 articles were published on this topic in 2020 alone. The articles were found and selected using the English-language keywords 'trigeminal neuralgia', 'ocular pain', 'coronavirus', and 'COVID-19'. Out of 900 articles, 7705 COVID-19 cases (including 728 trigeminal neuralgia cases) from 2019 to 2022 were found to be relevant to this study, but some of these were excluded due to non-sufficient clinical data or study design; ultimately, 7561 COVID-19 cases (including 628 cases of COVID-19 and trigeminal neuralgia) were included for analysis. We further classified the trigeminal neuralgia cases into those with known or unknown causes for associated ocular pain. The data were collected and analysed via Statistical Package for the Social Sciences, version 21.0 which provides the incidence rate of trigeminal neuralgia in 638 cases COVID-19 cases.

RESULTS

We reviewed 7561 cases of COVID-19 and selected 638 cases due to either trigeminal or ophthalmic neuralgia, 638 cases with trigeminal neuralgia (8.4 %); of these, 570 patients (7.8 %) with trigeminal neuralgia presented with COVID-19 and the involvement of ophthalmic neuroglia as a clear reason for ocular pain, while 48 patients (0.6 %) with trigeminal neuralgia and COVID-19 demonstrated ocular pain but with no clear cause. Overall, the patients with ophthalmic glial involvement (92.5 %) outnumbered the patients with no clear cause for ocular pain (7.5 %; Table I, Fig. 1).

Table I. The incidence rate of trigeminal neuralgia, by known and unknown reasons for ocular pain.

Study	Number of trigeminal (ophthalmic) neuralgia cases	Total COVID-19 cases
Known reason cases	590	7513
Abrishami *et al.* (2020)	69	142
Aggarwal *et al.* (2020)	68	196
Atum *et al.* (2020)	10	40
Chen *et al.* (2020)	23	535
Guan *et al.* (2020)	9	1099
Güemes-Villahoz *et al.* (2020)	35	310
Hong *et al.* (2020)	15	56
Karimi *et al.* (2020)	2	43
Lan *et al.* (2020)	3	81
Landecho *et al.* (2020)	6	27
Lee *et al.* (2020)	3	103
Loffredo *et al.* (2020)	13	1167
Lomi *et al.* (2020)	8	127
Ma *et al.* (2020)	4	216
Marinho *et al.* (2020)	12	12
Meduri *et al.* (2020)	3	29
Öncül *et al.* (2021)	16	197
Perlman *et al.* (2020)	218	2523
Rokohl *et al.* (2020)	11	108
Seah *et al.* (2020)	1	17
Sindhuja *et al.* (2020)	12	127
Sun *et al.* (2020)	2	102
Tostmann *et al.* (2020)	31	91
Wu *et al.* (2020)	12	38
Xia *et al.* (2020)	1	30
Xu *et al.* (2020)	2	30
Zhou *et al.* (2020)	1	67
Unknown reason cases	48	48
Total cases of trigeminal neuralgia	638	7561

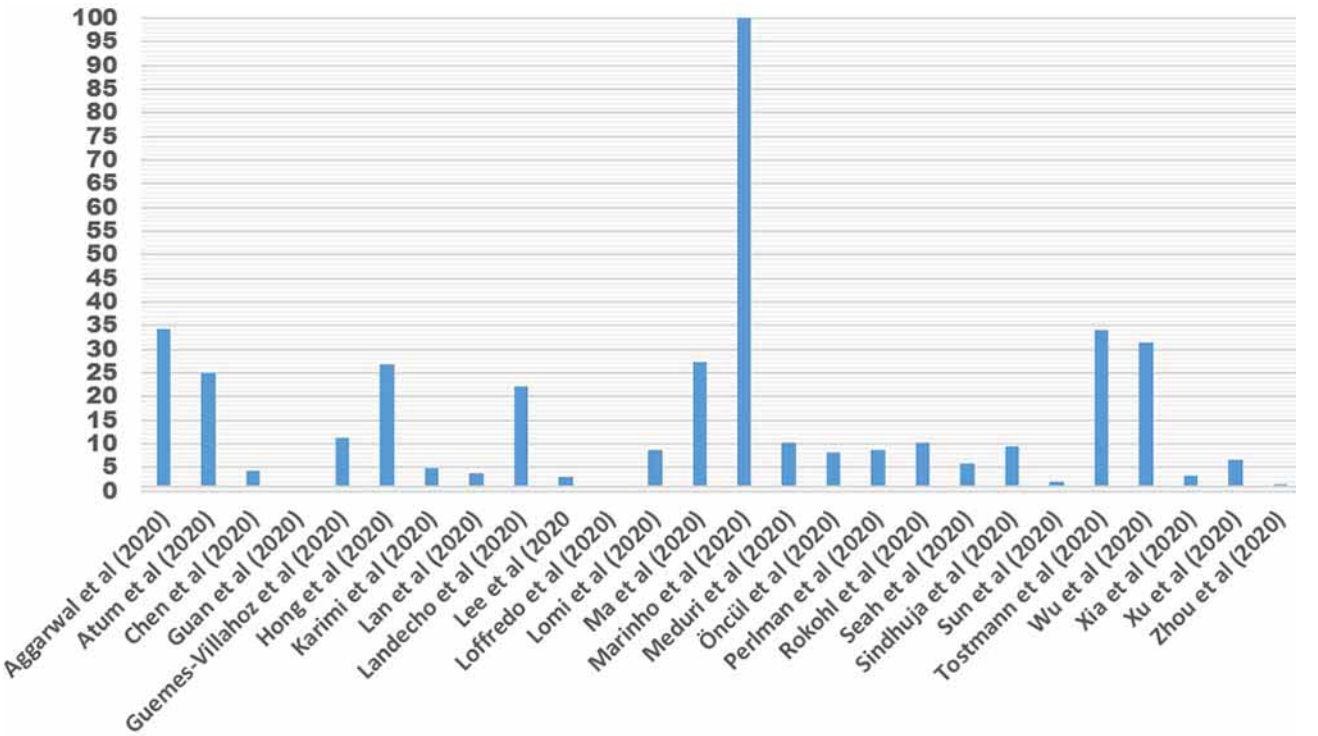

Fig. 1. The incidence rate of trigeminal neuralgia for each included study.

DISCUSSION

This meta-analysis found the overall incidence of trigeminal neuralgia (including those with known and unknown reasons for ocular pain, based on history and clinical examination) to be 8.4 % (Table I). The Ocular pain is a symptom of trigeminal neuralgia. Ocular pain was a presenting feature of COVID-19 in 0.8 % to 48.6 % of cases (Table I, Fig. 1), likely caused by the involvement of ophthalmic glia; only Nasiri *et al*. (2021) reported an incidence consistent with our finding of 7.8 % for this group. This study also found 48 cases with unknown causes of trigeminal neuralgia and no ocular pain or symptoms reported during or after COVID-19 (for an incidence of 0.6 %): Kasimov *et al*. (2022) reported 28 cases of post-COVID cavernous sinus thrombosis involving the ophthalmic division of the trigeminal nerve, Bohania *et al*. (2021) reported four cases; Vasanthpuram & Badakere (2021), Ferreira *et al*. (2020), Zhang *et al*. (2020), Molina-Gil *et al*. (2021), Emami & Margolin (2021), and Maksimova *et al*. (2022) each reported one case; Caggia *et al*. (2021) reported 10 cases.

Several case studies of trigeminal neuralgia in COVID-19 patients have been reported (Narasimhalu *et al*., 2021; Kaya & Kaya, 2022; Onoda *et al*., 2022); these three patients were older than 45 years and presented with a history of comorbid chronic conditions such as diabetes, hypertension with or without hyperlipidaemia, scoliosis, or lasting effects from recurrent brain surgeries. This suggests that trigeminal neuropathy can be the result of other chronic diseases, though Santovito & Pinna (2021) presented a case in which the COVID-19 vaccine was believed to induce trigeminal neuropathy, owing to no other significant findings in history or clinical investigation.

There are several theories to explain the neuropathological mechanism of this interaction. COVID-19 may infect neurons and glial cells (astrocytes and microglia), activating an innate reaction that produces a high serum protein S100B level associated with blood-brain barrier (BBB) permeability resulting in the severity of tissue injury (Aceti *et al*., 2020). As the viral infection becomes systemic, large amounts of inflammatory mediators such as cytokines, chemokines, interleukins, and antibodies are released, resulting in neural damage and downstream consequences (Klein *et al*., 2019). During the pandemic, severe COVID-19 was found to be the main

cause of mucormycosis infection in 88 % of COVID-19 intensive care unit patients because of compromised immunity; of these cases, 57 % involved the peripheral nervous system (Carlos and Pablo, 2021), 64 % involved the infraorbital nerve, and 52 % involved the maxillary branch of the trigeminal nerve (Bhuskute *et al*., 2022). Moreover, COVID-19 may infiltrate the nervous system through trans-synaptic neurons or other immunological or meningeal mechanisms affecting the cranial nerves (including the trigeminal nerves), and respiratory and enteric routes can circulate the virus into the brainstem nuclei via the hematogenous route (Franca *et al*., 2021). The virus can cause trigeminal neuralgia by attacking the trigeminal nuclei located in the brainstem. COVID-19 can also invade the nasal epithelium by binding to ACE2 receptors near the trigeminal nerve sensory branches (Fodoulian *et al*., 2020), irritation of the maxillary branch leading to redirection of pain to the trigeminal nuclei and neuralgia. Therefore, several mechanisms may explain trigeminal neuralgia in COVID-19.

Based on anatomical interpretation by Al Dorazi & Al Talalwah (2021), COVID-19 may lead to vasculitis, resulting in thrombosis, which can damage the trigeminal nerve. The vessel is lined with a simple squamous endothelial cell as COVID-19 binds to the ACE2 receptor and result in endothelial damage, therefore, the cell does not produce nitric oxide and prostacyclin, which prevents thrombosis. As COVID-19 binds to the endothelium of Vasa nervorum (the minor artery that supplies the trigeminal nerve or its branches) it produces trigeminal neuralgia. Further, thrombosis of the artery or vein due to COVID-19 causes dilatation, which compresses the nerve. Trigeminal neuralgia may result from vascular compression, as the trigeminal nerve travels along the thrombosing superior and anterior inferior cerebellar arteries and the superior petrosal veins (Hong *et al*., 2011).

Recently, COVID-19 was found to be a risk factor for cerebral vein thrombosis when combined with a fungal infection or when coronavirus binds with ACE2 receptors, resulting in vasculitis (Al Dorazi & Al Talalwah, 2021). The cavernous sinus and vein are lined by simple squamous endothelial cells, and as COVID-19 binds to the ACE2 receptor, it results in endothelial injury therefore the cell does not produce nitric oxide and prostacyclin which prevent thrombosis. Therefore, cavernous sinus thrombosis is a cerebral vein thrombosis caused by the transmission of the COVID-19 infection through the venous system (either superficial or deep veins such as facial or sinus veins); venous thrombosis can then result in vein engorgement, compressing the trigeminal nerve and leading to neuralgia. Cavernous sinus thrombosis can result from several other conditions, including an infection spread by the ethmoidal veins or sphenoid sinuses (Zhang & Stringer, 2010), changes to the cerebral, meningeal and diploic veins associated with dental procedures (Patel *et al*., 2020), or improper draining of the superior and inferior alveolar veins into cavernous sinuses. Cerebral vein thrombosis occurs in 13 persons per million annually, while cerebral vein thrombosis including cavernous sinus thrombosis occurs in 22–157 per ten million, and more often in females than in males (Devasagayam *et al*., 2016) due to hormonal imbalance leading to coagulopathy in several conditions contraceptive use, pregnancy, postpartum changes perimenopause and postmenopause.

Based on the basic venous draining system (Standring, 2005), pathogenic COVID-19 infection transmission can cause cavernous sinus thrombosis through superficial veins that transmit the infection through the facial skin via the superior and inferior ophthalmic veins, as well as through the scalp skin via the supraorbital and supra trochlear veins into the superior ophthalmic veins. Ocular pain is a symptom of COVID-19 (Sen *et al*., 2021), presenting in 10.3 % to 31.2 % of cases (Aggarwal *et al*., 2020; Rokohl *et al*., 2020). Furthermore, orbital fissure syndrome involving ophthalmoplegia is estimated to occur in 30 % of post-COVID cases of cavernous sinus thrombosis (Kasimov *et al*., 2022). A maxillary sinus infection can also occur due to COVID-19 infection if the maxillary veins drain backwards into the pterygoid plexus, and then into the cavernous sinuses via the emissary veins. As a result, post-COVID cavernous sinus thrombosis could compress the lateral wall of the trigeminal nerve and produce clinical features or cranial neurological deficits, such as dysfunction of the extraocular muscle, which is innervated by the oculomotor and trochlear nerves and the ophthalmic and maxillary branches of the trigeminal nerve. The trigeminal nerve also innervates the meninges above the tentorium; therefore, a headache can be caused by referred pain from trigeminal irritation or as a result of residual damage to the branch distributions from COVID-19 infection. However, because of its proximity to the cerebral veins, a headache can also be a serious sign of cerebral vein thrombosis if the vein becomes dilated and irritates the meninges. Therefore, physicians should examine the eye and other areas innervated by the cranial nerves using computerised tomography (CT) to exclude or document cavernous thrombosis, which can result in blindness.

Our results suggest that trigeminal neuralgia in these patients is due to compression of the trigeminal nerve by the lateral wall of the cavernous sinuses, and is likely a manifestation of COVID-19. Physicians should be aware of a patient's risk of developing trigeminal neuralgia during a COVID-19 infection. Awareness of neurologists or neurosurgeons may prevent chronic trigeminal neuralgia caused by COVID-19, through early medical or surgical intervention treatment. Further, ophthalmologists must be careful when examining patients presenting with trigeminal neuralgia, and they should use adequate personal protective equipment to avoid any spread of infection. The results of this study should also alert health administrators of further risks or potential consequences of a COVID-19 outbreak between medical staff and patients. The limitation of the study is that neurological deficits can develop for up to a year, and irregular follow-up may hide the fact of COVID-19 complications that may become a long-term condition in chronic disease.

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RESUMEN: El nervio trigémino es el quinto par craneal, que transmite las sensaciones faciales, y se divide en las ramas oftálmica, maxilar y mandibular. El daño a este nervio puede causar neuralgia del trigémino, una condición clínica que también puede presentarse en pacientes con enfermedad por coronavirus 2019 (COVID-19). Este metaanálisis revisa los casos clínicos de neuralgia del trigémino informados en pacientes con COVID-19 desde 2019 hasta 2022, describe el mecanismo anatómico del dolor y su radiación e identifica otros síntomas asociados. Realizamos una búsqueda bibliográfica para identificar informes de pacientes con COVID-19 que desarrollaron neuralgia del trigémino y examinamos estos casos en busca de prevalencia y cualquier fuente identificada de dolor ocular asociado. De los estudios relevantes identificados, 638 pacientes con COVID-19 desarrollaron neuralgia del trigémino de un total de 7561 casos de COVID-19 (8,4 %). De los 638 casos, 590 (7,8 %) tenían causas conocidas de dolor ocular, mientras que la causa del dolor ocular era desconocida en 48 casos (0,6 %). La neuralgia del trigémino se desarrolló con poca frecuencia en pacientes con COVID-19, y los casos con causas conocidas de dolor ocular fueron más comunes que los casos con causas desconocidas. Comprender el vínculo entre COVID-19 y la neuralgia del trigémino puede ayudar a prevenir más complicaciones y mortalidad en estos pacientes, así como a mejorar la atención de los pacientes con estas afecciones en el futuro. Además, comprender estos nuevos problemas clínicos puede preparar a muchos tipos de médicos para protegerse mejor en caso de un brote de COVID-19 entre el personal médico en diferentes departamentos de hospitales, como clínicas, salas de emergencia y quirófanos.

PALABRAS CLAVE: COVID-19; Neuralgia trigeminal; Nervio trigémino; dolor oftálmico; Trombosis.

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