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SHORT COMMUNICATION

Post-COVID-19 olfactory dysfunction: carbamazepine as a treatment option in a series of cases

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Abstract

Olfactory dysfunction is reported frequently in patients with coronavirus disease 2019. However, an effective treatment for this dysfunction is unknown. The present study evaluated carbamazepine as a treatment option for olfactory dysfunction based on its use in cases of neuralgia, especially of the V cranial nerve. The study included 10 patients with coronavirus disease with olfactory complaints who were part of a cohort of 172 coronavirus disease patients monitored for late neurological manifestations. Carbamazepine was administered for 11 weeks. The adverse effects reported were drowsiness (9/10) and dizziness (2/10); 9 of the 10 patients reported improved olfactory function after carbamazepine treatment. While the role of carbamazepine in the control of post-coronavirus disease olfactory dysfunction could not be confirmed in this study, the satisfactory response observed in most patients in this series suggests that further studies are warranted.

Keywords Anosmia · Carbamazepine · COVID-19 · SARS-CoV-2

Introduction

Patients with coronavirus disease 2019 (COVID-19) frequently exhibit respiratory symptoms. However, neurologic manifestations, such as headache, impaired consciousness, seizures, abnormalities of the peripheral nervous system, and olfactory dysfunction have also been reported (Burks et al. 2021; Ahmad and Rathore 2020). It should be noted that anosmia, ageusia, hypogeusia, and hyposmia could occur in isolation (Ellul et al. 2020; Mercante et al. 2020; Cho et al. 2020; Lechien et al. 2020).

Previous studies have reported the presence of sudden anosmia in approximately 84% of COVID-19 patients, and approximately 50% of these patients recover completely (Kosugi et al. 2020; Boscolo-Rizzo et al. 2020). In COVID-19 patients, magnetic resonance neuroimaging has detected T1 hyperintensity in the straight gyrus or olfactory bulbs (Politi et al. 2020). In addition, clinicopathological studies have indicated the presence of viral particles in the olfactory mucosa of COVID-19 patients (Morbini et al. 2020). These findings suggest that SARS-CoV-2 can cross the neural–mucosal interface of the olfactory mucosa, penetrate the primary olfactory pathway, and invade the central nervous system (CNS).

The persistence of anosmia and symptoms of parosmia are among patients' complaints of worse quality of life after COVID-19. Smell disorders can be associated with unpleasant odors, causing nausea, vomiting, loss of appetite, and weight loss. To mitigate more damage after the acute phase of COVID-19, a therapeutic approach and rehabilitation should be considered for treatment of patients who have olfactory and taste complaints.

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This study primarily describes the use of carbamazepine as a treatment option based on the previously established mechanism of action of this drug. Carbamazepine acts as a neuronal membrane stabilizer in cases of neuralgia, especially in the V cranial nerve (Baron et al. 2010).

Patients and methods

Patients

There were 172 patients who had COVID-19 that were being monitored for late neurological manifestations at the Hospital Universitário Gaffrée e Guinle (HUGG) in Rio de Janeiro, Brazil, between November 10, 2020, and January 30, 2021. Due to persistent complaints of anosmia/parosmia associated with olfactory nerve dysfunction during the acute phase of COVID-19, 10 patients were treated with carbamazepine. Treatment with carbamazepine was based on the hypothesis that SARS-CoV-2 might cause changes in the olfactory nerve similar to trigeminal neuralgia. Carbamazepine stabilizes neuronal membranes and is used to treat chronic neuropathic pain (Baron et al. 2010).

All participants presented with a diagnosis of COVID-19 infection that was based on the detection of the SARS-CoV-2 genome using the reverse transcription-polymerase chain reaction (RT-PCR) on material obtained using a nasopharyngeal swab. Each patient presented a mild form of the disease, without the need for hospitalization and mechanical ventilation, but reported an impaired quality of life due to a dysfunctional olfactory ability.

Each patient agreed to participate in the study and signed an informed consent form. The study was approved by the local research and ethics committee (HUGG, CAAE: 33,659,620.1.1001.5258).

Pre-treatment tests

Before beginning the administration of carbamazepine, all patients underwent laboratory tests (hematology and biochemistry tests, including for serum sodium levels) and were questioned about heart disease or any contraindication to the use of this drug. Magnetic resonance imaging (MRI) was performed to detect brain and cranial nerve abnormalities associated with COVID-19 olfactory dysfunction. The MRI protocol included high-resolution 3D sequences to evaluate the olfactory bulb. For each patient, 3D FLAIR, post-contrast 3D T1-weighted images (WI), coronal 3-mm slice STIR, and coronal fat-suppressed post-contrast T1-WI were acquired. In addition, whole-brain T2-WI, diffusion-WI, and pre-contrast T1 were included in the protocol. The patients also underwent clinical and neurological examinations.

Therapeutic treatment

An initial dosage of 100 mg/day of carbamazepine was administered for three consecutive days; the dose was then increased by 100 mg/day every 5 days until it reached 400 mg/day. Patients who did not report an improvement in olfactory dysfunction received a maximum dose of 400 mg/day. Carbamazepine was administered for 11 weeks, except in one patient who stopped using the medication after 1 month of treatment due to drowsiness and dizziness. The evaluation of the treatment efficacy for olfactory dysfunction was performed by questioning each patient regarding changes or improvement in their olfactory ability.

Results

The study included 10 patients (9 women and 1 man) less than 50 years of age. Only 1 patient had a comorbidity with an outcome worse than COVID-19. The duration of the olfactory complaints lasted 1–9 months: 4 months in 2 patients, 6 months in 3 patients; the other 5 patients remained symptomatic for 1, 3, 7, 8, and 9 months.

Among the 10 patients, 5 patients had received previous treatment with oral or intranasal corticosteroids without improvement, and 6 patients received olfactory training (repeated smelling of a set of odorants for a few seconds each, at least twice a day) with mild or no improvement.

Six patients underwent brain MRI. Two of them had bilateral hypersignal intensity on 3D FLAIR images, with minimum gadolinium enhancement in the bilateral olfactory bulb on post-contrast 3D T1-WI, suggestive of olfactory neuritis (Fig. 1). No abnormal signal intensity was observed in the gyrus rectus of any patient. One patient had right ethmoidal sinusitis; the other three MRI scans did not show any abnormalities.

The median duration of drug treatment was 51.5 days (range: 36–118 days). Five patients reported complete improvement from the carbamazepine, 1 patient reported extensive but not complete improvement, and 3 patients considered their improvement to be mild; only 1 patient reported no improvement. Regarding the therapeutic response and the administered dosage, improvement was reported from 1 patient at 400 mg/day, 5 patients at 300 mg/day, 1 patient at 200 mg/day, and 2 patients at 100 mg/day. The adverse effects reported were drowsiness (9/10) and dizziness (2/10). All demographic, clinical, and therapeutic characteristics are shown in Table 1.

Discussion

Although most patients with COVID-19 recover their olfactory ability, some may experience unresolved unpleasant smells. This persistent symptom is frustrating and can

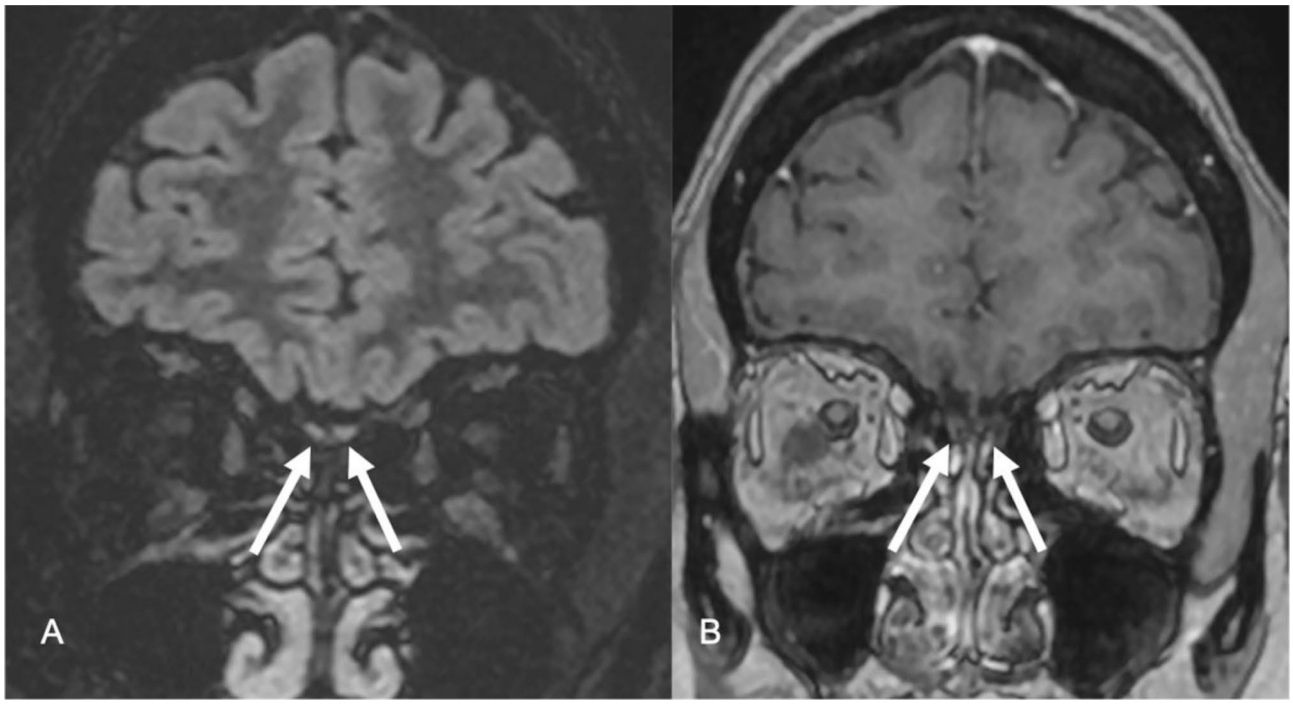

Fig. 1 MRI showing a bilateral hypersignal on coronal 3D FLAIR. **A** Images with mild contrast enhancement on post-contrast coronal 3D T1-weighted imaging. **B** Bilateral olfactory bulb (arrows) in post-COVID-19 infection. The brain MRI is from Patient 4, who had complete olfactory restoration

worsen the quality of life. Several interventions are currently being studied (Whitcroft and Hummel 2020); however, data regarding their efficacies are lacking. When olfactory dysfunction persists for more than 2 weeks, possible treatments should be considered (Whitcroft and Hummel 2020).

Some viruses cause olfactory damage through an induced inflammatory response. Loss of olfactory function has been described in infections caused by other viruses, but their incidence is reduced; COVID-19 causes much more olfactory loss than the influenza virus. Interestingly, in COVID-19 infections, even patients without respiratory symptoms, such as coryzal symptoms, may have impaired olfactory function (Kanjanaumporn et al. 2020).

Neural circuits are responsible for transmitting olfaction from the olfactory epithelium (OE) to cortical areas for multisensory integration. The initial olfactory stimulus occurs in the OE (Whitman and Greer 2009), where there are at least five cell types, including olfactory sensory neurons (OSNs) (van Riel et al. 2015). OSNs are bipolar neurons with axons that have synapses in the olfactory bulb and dendrites that project into the nasal cavity. The axons of all OSNs synapse with second-order olfactory neurons (mitral and tufted cells) whose axons project to various olfactory areas of the CNS (Attems et al. 2015; Diodato et al. 2016). Interruption at any point in this circuit can lead to olfactory impairment. Anosmia occurs due to conductive or sensorineural olfactory loss (Goncalves and Goldstein 2016). Temporary anosmia related to conductive loss is caused by impaired nasal airflow, and it is reversible when the obstruction caused by nasal congestion or swelling of the nasal respiratory epithelium disappears. Sensorineural loss implies dysfunction of the OSNs of the OE, and it may be permanent or have a longer time course (Goncalves and Goldstein 2016).

Several possible mechanisms have been suggested for SARS-CoV-2 anosmia. Evidence supporting that SARS-CoV-2 causes conductive olfactory dysfunction includes the time of onset of anosmia, which in up to 65.4% of patients, occurs at the same time as general symptoms (Lechien et al. 2020; Spinato et al. 2020), and that it is temporary with recovery taking place in 1 week in most patients with COVID-19 (Lechien et al. 2020). However, disruption of the OE by local infection can occur and affect the OSNs; in this case, the olfactory dysfunction persists after the upper respiratory infection symptoms have cleared until the damaged nasal OE regenerates, indicating an additional sensorineural contribution (Jafek et al. 1990; Yamagishi et al. 1994).

Coronaviruses use a protein spike (S protein) to bind to the host cell membrane (Kanjanaumporn et al. 2020). Both SARS-CoV and SARS-CoV-2 use human angiotensin-converting enzyme 2 (ACE2) receptors to mediate their entry into the cell interior (Hoffmann et al. 2020). In patients with SARS-CoV, a high level of ACE2 expression has been detected in the nasal respiratory epithelium (Bertram et al. 2012), more specifically in hair cells, consistent with nasal

Table 1 Demographic, clinical, and therapeutic data of patients with post-COVID-19 cacosmia

Patient	Sex	Age (years)	Comorbidities	Swab	Days since COVID-19 first symptoms	Days since olfactory impairment	MRI results (days since COVID-19 onset)	Previous treatment	Days since start of CBZ	CBZ (mg) dose for improvement	Improved sense of smell	Adverse effects
1	F	21	Hypothyroidism	+	297	284	Normal (90 days)	ALA, olfactory training	118	400 mg	Complete	Drowsiness
2	F	44	No	+	197	228	Normal (14 days)	Antiemetic	55	300 mg	Complete	Drowsiness and dizziness
3	F	21	No	+	201	158	Unrealized	ALA	20	300 mg	Mild	Drowsiness
4	F	46	No	+	273	273	Not normal (150 days)*	Olfactory training, oral corticosteroid	86	300 mg	Complete	Drowsiness
5	F	27	Allergic rhinitis	+	300	299	Normal (180 days)	ALA, olfactory training, oral and nasal corticosteroid	48	200 mg	Mild	Drowsiness
6	F	29	No	+	281	290	Right ethmoidal sinusitis (180 days)	B vitamins, olfactory training, oral corticosteroid	67	Not applicable	None	Drowsiness
7	F	24	No	+	265	189	Not normal (120 days)*	Olfactory training, Oral and nasal corticosteroid	46	300 mg	Complete	Drowsiness and dizziness
8	F	26	Obesity	+	281	290	Unrealized	No	67	100 mg	Complete	None
9	F	47	No	+	210	210	Unrealized	No	21	100 mg	Large	Drowsiness
10	M	23	No	+	281	331	Unrealized	Olfactory training, nasal corticosteroid	36	300 mg	Mild	Drowsiness

Source: outpatient follow-up clinic for neurological manifestations in post-COVID-19 patients

F, female; *M*, male; +, positive; *ALA*, alpha-lipoic acid; *CBZ*, carbamazepine

*Bilateral gadolinium enhancement in the olfactory bulb suggestive of olfactory neuritis

viral entry into human hosts (Sims et al. 2005). This is likely to cause direct damage to the OE, since these cells express receptors for SARS-CoV-2, including ACE2 and serine protease 2 transmembrane receptors. These findings suggest local changes that could cause conductive and sensorineural olfactory dysfunction. However, olfactory disorders can also result from viral infections that affect OSNs with retrograde propagation to higher-order neurons and their CNS projections.

In addition to anosmia and hyposmia, olfactory dysfunctions such as parosmia (distorted sense of smell) and olfactory hallucinations (smells perceived in the absence of odor) can occur in conditions such as epilepsy, migraine, meningitis, and infectious CNS disorders (Hong et al. 2012). Retrograde olfactory neuroinvasion being the underlying cause of anosmia has been studied the most in the cases of herpes simplex encephalitis (HSE), in which viruses are able to spread retrograde through the olfactory and trigeminal nerves; however, the exact mechanism is still unknown (Armien et al. 2010). In HSE mouse models, animals that survived the acute phase of infection showed diffuse infiltration of immune cells through the brain, with profound atrophy of the piriformis and entorhinal cortices and amygdala (Armien et al. 2010). Indeed, the degree and quality of olfactory deficits in post-HSE patients vary, suggesting that some patients may suffer from a more "core" pattern of olfactory impairment involving limbic areas (Landis et al. 2010). The degree of CNS involvement in COVID-19 is not entirely clear; in cases with more pronounced and persistent olfactory dysfunction, further studies may show whether neuroinvasion and neuronal changes resulting from retrograde propagation through the olfactory bulb are analogous to those seen in HSE infection.

Another possible explanation for the olfactory dysfunction observed in COVID-19 patients could be related to the distorted perception of afferent olfactory stimuli linked to neuronal damage. Similar to neuropathic pain, neuronal damage alters the neurophysiological properties of afferent neuronal pathways (Baron et al. 2010), leading to spontaneous ectopic activity with heightened sensitivity to afferent stimuli of the hyperexcitability type; this is induced and maintained by a number of factors, including voltage/sodium channel–dependent instability.

The MRI of patients with olfactory dysfunction showed inflammation and neuritis in the olfactory region. Carbamazepine stabilizes hyperexcited neuronal membranes and is a well-established treatment for trigeminal nerve neuralgia (Cruccu et al. 2020). Since our patients also had neuritis, which was probably related to the olfactory nerve, we used carbamazepine as a therapeutic option. Nine out of 10 patients reported olfactory improvement from the carbamazepine treatment; 5 patients (50%) reported complete improvement. In describing olfactory restoration, patients referred mainly to the recovery of the sense of smell and a reduction in the sensation of smelling unpleasant odors. Some patients complained of episodes of sensing unpleasant odors lasting for seconds; these episodes no longer occurred after treatment with carbamazepine.

Carbamazepine modulates voltage-gated sodium channels (VGSCs), which causes an inhibition of action potentials, prevents repetitive and sustained firing, and results in a consequent decrease in synaptic transmission. Similar to other anticonvulsants, carbamazepine is suggested to bind to the alpha subunit of VGSC, specifically in a binding pocket formed by the outer pore loop and the pore-lining portion of domain IV (Gambeta et al. 2020). By stabilizing nerve conduction, carbamazepine could theoretically reduce neuronal excitability resulting from an inflammatory insult at the level of either OSNs or second-order olfactory neurons and in the projections to the various olfactory areas of the CNS. Additionally, carbamazepine potentiates the action of gamma-aminobutyric acid (GABA), which is a physiological neurotransmitter that inhibits the generation of action potentials.

Most of our patients had already tried corticosteroids and olfactory training. Five patients had been treated previously with corticosteroids (nasal or oral), and 6 patients underwent daily olfactory training. All participants agreed that there was little or no improvement in olfactory dysfunction. Although olfactory training was used as an intervention, its mechanism is not fully understood. It is possible that repeated stimulation of olfactory neurons can increase their regenerative capacity, due to the neuroplasticity potential of neurons. Daily olfactory stimulation has been suggested to be a safe, efficacious, and inexpensive treatment method (Levy 2020).

Oral corticosteroids are not recommended for treating olfactory dysfunction because of insufficient evidence of their efficacy and the risk of side effects. Intranasal corticoids can be administered in specific patients, especially in the setting of chronic rhinosinusitis (Levy 2020; Whitcroft and Hummel 2020).

As adjuvant therapies, vitamin A and systemic omega-3 fatty acids could hypothetically improve neurogenesis and neuroregeneration. However, there is no evidence for significant practical results (Levy 2020). Half of our patients reported olfactory improvement from a daily dose of 300 mg of carbamazepine. Most patients experienced side effects, including drowsiness and dizziness. These effects diminished over time, and they might be mitigated by careful dosage escalation. In this context, the role of carbamazepine in the control of olfactory dysfunction could not be determined; however, the satisfactory response observed in most patients in our case series suggests that further studies are warranted.

Limitations

Due to the need for social restriction during the pandemic, the MRI study with a special interest in olfactory pathways was a limitation of the study. Only 6 patients were able to receive the MRI; among which, two had abnormalities in the olfactory bulb. It is important to note that patients underwent neuroimaging after the acute phase of the disease; this could reduce the chances of detecting changes. The lack of a comparison group was another limitation; however, the proposal of the study was the description of a series of cases. An intervention study with a designated control group might provide further insight into the treatment of olfactory dysfunction in patients with COVID-19.

Conclusion

This is the first study in the literature on the use of carbamazepine to treat olfactory dysfunction in post-COVID-19 patients. While the role of carbamazepine in the control of post-COVID-19 olfactory dysfunction could not be confirmed in this study, the satisfactory response observed in most patients in this series suggests that further studies are warranted. A high incidence of drowsiness may be a concern in this therapy.

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Declarations

Conflict of interest The authors declare no competing interests.

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