Permanent anosmia and ageusia after resection of a left temporoinsular low-grade glioma: anatomofunctional considerations

Case report

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Five percent of the general population has olfactory or gustatory disorders, although most do not complain about it. However, in some cases, these symptoms can be disabling and may affect quality of life. Anosmia was reported as a possible complication following head injury and neurosurgical procedures, particularly after the resection of tumors located in the anterior fossa and the treatment of aneurysms in the anterior circulation. Nonetheless, in all of these situations, olfactory dysfunction could be explained by damage to the peripheral olfactory system.

Here, the authors report a case of complete anosmia associated with ageusia following awake resection of a low-grade glioma involving the left temporoinsular region, with no recovery during a follow-up of 3 years. The frontal lobe was not retracted, and the olfactory tract was not visualized during surgery; therefore, postoperative anosmia and ageusia are likely explained by damage to the cortex and central pathways responsible for these senses. The authors suggest that the patient might have had a subclinical right hemianosmia before surgery, which is a common condition. After resection of the central structures critical for smell and taste processing in the left hemisphere, the patient could have finally had bilateral and complete olfactory and gustatory loss.

This is the first known report of permanent anosmia and ageusia following glioma surgery. Because these symptoms might have been underestimated, more attention should be devoted to olfaction and taste, especially with regard to possible subclinical preoperative deficit.

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Key Words • anosmia • ageusia • smell • taste • low-grade glioma • temporoinsular tumor • oncology

ODOR can be defined as a particular sensation elicited by the action of certain chemical substances on the olfactory system, and olfaction is the function whereby odors are perceived.57 Anosmia is an inability to perceive odor, and various reports have declared that it occurs in approximately 5% of the general population.4,31,60 Hypogeusia (that is, the diminished capability to perceive and discriminate tastes) can also be found in about 5% of the population, but complete ageusia seems to be very rare, and generalized taste disorders for all 4 taste qualities affect only 0.85% patients presenting to a specialized medical center.58 Indeed, most patients erroneously report both smell and taste disorders given the fact that these two senses are functionally associated, but upon testing, severe generalized taste loss as a clinical entity is very rare.41

Although these symptoms are usually seen as minor deficits, their implications can be important. Olfactory loss has been associated with a greater incidence of depression30 and decreased quality of life,15 since more than 70% of patients with chemosensory disorder claim that it interferes with their daily living activities, including preparing and taking food.59 Furthermore, a good sense of smell has been found to be important for personal hygiene, social interaction, and sexual relations.27

Here, we describe a patient in whom anosmia and ageusia developed after the resection of a low-grade glioma located within the left temporoinsular region. Surgery was performed under local anesthesia using intraoperative mapping via direct electrical stimulation at both the cortical and subcortical levels to optimize the extent of resection while preserving brain function.15 The patient has been followed up for 3 years after surgery, with a

Abbreviations used in this paper: OFC = orbitofrontal cortex; PGA = primary gustatory area; POC = primary olfactory cortex.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
normal neurological examination except no recovery of olfactory and gustatory functions. To our knowledge, this is the first report of permanent anosmia and ageusia following glioma resection, as a result of damage to the brain cortex and central pathways that lead to smell and taste perception. The mechanisms of this rare deficit are discussed.

Case Report

History and Examination. This 61-year-old right-handed female ophthalmologist without a medical history experienced 2 partial epileptic seizures in May 2008, with olfactory and gustatory aura and then with language disturbances. Magnetic resonance imaging revealed a lesion compatible with a low-grade glioma within the left temporoparietal region, involving the insula, anterior temporal lobe, uncus, and amygdala, but not the hippocampus (Fig. 1A). An antiepilepsy drug (valproate) was given, allowing seizure control. The neurological examination was normal, with no sensorimotor, visuospatial, or language deficits. The patient did not report smell or taste disorders. Because of the volume of the tumor (45 ml), resection was proposed.

Operation. In September 2008, the patient was surgically treated while under local anesthesia (asleep-awake-asleep protocol using propofol and remifentanil). A frontotemporal craniotomy was performed, and intraoperative ultrasonography was used to delineate the lesion. A bipolar electrode with 5-mm spaced tips delivering a biphasic current (pulse frequency 60 Hz, single pulse phase duration 1 msec, amplitude 3 mA; Nimbus, Hemodia) was applied to the patient’s brain to map the cortex before resection. According to a method we previously described, we instructed the patient to name pictures presented on a computer screen. A speech therapist was present in the operating room to evaluate any language disturbances. Two crucial language sites were identified at the cortical surface: stimulation over the rolandic operculum induced speech arrest and stimulation over the posterior portion of the superior temporal gyrus induced anomia (Fig. 1B).

The temporal part of the tumor was removed according to these functional boundaries. Thus, the insula was approached through the temporal operculum using a subpial dissection. Stimulation was applied over the insular surface and did not induce any language disturbances, except on its anterior part (anarthria), as already observed. Its posterior portion was resected until the lateral part of the lenticular nucleus was encountered in the depth. Indeed, stimulation of the lateral part of the left lentiform nucleus induced articulatory disturbances, as previously reported. During this second surgical stage, resection and subcortical stimulation were used in an alternating way to prevent damage to eloquent deep structures. Within the temporal stem, the resection was extended up to the inferior frontooccipital fascicle, which induced semantic paraphasias when stimulated. Posteriorly, the temporal resection was continued in the depth until phonemic paraphasias were induced, corresponding to the temporal part of the arcuate fasciculus.

It is worth noting that no olfactory or gustatory responses were induced by electrical stimulation.

At the end of the procedure, the temporal pole and amygdala were removed, whereas the hippocampus was preserved because it was not invaded by tumor on preoperative MRI in a patient with no seizures. Thus, all margins of the surgical cavity were in contact with eloquent structures to achieve maximal tumor removal with preservation of functional areas.

Postoperative Course. Immediately after surgery, the patient experienced transitory language worsening, which completely resolved within 5 days. There were no local or general complications. However, the patient reported complete loss of smell and taste. A neurological examination was performed, and no somatosensory disturbances of the face, mouth, or tongue were noted. Yet, a total lack of sense to any odor or taste (sweet, bitter, salty, or sour) was observed upon testing by evaluating the ageusia with oropharyngeal stimulation. The patient was unable to tell if an olfactory stimulus was nearby (for instance, if blindfolded, she could not tell when coffee was nearby), although she did have nasal sensation (for example, to ammonia). Without any specific treatment for this problem, the patient was followed up for 3 years and did not recover any olfactory or gustatory senses. Nonetheless, she was able to return to work full time as an ophthalmologist after surgery and lives a normal life, with no seizures despite the interruption of the antiepilepsy drug.

Neuropathological examination revealed a WHO Grade II glioma.

Postoperative MR imaging revealed subtotal resection, with a 93% extent of resection given a deep residue (3 ml) within the anterior and deep part of the insula, which elicited language disorders during intraoperative stimulation (Fig. 1C). Control MR images have been obtained every 6 months, and the residual lesion had very slow growth (increase of 2 mm in the mean diameter in 3 years) with no adjuvant treatment (no chemotherapy and no radiotherapy).

Discussion

Anosmia and Ageusia

Throughout the evolution of species, the importance of smell and taste for vertebrates to adapt to the environment and drive their behavior progressively declined, as vision seemed more significant for most primates. Five percent of the population has some olfactory or gustatory disorder, although most people do not even complain about it. In some cases, however, these symptoms can cause mood changes leading to decreased appetite, ingestion of spoiled food, body odor, sexual dysfunction, lack of awareness of dangerous toxins, and thus a decrease in the quality of life.

Loss of smell can be present in many forms: anosmia (complete olfactory dysfunction), partial anosmia (odorant-specific insensitivity), hyposmia (generally reduced olfactory ability), parosmia (olfactory dysfunction resulting in the perception of all smells as unpleasant), and phantosmia (olfactory hallucinations, often unpleasant). Gustatory dysfunction can also be associated with
Anosmia and ageusia after glioma resection

Olfactory disorders. The most prevalent factors associated with smell or taste loss include aging, head trauma, neurodegenerative disorders, upper respiratory infections, chronic rhinitis, and allergies. Indeed, humans experience a gradual loss of olfactory acuity between the years of 30 and 50, followed by a sharp decline after 70; up to 50% of individuals over 65 years of age can experience a complete loss of olfactory ability. Head trauma can result in shearing injury at the level of the olfactory nerves as they penetrate the cribriform plate toward the olfactory bulb. Olfactory dysfunction can also be associated with moderate to severe head injury. However, so-called trivial head injuries accounted for 11.8% of cases, with olfactory changes following workplace falls or blows to the head. Significant olfactory dysfunction is common in patients with Alzheimer disease. Hyposmia is also recognized as one of the major nonmotor symptoms of Parkinson disease. Infrequent etiologies include environmental causes, medications (especially antiepilepsy drugs), cancer treatment, and even general anesthesia.

Fig. 1. A: Preoperative axial FLAIR MR images showing a hypersignal involving the left temporoinsular structures. B: Intraoperative photograph obtained before resection (left), showing letter tags that indicate tumor boundaries. Stimulation over the rolndic operculum induced speech arrest (1, precentral part; 2, postcentral part), and stimulation over the posterior portion of the superior temporal gyrus induced anosmia (10). Intraoperative photograph obtained after a resection (right) performed according to functional boundaries. Stimulation over the anterior part of the insula (star) and over the lateral part of the lentiform nucleus induced articulatory disturbances (11), stimulation of the inferior frontooccipital fascicle (white matter bundle running in the roof of the sphenoidal horn of the ventricle) generated semantic paraphasia (13), and stimulation of the temporal part of the arcuate fascicle (posterior part of the cavity) elicited phonemic paraphasia (12). C: Postoperative axial FLAIR MR images obtained 3 months after surgery, demonstrating subtotal resection of the WHO Grade II glioma (confirmed by neuropathological examination), with residue in the anterior insula because this structure was crucial for language.
In addition, anosmia can occur after neurosurgical procedures. Patients with anterior fossa tumors often present with postoperative olfactory dysfunction because of the difficulty in preserving the olfactory nerve. Intraoperative spatula use to retract the frontal lobe can damage the olfactory bulb or nerve by shearing or stretching the olfactory filaments, by direct pressure from spatula to nerve, or by destruction of the vessels supplying the olfactory structures—explaining why anosmia was reported as a common postoperative deficit after clipping aneurysms at the anterior circulation or after endovascular coiling. However, in all of these situations, olfactory dysfunction could be explained by damage to the peripheral olfactory system. Moreover, patients experienced only anosmia and not ageusia.

In the patient in our case, the frontal lobe was not retracted and the olfactory tract was not visualized during surgery. Therefore, postoperative anosmia and ageusia are likely explained by damage to the cortex and central pathways responsible for these senses.

**Neural Basis of Olfactory and Gustatory Functions**

Olfaction can be divided into 2 components: odor detection and odor perception. The first part of the process begins in the nasal cavity, where odorants bind to receptors of the first cranial nerve neurons. The axons of these neurons pass through the cribriform plate and bundle into the olfactory nerve, which enters the olfactory bulb. The olfactory tracts run into the olfactory sulcus and reach the POC. Thus, this stage is related to the peripheral olfactory system, damaged after neurosurgical procedures in case reports of anosmia in the literature.

Odor perception depends on central nervous processing. Smell sensations, unlike sensations from other senses, go straight to the cortex without being processed first in the thalamus. The POC structures include the piriform cortex and closely associated areas of the anterior olfactory nucleus, anterior perforated substance, and olfactory tubercle, as well as the anterior portion of periamygdaloid cortex and amygdala. The secondary olfactory cortex is mainly located in the insula and entorhinal cortex. Projections from the POC reach the insula, and although not traditionally considered part of the olfactory pathways, the insula does respond to odors on functional neuroimaging studies.

Moreover, the anterior insula also represents the PGA together with the frontal operculum. In primates, the taste pathways project from the nucleus of the solitary tract, at the brainstem, directly to the taste thalamus (ventroposterior medial nucleus), and thus to the primary taste cortex in the anterior insula. Unlike in olfaction, taste stimuli appear to activate only the insula and operculum, sparing the piriform region, making it plausible that these areas correspond to the PGA. Deficits in gustatory and olfactory perception following insular stroke support the crucial role of this structure for these functions. For instance, Mathy et al. described a patient with bilateral ageusia after left insular and opercular ischemic stroke and illustrated the possible predominance of the left cortical hemisphere for taste perception in a right-handed person.

Olfaction and taste are two different senses, but they are very much related. Without olfaction, flavor is lost and food perception is limited to basic tastes. These taste-smell interactions that give rise to all flavors are likely to occur within higher structures: the OFC is the prime candidate. Rolls and colleagues have performed a series of studies in which gustatory, olfactory, visual, and oral somatosensory stimuli were presented to awake monkeys. Responses were recorded from neurons located in the caudal OFC, extending into the ventral insula. The authors identified unimodal taste, smell, visual, fat, and texture cells that were interspersed with multimodal cells that responded to independent stimulation of 2 or more modalities. They discovered a taste area in the lateral part of the OFC and showed that this was the secondary taste cortex, given that it received a major projection from the PGA. More medially, there is an olfactory area. Anatomically, there are direct connections from the POC to the posterior OFC, which in turn has onward projections to a middle part of the OFC, another gustatory region. A review of functional neuroimaging studies in patients with posttraumatic olfactory deficit showed functional involvement of the OFC and temporal lobe. Other neuroimaging studies evidenced a network likely responsible for taste and odor integration and hence for flavor perception, with activations in the insula, operculum, OFC, and anterior cingulate cortex.

In addition, the amygdala is believed to represent the limbic part of the olfactory system, influencing the affective component of pleasant or unpleasant odors. It seems to be a strategic locus where olfactory and neuroendocrine stimuli are integrated to modulate feeding behavior. This structure is connected to the caudal OFC, receiving inputs via the mediodorsal nucleus of the thalamus pars magnocellularis, which itself receives afferents from temporal structures such as the prepiriform (olfactory) cortex, amygdala, and inferior temporal cortex. Functionally, odor intensity is associated with piriform cortex and amygdala activity, whereas the OFC is involved in odor identification and olfactory memory. The anterior cingulate cortex, also known as the limbic lobe, is activated by olfactory stimulation. According to some reports, this activation is independent of valence, while according to others, the anterior cingulate cortex is activated only in response to pleasant odors.

**Smell and Taste Deficits in Brain Surgery**

Olfactory and gustatory phenomena accompany some cases of temporal and/or insular epilepsy, as observed in our patient. Furthermore, changes in taste intensity perception, especially elevated citric acid recognition thresholds, were noted following anterior temporal lobectomy for the treatment of epilepsy. Patients were also evaluated using PET, with increased regional cerebral blood flow bilaterally in the caudolateral OFC, in the right anteromedial temporal lobe, and in the right caudomedial OFC. These findings suggest that although taste sensation could be computed in the primary taste cortex, recognition requires further processing by structures located in the anteromedial temporal lobe. We propose that the deficit in gustatory stimuli recognition may be attrib-
utable to disruption of the neural circuitry by the surgical procedure, possibly from the amygdala to the secondary gustatory area.

In our case, in addition to resecting the insula, we also removed the anterior temporal lobe and amygdala. In other words, the resection included both primary and secondary olfactory cortex, as well as the PGA. In addition, we cut the uncinate fascicle, which is a ventral associative hooklike-shaped bundle that connects the anterior temporal lobe and amygdala with the medial and lateral OFC.²⁴,⁵⁰ We were able to remove a part of this tract in the left dominant hemisphere without eliciting language disorders because of compensation by the inferior occipitofrontal fascicle that was detected and preserved intraoperatively. Indeed, we have already demonstrated that this inferior occipitofrontal fascicle subserved the ventral semantic pathway and should be mapped using subcortical stimulation.¹⁷,²⁸

At first glance, because of the brain regions removed and their implication in olfactory and gustatory functions, it would not seem surprising to have generated permanent anosmia and ageusia. On the other hand, it is difficult to understand why combined smell and taste loss after cerebral surgery has never been reported in the literature, especially following resection of a glioma involving the left temporinsular region.¹⁴,⁵⁰ In low-grade glioma, this could be explained by mechanisms of brain plasticity, allowing functional compensation as a result of the slow growth of this kind of tumor, as previously demonstrated for sensorimotor and language functions.¹⁵ Nonetheless, in the patient in the present case, the growth rate of the glioma was very slow, as demonstrated by the increase of only 2 mm in mean diameter within the 3 years following resection, with no adjuvant treatment (because there was no sign of anaplasia on neuropathological examination). As a consequence, it is puzzling to note that olfactory and gustatory areas did not have the possibility of functional reorganization. Another explanation could be represented by the seizures themselves, because epilepsy may cause a generalized decrease in olfactory functioning.⁶⁴ Nonetheless, partial seizures, even with olfactory and gustatory auras, are very frequent in (insula)-temporal gliomas, while postsurgical anosmia and ageusia are exceptional. Finally, regarding medications, the patient had no treatment after surgery, especially no antiepilepsy drugs (no seizures). In addition, when the patient was preoperatively treated with valproate, she had no olfactory or taste deficit. Finally, no drugs were given during surgery, except for the propofol and remifentanil, which are not known to cause olfactory or taste dysfunction and have never, in our experience with hundreds of procedures, elicited anosmia or ageusia in other patients who have undergone awake surgeries.¹⁶ Therefore, a role for medications in causing this disorder seems unlikely.

Therefore, even if no objective smell examination was performed, we can still suggest that the patient already had a subclinical hemianosmia before surgery, since it is estimated that 15% of normosmic persons demonstrate lateralized smell loss and that the majority of them will not notice this difference between nostrils as long as olfactory function of the better nostril remains within the normal range.²⁴ Indeed, projections in the human olfactory pathway are mostly ipsilateral, with only minor contralateral projections via the anterior commissure.⁵³ Although controversy exists, researchers tend to believe that perceptual functions, such as intensity judgments and quality of discrimination, are better performed when stimuli are presented to the right nostril and thus the right hemisphere and that odor naming may be better when stimuli are presented to the left nostril and thus the left hemisphere.²⁴,⁵⁷ Similarly, the gustatory pathway is thought to be largely ipsilateral, even if there is some evidence of contralateral connectivity.¹ Therefore, in our patient, a previous virus-related upper respiratory infection or a “trivial” and forgotten head injury could have damaged the right olfactory nerve without producing symptoms before the surgery. However, after removing crucial structures for taste and smell in the left hemisphere, olfactory and gustatory sensations could not be perceived anymore, leading to permanent anosmia and ageusia. In addition, the OFCs were preserved, but the connections necessary for smell inputs to reach the left OFC were interrupted. We can hypothesize that gustatory stimuli could reach the intact right OFC, but the patient might not be able to recognize stimuli because of the lack of connections between both OFCs (anterior commissure has just a minor role). Finally, we can also suggest that the patient was unable to recognize gustatory and olfactory stimuli, since the uncinate fascicle, which is important in carrying sense information from the anterior temporal pole to the OFC, was cut.

Conclusions

We report the first case of complete and permanent anosmia and ageusia following resection of a left temporinsular low-grade glioma. Although this postoperative deficit is rare, it can affect a patient’s quality of life. Because these symptoms might have been underestimated, more attention should be devoted to olfaction and taste, especially with regard to possible subclinical preoperative deficit.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Duffau. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of all authors: Duffau. Study supervision: Duffau.

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