COVID-19, ANOSMIA AND ALZHEIMER'S DISEASE. A CASE REPORT OF A 81-YEAR-OLD PATIENT

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Abstract

Objectives. Among people over the age of 65, the prevalence of olfactory disorders can reach nearly 14%. The buildup of beta-amyloid plaques and tau neurofibrillary tangles in neurons in the hippocampus and entorhinal cortex causes olfactory dysfunction, a decline in memory and learning processes, and, eventually, Alzheimer's disease. According to current research, people aged 57 to 85 who have hyposmia are twice as likely to develop dementia within five years as people of the same age who do not have hyposmia. Anosmia is one of the most common COVID-19 symptoms.
Methodology. An 81-year-old female patient is referred to the psychiatry clinic by her family physician after presenting with a two-year history of panic attacks, anxiety, and anosmia following the SARS-CoV-2 infection. At the first visit, the patient was examined neurologically, psychiatrically, and neurocognitively with the Mini-Mental State Examination-2 and Cognitive Reserve Questionnaire. The patient was recommended for laboratory tests, magnetic resonance imaging scan, and a complex neuropsychological evaluation.
Results. The score on the Mini-Mental State Examination-2 (standard version) was 28/30, with fluent language, high cognitive reserve (score of 168), normal muscle tone and strength, and no evidence of cerebellar dysfunction or balance impairment with a normal gait. The extensive neuropsychological evaluation scores were: Mini-Mental State Examination-2 (extended version) 42/90; three words from 25 retained from short story recall; Montreal Cognitive Assessment 20/30; poor verbal fluency (patient was able to produce only six animal names and one word that starts with the letter F in one minute); and impaired visuospatial and executive abilities. Brain imaging results reveal-moderate cortical atrophy, cerebral microangiopathy modifications with leukoaraiosis, and cerebral lacunarism.
Conclusions. Olfactory impairment is a possible sign of prodromal dementia. Infection with the SARS-Cov-2 virus has worsened cognitive decline in patients with Alzheimer's disease.

Keywords: anosmia, Alzheimer's disease, COVID-19, cognitive decline, cognitive reserve.

Introduction

Olfactory function loss begins at 60 years of age and worsens significantly after 70. In many cases, olfactory disorders are the result of a disease. Smell evaluation can reveal various types

of olfactory deficits. Anosmia is defined as the inability to detect all (total) or some (partial) odors. A reduced sensitivity to odors is known as hyposmia or microsmia. Dysosmia is a distorted sense of smell. Olfactory agnosia is defined as the inability to identify odors despite normal detection and discrimination abilities. Phantomtosmias are olfactory hallucinations. Many common diseases can impair one's sense of smell, either permanently or temporarily. The diseases that cause olfactory disorders range from common colds to neurodegenerative diseases. Local nasal diseases (allergic rhinitis, nasal polyposis and sinus disease), head trauma, and upper airway viral and bacterial infections are the most common causes of olfactory loss. Some neurodegenerative diseases, such as Alzheimer's disease (AD) and various forms of Parkinson's disease (PD), are accompanied by olfactory disorders even in their early stages (Fioretti, Fusetti, & Eibenstein, 2011).

Since the 1950s, studies have suggested that microbial infections induce neurodegenerative disorders. Scientists suspected at the time that acute viral infections might induce long-term brain damage (Ball, 1986). Despite accumulating data supporting this relationship, the virus's mechanism of neurodegeneration remains unexplained. According to one prevalent view, viral infection generates an aberrant immune response that lasts for years and finally leads to neurological damage linked to certain brain illnesses (Ball, 1982). Evidence that viral infection plays a role in Alzheimer's disease has long been studied (Liu, Jiang, & Li, 2023).

According to new research focusing on older adults, a diminished sense of smell is linked to a faster accumulation of Alzheimer's disease-related pathologies seen on brain scans. The findings add to the growing body of evidence that loss of smell (anosmia) is a key early indicator of Alzheimer's disease-related cognitive impairment and the accumulation of harmful proteins like amyloid-beta and tau (Tian, Bilgel, Moghekar, Ferrucci, & Resnick, 2022).

Researchers in Argentina, in collaboration with the Alzheimer's Association Consortium on Chronic Neuropsychiatric Sequelae of SARS-CoV-2 Infection, followed 766 adults aged 55 to 95 who had been exposed to COVID-19 for a year, administering a battery of physical, cognitive, and neuropsychiatric tests. In the study group, 88.4% were infected, while 11.6% were not. Clinical testing revealed that two-thirds of infected participants had functional memory impairment, which was severe in half of them. Another set of cognitive tests revealed three groups with poor performance ("Persistent Loss of Smell Due to COVID-19 Closely Connected to Long-Lasting Cognitive Problems", 2023):

- 11.7% had memory-only impairment,
- 8.3% had attention and executive function impairment, and
- 11.6% had multidomain (memory, learning, attention, and executive function) impairment.

According to statistical analysis, persistent loss of smell was a significant predictor of cognitive impairment, but the severity of the initial COVID-19 disease was not (de Erausquin et al., 2022).

Autopsy studies have connected odor identification loss to plaques and tangles in the olfactory bulb, entorhinal cortex, and cornu ammonis areas of the hippocampus. Several clinic-based, case-control, cross-sectional, or chosen participant investigations have discovered associations between olfactory loss and cognitive decline, moderate cognitive impairment (MCI), or Alzheimer's disease (AD) dementia. This shows that odor identification impairment may be a risk factor for Alzheimer's disease-induced amnestic MCI (aMCI) or predict progression from aMCI to AD dementia. Furthermore, anosmia has been connected to Lewy bodies, meaning that decreased olfaction might be a sign of Lewy body dementia or vascular dementia. Several longitudinal investigations on olfactory impairment and development from MCI to dementia have been performed (Roberts et al., 2016).

Common neuropathologies linking anosmia and MCI in older adults are cerebral neurodegenerative and microvascular lesions (Dong et al., 2022).

Tian et al.'s (2022) findings revealed that each lower performance point on the smell identification test was associated with a 22% increased risk of developing MCI. Even after the researchers controlled for age, gender, race, education, smell test version, apolipoprotein E (APOE 4) gene carrier status, smoking, increased depressive symptoms, and vascular disease, the relationship remained similar.

Lower olfactory scores were associated with higher levels of Alzheimer's pathology in the brain, particularly in regions associated with the sense of smell, such as parts of the orbital frontal cortex, and memory and learning regions, such as the temporal lobe, according to PET brain scans of this subset of participants. Furthermore, participants who experienced a greater decline in olfactory function over time had higher levels of amyloid and tau in some areas related to both smell and memory function (Tian et al., 2022).

Because the olfactory sensory epithelium and the olfactory bulb are so close together, COVID-19 infection may still have an impact on cognitive function even after recovery. Some people with neurodegenerative diseases like Alzheimer's and Parkinson's disease have been found to have a connection between dementia and a disordered sense of smell. Damage to the bulb causes anxiety and a depressive-like state, according to animal studies. The idea that "viral invasion of the [central nervous system] can be a trigger for neurodegeneration resulting in later neurological deficit, is not a new one" (Kay, 2022). As the quoted author showed, it is supported by previous flu pandemics.

All human coronaviruses (CoVs) are opportunistic pathogens of the central nervous system (CNS), including SARS-CoV-2 (Desforges et al., 2019). SARS-CoV-2 infection causes neurological symptoms such as confusion, headache, hypogeusia/ageusia, hyposmia/anosmia, dizziness, epilepsy, and acute cerebrovascular disease (Jiménez-Ruiz, García-Grimshaw, & Ruiz-Sandoval, 2020). These symptoms are caused by the virus's direct entry into the central nervous system (CNS) and the subsequent interaction between the virus' spike protein and the angiotensin-converting enzyme 2 (ACE2).

New research suggests that SARS-CoV-2 could cause CNS damage either directly or indirectly by activating the host immune response, resulting in demyelination, neurodegeneration, and cellular senescence. As a result, it may accelerate brain aging, promoting the development of neurodegenerative diseases like dementia (de Erausquin et al., 2021).

Moderate correlations between measures and subjective ratings of olfactory perception are frequently explained by the semi-conscious nature of olfactory perception in comparison to other human senses. People are more likely to overestimate their olfactory capacity as hyposmia develops gradually, such as with aging or neurodegenerative diseases (White & Kurtz, 2003). Overestimation and underestimation of abilities are caused by deficits in metacognitive knowledge, a concept known as anosognosia, which is relatively common in neurodegenerative diseases. Olfactory awareness, in particular, is negatively related to age (cognitive decline, particularly in memory and executive control such as attention) (Tahmasebi, Zehetmayer, Stögmann, & Lehrner, 2019).

Methodology

Neuropsychological tests, neurological and psychiatric examinations, laboratory tests and brain imaging were performed to evaluate the patient. Three neuropsychological assessments of 60–

90 minutes each were required. The patient and the caregiver participated in a semi-structured clinical interview conducted by the psychiatrist and neuropsychologist.

Case presentation

An 81-year-old female patient is referred to the psychiatry clinic by her family physician after presenting with a two-year history of panic attacks, anxiety, and anosmia following the SARS-CoV-2 infection. Previous medical history indicates hypertension, dyslipidemia, and vitamin D deficiency.

A highly educated patient, she cares for her immobilized husband after a stroke. The patient worked as an architect and then as an interior designer. She is passionate about painting, gardening, and spending a lot of time in the garden of the house, where she repairs and paints old flowerpots (she rehabilitates them). After the COVID infection, sleep disturbances and anxiety with panic attacks occur. Feelings of worthlessness are also increasing: "I don't smell anymore, I don't make food as good, I'm afraid I'll leave the gas open."

The patient received treatment from a family physician for olfactory disorders and insomnia for two years. At the first visit, the patient was examined neurologically, psychiatrically, and neurocognitively with the Mini-Mental State Examination-2 (MMSE-2).

- the score on the Mini-Mental State Examination 2 (standard version) was 28/30, with fluent language;
- normal muscle tone and strength, and no evidence of cerebellar dysfunction or balance impairment with a normal gait.

Despite the fact that the MMSE-2 cognitive assessment score was 28, indicating that there was no cognitive deficit, the neurologist decided that the patient should undergo two more complex neuropsychological assessments, including a cognitive reserve assessment, and that she should be accompanied by her daughter to the subsequent appointments.

At the second session, the patient and her daughter completed the "Cognitive Reserve Index - R-IRCq" Romanian version questionnaire. The high score of 168 implies a strong cognitive reserve and, as a result, resistance to potential brain pathology.

The score for the MMSE-2 extended version is 42/90; three words from 25 are retained from short story recall; and 11 point at the processing speed (item), which measures perceptual-motor speed and incidental learning (i.e., symbol pair formation). Based on these results, the neurologist decides that the patient should have various blood tests, vitamin B12 and folate supplementation, and a brain MRI.

The third neuropsychological evaluation was performed after 30 days to eliminate the test-retest learning effect. This time, the Montreal Cognitive Assessment (MoCA), Trail Making Test A (TMTA) and B (TMTB), Digit Span forward and backward, and the verbal fluency test (F letter and animal category) were employed. The neuropsychological assessment scores are presented in Table 1.

Table 1
Results of the neuropsychological assessment

Assessment	Score	Cognitive impairment
MoCA	20/30	Impaired moderately
TMT A	67 sec	Impaired
TMT B	356 sec	Impaired
Digit span forward/backward	(F) 5 digits / (B) 4 digits	Impaired
Verbal fluency - F	1/11	Impaired
Verbal fluency - animals	6/25	Impaired

Figures 1 and 2 illustrate the MMSE-2 items and how the patient resolved them.

Figure 1
Praxis, drawing two intersecting pentagons

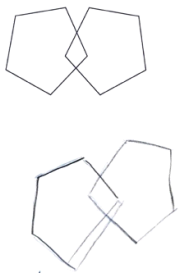
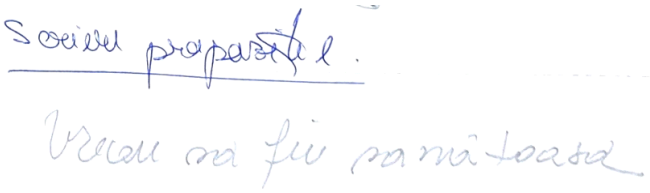
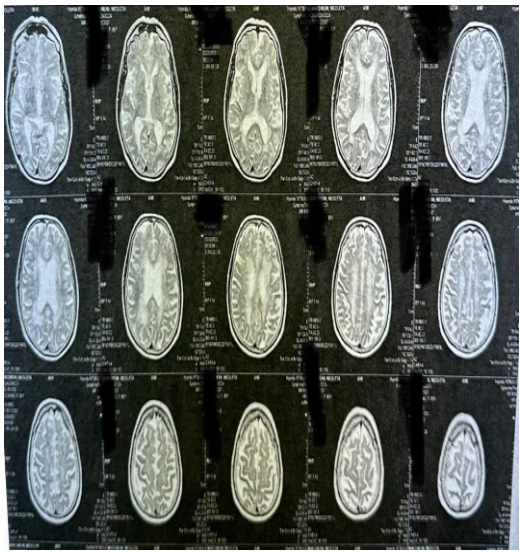


Figure 2
Sentence writing



The latest neuropsychological evaluation shows ~~a~~ moderate cognitive deterioration. Brain imaging results reveal moderate cortical atrophy, cerebral microangiopathy modifications with leukoaraiosis, and cerebral lacunarism.

Figure 3
Brain magnetic resonance imaging

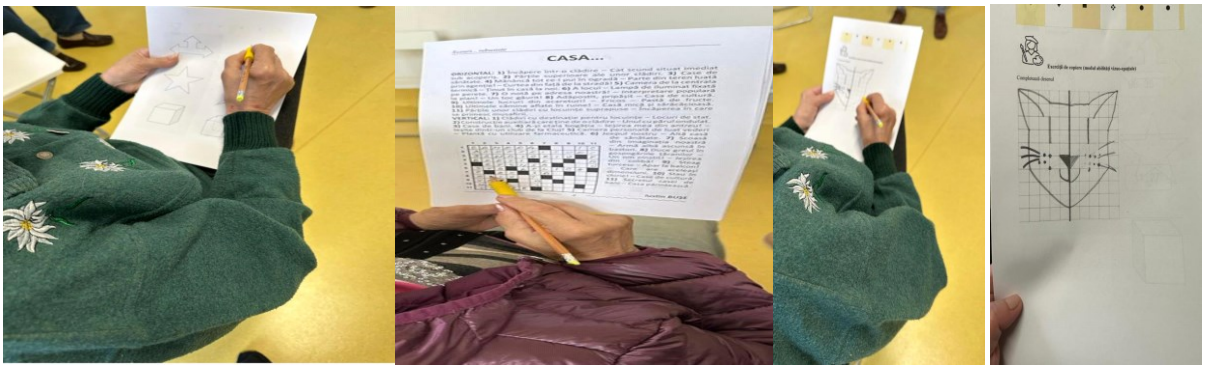


Following the psychiatric assessment, the patient was diagnosed with anxiety-depressive disorder and prescribed an antidepressant and anxiolytic (if needed) for panic attacks and insomnia. Treatment for the diagnosis of Alzheimer's dementia is given by the neurologist, memantine, the dose going up to 20 mg/day, and every six months injections with a brain trophic or perfusable (if the patient prefers this mode of administration).

To improve cognitive skills and reduce anxiety-depressive symptoms, the patient was recommended to participate in psychoemotional support groups and cognitive stimulation activities. Figure 4 shows some of the cognitive stimulation activities in which the patient participated.

Figure 4

Cognitive stimulation activities



Discussions

The effects of environmental enrichment on brain health and cognition were first discussed by Diamond, Krech, and Rosenzweig in 1964. Rats that are kept in complex environments with toys, space, equipment for climbing and exercising on, and plenty of social interactions with their cage mates have a cortex that is thicker and more developed cognitively than rats that live miserable solitary lives in basic, unenriched housing (Diamond, Rosenzweig, Bennett, Lindner, & Lyon, 1972).

The presence of AD pathology in the entorhinal cortex, hippocampus, and other temporal regions results in an inability to store and retrieve smell memories and, as a result, correctly identify odors. Olfactory loss in Alzheimer's disease and Parkinson's disease is caused by cholinergic deficits caused by a variety of mechanisms, including damage to the nucleus basalis (a key cholinergic nucleus that projects to brain regions involved in olfaction) (Roberts et al., 2016).

Infectious agents, particularly viruses, are thought to play a role in the pathogenesis of Alzheimer's disease. According to this theory, the viral particles evade the host immune system, resulting in chronic infection and the accumulation of Aβ and phosphorylated tau in the brain. While several AD-related candidate viruses have been documented in previous studies, the specific mechanisms are unknown. Furthermore, these research findings are correlational rather than causal. This hypothesis is still being validated, as therapeutic strategies targeting it are being questioned. The frequent neurological manifestations of SARS-CoV-2 have prompted researchers to consider the resulting epidemic of neurodegenerative diseases. Several studies have found cognitive impairment in COVID-19-infected people, implying that COVID-19 contributes to the development of Alzheimer's disease (Liu et al., 2023).

Anosmia serves as a bridge between AD and COVID-19 because loss of smell is an early-determining symptom of AD and an early marker of COVID-19. As a result, anosmia could be the missing link between these two pathologies. Anosmia is characterized by neurological complications that are frequently linked to AD and COVID-19, both of which involve neuro-psychiatric impairments. Thus, treatment strategies aimed at alleviating anosmia may have a significant impact on the progression of both AD and COVID-19. Overall, anosmia, the missing link, may become the common link for treating global crises (Mohammad Azizur et al., 2021).

To detect the potential long-term neurological consequences of SARS-CoV-2 infection, a longitudinal follow-up of COVID-19 patients, particularly older adults and severe cases, is required. Biomarkers, in this scenario, represent reliable tools for early monitoring of COVID-19 patients and early detection of those at high risk of developing neurological sequelae, such as Alzheimer's disease (Ciaccio et al., 2021).

Conclusions

Complex neuropsychological assessments, along with the incorporation of the cognitive reserve assessment for highly educated individuals, aid in the early detection of Alzheimer's disease. When cognitive decline is present, engaging in cognitive stimulation activities helps sustain a cognitive plateau.

Early research points to cognitive symptoms brought on by COVID-19-induced degenerative processes. All of this evidence points to the likelihood that dementia develops in many of these cases as a result of long-term cognitive damage (Kay, 2022).

The significance of routine long-term neurocognitive evaluations following COVID-19 infection recovery has been underlined. Since cognitive impairment may impair social and professional functioning, early intervention may enhance the quality of life for those who are affected (Shariff et al., 2023).

Healthcare services must develop plans to address the changing requirements of patients with dementia and cognitive impairment, as well as those with psychological and neuropsychiatric symptoms. In addition to identifying strategies to address the rapid progression of cognitive and behavioral symptoms faced by many individuals with pre-existing cognitive impairment, whose care has been significantly disrupted during the pandemic, initiatives need to address the screening, treatment, and monitoring of such symptoms during the ongoing pandemic (Palmer, Kivipelto, Gianni, Banaj, & Spalletta, 2021).

For a variety of reasons, cognitive training is regarded as an efficient nonpharmacological intervention. In recent times, this therapy has gained popularity due to its lower risk and contraindications compared to pharmaceutical techniques (Giuli et al., 2016).

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