Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

to enable use of blood biomarkers for diagnosis of neurodegenerative diseases to become a clinical reality.

We declare no competing interests.

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The mechanisms of smell loss after SARS-CoV-2 infection

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COVID-19 has brought the importance of smell to the public's attention. In addition to the roles of olfaction in hygiene, pleasure, and nutrition, this underappreciated sense serves as an early warning system for environmental hazards such as spoiled food, fire, leaking natural gas, and air pollution. The olfactory system's receptor cells are uniquely exposed to the outside environment, making them, along with other epithelial cells crucial for their function, susceptible to damage from airborne viruses, bacteria, and nanoparticles. As first order neurons, olfactory receptor cells can transport xenobiotics from the environment directly to the brain. Smell loss has been associated with early mortality and can signal the first stages of Alzheimer's disease and Parkinson's disease.[2,3]

In a Rapid Review in *The Lancet Neurology*, Michael Xydakis and colleagues[1] discuss the possible causes and the longevity of olfactory dysfunction associated with viruses, in particular SARS-CoV-2. They postulate that individuals who have smell loss due to COVID-19 might have increased susceptibility to future neurological disorders. There is precedent for this thinking.

In a 2-year longitudinal study of 1604 adults (aged >65 years) without dementia,[2] cognitive decline was greater for those who had anosmia and carried at least one *APOE* ε4 allele than for normosmics who had no *APOE* ε4 allele (odds ratio 4·9, 95% CI 1·6–14·9), emphasising the importance of genotype with respect to loss of olfactory function and future cognitive decline. Cognitive decline was greatest in women with olfactory dysfunction and at least one *APOE* ε4 allele (odds ratio 9·7, 1·3–70·4). Before the discovery of genetic mutations and toxins (eg, 1-methyl-4-phenylpyridinium) that can damage dopaminergic neurons, viruses were considered the primary cause of Parkinson's disease.[3] More than 90% of patients with Parkinson's disease have some degree of smell loss that precedes the motor symptoms by 4–8 years and, in some people, by up to 10 years.[3] During the 1918 influenza pandemic, approximately 80% of individuals who recovered from encephalitis lethargica subsequently developed symptoms similar to those of Parkinson's disease.[4]

Several airborne viruses adversely affect the ability to smell. Indeed, the most frequent causes of permanent smell loss are virus-induced acute upper respiratory infections, including those caused by respiratory syncytial viruses, rhinoviruses, coronaviruses, and influenza viruses.[5] Aside from the initial inflammation-related nasal blockage that accompanies most upper respiratory infections, incomplete damage to the olfactory neuroepithelium is common. Such damage is cumulative and can lead to greater pathogenic epithelial vulnerability later in life.[6] Environmental factors, including viruses, seem to be more important than genetic ones in relation to age-related olfactory decrements.[6] Rats reared in pathogen-free environments have less age-related decline in mature olfactory neurons than rats reared in standard laboratory conditions.[7] Although the olfactory epithelium can regenerate, the process of regeneration is rarely complete after severe viral infections,

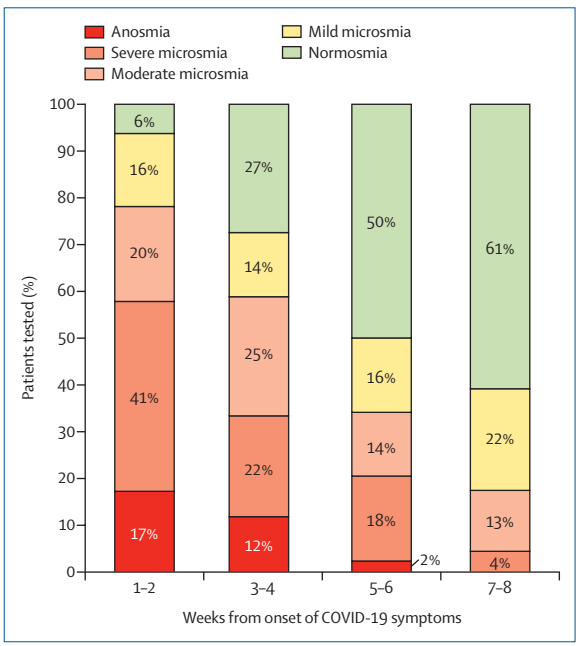

Figure: **Degrees of olfactory function since the onset of COVID-19 symptoms**

Follow-up was done with a 40-item smell identification test. The longer the time since the onset of symptoms, the more likely patients were to have normal olfactory function. One patient was followed up between 8–9 weeks and was included in the 7–8 weeks group. Reproduced with permission from Moein and colleagues.[9]

resulting in a patchy and thin epithelium containing islands of interspersed metaplastic squamous epithelia and fewer cilia, olfactory receptor cells, and supporting cells.[8] The proportion of the roughly 6 000 000 receptor cells in the human olfactory epithelium that needs to be damaged to produce noticeable olfactory deficits is unknown.

It is in this context of degeneration and regeneration that the effect of COVID-19 on olfaction can be seen. In a quantitative study addressing the reversal of smell loss due to COVID-19, which was not included in Xydakis and colleagues' Rapid Review, Moein and colleagues[9] found that 96 (96%) of 100 patients who were admitted to hospital for COVID-19 had measurable olfactory dysfunction near the end of the acute phase of their disease. Retesting 82 of these patients up to 8 weeks after the onset of COVID-19 symptoms found that 50 participants no longer had measurable olfactory dysfunction (61%; normosmia), 18 had mild dysfunction (22%; mild microsmia), 11 had moderate dysfunction (13%; moderate microsmia), and 3 had severe dysfunction (4%; severe microsmia). None of the patients had total smell loss (anosmia) when retested at 7–8 weeks after the onset of COVID-19 symptoms (figure).

In their Rapid Review, Xydakis and colleagues[1] discuss a multitude of possible causes for the smell loss associated with COVID-19 and highlight that supporting data are largely absent for most of them. Perhaps the smell loss associated with COVID-19 is simply the same, in both the degree and pathogenesis, as that of most upper respiratory infections. Men with COVID-19 appear to be more susceptible to smell loss than are women with this disease,[9] a sex association similar to that seen with the common cold. The trajectory of return of function appears to be similar for COVID-19 and the common cold, although more detailed studies are needed.[10] The widespread awareness of smell loss from COVID-19 suggests it has a greater effect on the smell system than either the common cold or influenza. However, this suggestion could be misleading. For example, in the case of the common cold, nearly every affected individual has smell loss that is attributed to nasal congestion (as the loss largely dissipates once congestion subsides). Smell loss could also reflect underlying subtle inflammation or damage to the olfactory epithelium during infection. Moreover, when objectively measured, some degree of smell dysfunction can remain for days after the resolution of common cold-related congestion.[10] Since, unlike the common cold, COVID-19 is rarely accompanied by noticeable nasal congestion, the absence of an obvious explanation for the associated smell loss would magnify the apparent uniqueness of the loss. Could the smell loss associated with COVID-19 be the same as that of the common cold? Do *ACE2* gene variants affect olfactory sequelae? Future research should be done to answer these questions.

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Clinical decision making in MOG antibody-associated disease

With the development of sensitive and specific cell-based assays, the detection of IgG antibodies targeting conformationally preserved full-length human myelin-oligodendrocyte glycoprotein (MOG) has differentiated anti-MOG antibody-associated disease (MOGAD) from other demyelinating disorders.[1,2] The distinction of MOGAD from aquaporin-4-associated neuromyelitis optica spectrum disorder (AQP4-NMOSD) and multiple sclerosis emphasises the divergent pathophysiological, clinical, therapeutic, and prognostic implications of these diseases[2]. In *The Lancet Neurology,* Marignier and colleagues[3] provide a Personal View on the immunology, pathology, clinical spectrum, and treatment of MOGAD, based on a workshop at the 2019 meeting of the European Committee for Treatment and Research in Multiple Sclerosis.

The phenotypic spectrum of MOGAD has been reliably reproduced in international cohorts; classic presentations associated with anti-MOG antibodies include acute disseminated encephalomyelitis (ADEM) in children, and optic neuritis and myelitis affecting all ages.[4] MOGAD is the most common neuroinflammatory disease in children, but affects all age groups with little evidence of any sex or ethnic groups being affected more frequently than others. By contrast, AQP4-NMOSD is uncommon in children, and is more common in Afro-Caribbean populations than in other ethnic groups. Why young children are predisposed to ADEM, whereas adolescents and adults preferentially manifest optic neuritis or myelitis, is unknown.[4]

MOGAD is not only a disorder of white matter: grey matter involvement in childhood ADEM is common. Cortical lesions have been described in patients with ADEM who present with seizures or encephalitis.[5] Radiological characterisation shows that optic neuritis is typically associated with anterior optic nerve involvement with disc swelling,[6] and myelitis often affects the conus and central grey matter.[3] Except for patients with paediatric ADEM, brain MRI is commonly normal in patients with MOGAD, although some adults have large ill-defined white matter lesions without encephalopathy.[6,7]

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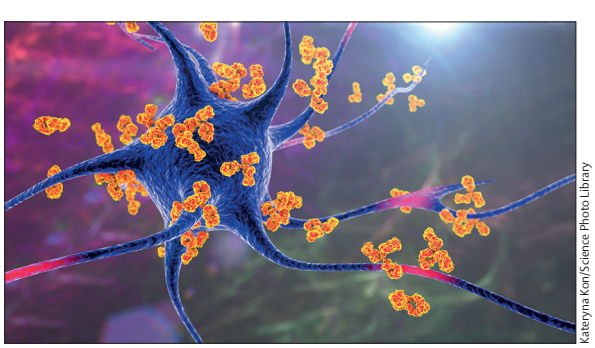
Clinical acumen is essential in diagnosing MOGAD, as testing patients who have a low pretest probability can stretch the specificity of a biomarker. Despite the high specificity of live cell-based assays for the detection of serum anti-MOG antibodies,[3] testing unselected patients with multiple sclerosis will lead to a large number of false-positive results.[8] Testing patients with a high pretest probability, including those with ADEM, optic neuritis, or myelitis, and a brain MRI scan not compatible with multiple sclerosis, will reduce the number of false positive results, but must be carefully balanced with the risk of missing patients who have



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