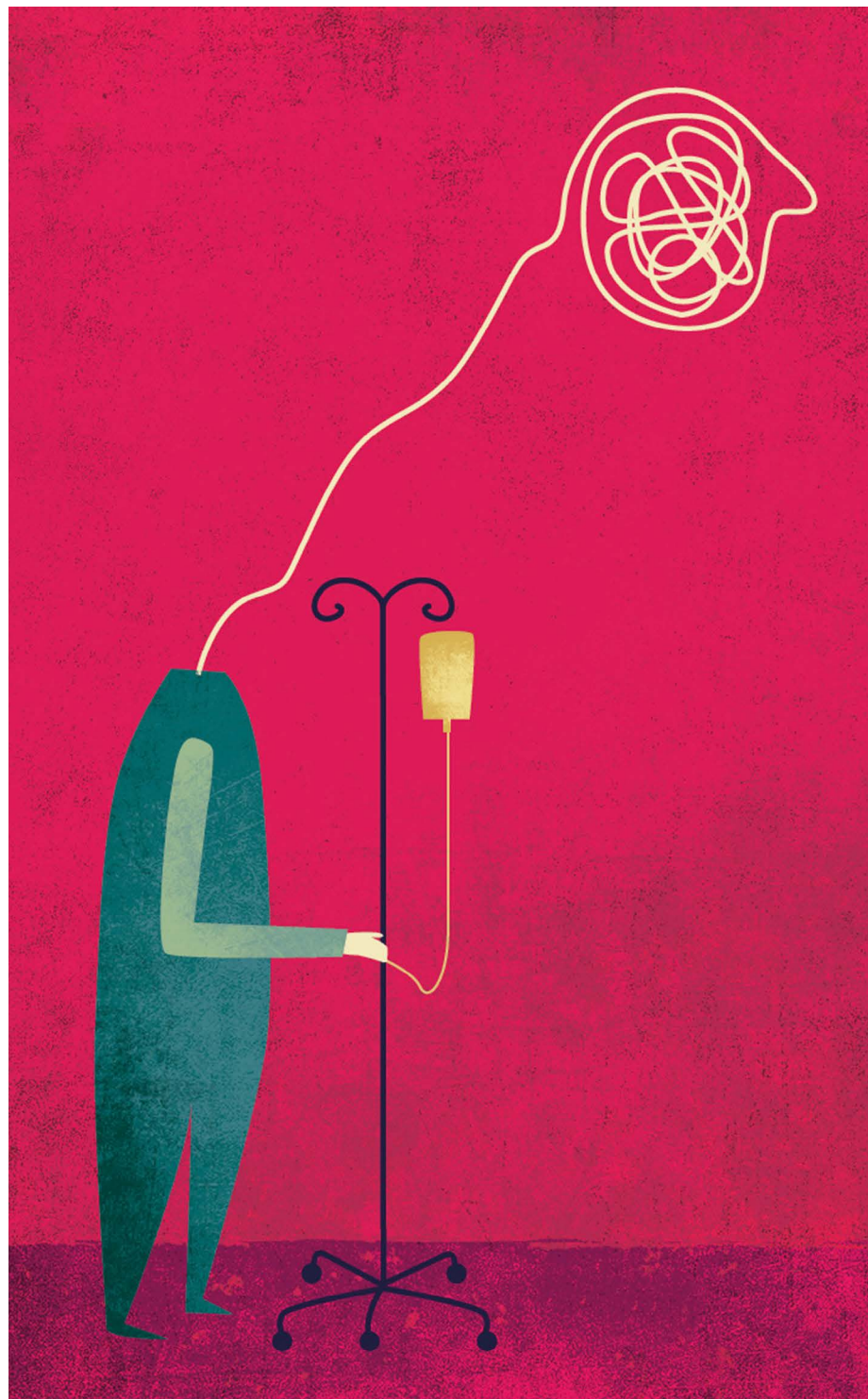


THE LINK BETWEEN DELIRIUM AND DEMENTIA



Delirium is very common on COVID wards. Researchers are testing whether these temporary bouts of confusion could bring on permanent cognitive decline.
By Carrie Arnold

In her job as a physician at the Boston Medical Center in Massachusetts, Sondra Crosby treated some of the first people in her region to get COVID-19. So when she began feeling sick in April, Crosby wasn't surprised to learn that she, too, had been infected. At first, her symptoms felt like those of a bad cold, but by the next day, she was too sick to get out of bed. She struggled to eat and depended on her husband to bring her sports drinks and fever-reducing medicine. Then she lost track of time completely.

For five days, Crosby lay in a confused haze, unable to remember the simplest things, such as how to turn on her phone or what her address was. She began hallucinating, seeing lizards on her walls and smelling a repugnant reptilian odour. Only later did Crosby realize that she had had delirium, the formal medical term for her abrupt, severe disorientation.

"I didn't really start processing it until later when I started to come out of it," she says. "I didn't have the presence of mind to think that I was anything more than just sick and dehydrated."

Physicians treating people hospitalized with COVID-19 report that a large number experience delirium, and that the condition disproportionately affects older adults. An April 2020 study in Strasbourg, France, found that 65% of people who were severely ill with coronavirus had acute confusion – a symptom

FATINHA RAMOS

of delirium¹. Data presented last month at the annual meeting of the American College of Chest Physicians by scientists at the Vanderbilt University Medical Center in Nashville, Tennessee, showed that 55% of the 2,000 people they tracked who were treated for COVID-19 in intensive-care units (ICUs) around the world had developed delirium. These numbers are much higher than doctors are used to: usually, about one-third of people who are critically ill develop delirium, according to a 2015 meta-analysis² (see ‘How common is delirium?’).

Delirium is so common in COVID-19 that some researchers have proposed making the condition one of the disease’s diagnostic criteria. The pandemic has sparked physicians’ interest in the condition, says Sharon Inouye, a geriatrician at the Marcus Institute for Aging and Harvard Medical School in Boston, who has studied delirium for more than 30 years.

As clinicians face the immediate realities of confusion and agitation on their wards, Inouye and other researchers are concerned about the future. In the past decade, long-term studies have revealed that a single episode of delirium can increase the risk of developing dementia years later³, and accelerate rates of cognitive decline in those who already have the condition⁴. The reverse is also true: having dementia makes someone more likely to develop delirium³. A set of simple steps, such as ensuring a family member is present to help people orient themselves, can reduce the incidence of delirium by 40%, but doctors struggle to follow that advice on COVID-19 wards.

But the links between delirium and dementia have been difficult to untangle: researchers need to follow patients for years to get results. The surge in people with delirium produced by the pandemic has focused attention on the condition and provided scientists with a unique opportunity to follow patients and determine if and how delirium might affect long-term cognition. Researchers have launched several studies to explore the long-term neurocognitive impacts of COVID-19, including dementia, and Inouye and others hope that this work will allow researchers to explore the links between the two conditions in real time.

If the pandemic can be said to have a silver lining, says Inouye, it has been to spur interest in how delirium can lead to dementia – and vice versa. What’s more, says Catherine Price, a neuropsychologist at the University of Florida in Gainesville, the spread of COVID-19 “has highlighted the blurring of the lines between delirium and dementia, especially with more older adults in our populace”.

Neglected condition

Inouye’s interest in delirium began when she landed her first job as an internal-medicine physician at a Veterans Administration hospital

in Connecticut in 1985. In her first month there, she treated more than 40 people for a variety of conditions. Six of them developed delirium during their stay; none seemed to return to their previous level of physical and mental health. To Inouye, the connection between her patients’ delirium and their poor prognosis was obvious. When she confessed her suspicions to her bosses, however, they just shrugged. Their attitude, Inouye says, was that delirium was just one of those things that happened.

“Why is it okay for older adults to come in the hospital and lose their minds?” Inouye asked. Answering this question, she says, would be “an uphill battle my entire career”.

Shortly after, she began a two-year fellowship to study the condition in depth. Her work showed that delirium occurs when several stressors converge. Pre-existing vulnerabilities such as chronic disease or cognitive impairment can combine with precipitating factors including surgery, anaesthesia or overwhelming infection to cause a sudden onset of confusion, disorientation and attention difficulties, especially in older adults⁵.

“Delirium easily occurs when the brain is unable to compensate for a stressful situation,” explains Tino Emanuele Poloni, a

neurologist at the Golgi Cenci Foundation outside Milan, Italy. Researchers think that the underlying biological causes are inflammation and an imbalance in neurotransmitters – chemical messengers such as dopamine and acetylcholine.

Inouye’s mounting clinical experience has taught her that regardless of what precipitates delirium, around 70% of those with symptoms eventually recover completely. In the 30% who don’t, however, an episode of delirium predicts a downward spiral over a period of months that leads to profound cognitive impairment, even to symptoms of dementia.

More-formal studies have reinforced the link, to varying degrees. Inouye investigated a group of 560 people aged 70 or older who had undergone surgery, and saw that cognitive decline over the subsequent 36 months was three times faster in those who developed delirium than in those who did not have the condition⁶. A 2020 meta-analysis of 23 studies showed that delirium during a hospital stay was associated with 2.3 times greater odds of developing dementia⁷. And work⁸ by a team of Brazilian scientists showed that, in a group of 309 people with an average age of 78 years, 32% of those who developed delirium in hospital progressed to having dementia, compared with just 16% of those who did not become delirious (see ‘Delirium and cognitive decline’).

What’s more, the longer a person is delirious, the greater their risk of subsequent cognitive impairment, according to a 2013 study by psychologist James Jackson at Vanderbilt University, and his colleagues⁹. Work by Inouye, Jackson, and other researchers found that the reverse was also true: even after controlling for age, existing dementia symptoms increased the chances of developing delirium³.

Causing confusion

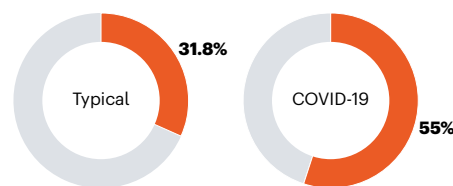
Scientists still don’t agree whether the link between delirium and dementia is strong only in those who would have developed dementia anyway, or whether delirium increases the risk of cognitive decline even in individuals who are not predisposed to it. Nor can they say precisely what it is about delirium that could provoke dementia. If researchers could identify these connections, then perhaps they could prevent delirium from escalating into dementia.

“We don’t understand the mechanisms of delirium at all – we really don’t. And there is no successful management of delirium from a pharmaceutical standpoint,” Price says.

Scientists have developed three hypotheses to explain how delirium might provoke dementia. One line of thinking holds that an accumulation of toxic cellular trash in the brain could cause short-term delirium and lead to longer-term damage. The body usually clears this molecular rubbish by way of

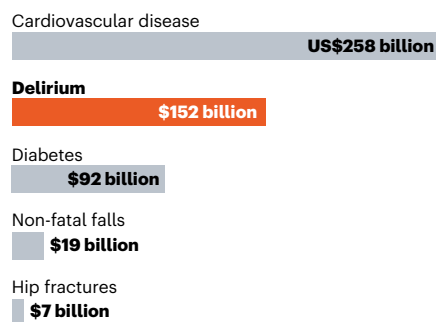
HOW COMMON IS DELIRIUM?

Typically, almost one-third of people who are critically ill will have an episode of delirium; for COVID-19, the proportion rises to more than half.



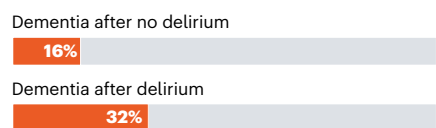
THE COST OF DELIRIUM

In the United States, the annual health-care costs for delirium are higher than those for many other conditions common in older adults.



DELIRIUM AND COGNITIVE DECLINE

People who experience delirium during hospitalization are at increased risk of cognitive decline after discharge, according to a study of 309 patients in Brazil.



Feature

the bloodstream and the lymphatic system, which is a network of channels filled with cerebrospinal fluid. Damage to vessels from an acute episode of delirium could persist and trigger dementia, or a brain that experiences delirium could become more prone to vascular problems in future.

The second suspect is inflammation, which often troubles people who are hospitalized for infections, respiratory distress or cardiovascular disease. Surgery and severe infections can cause a build-up of cellular detritus in the brain, which triggers more inflammation. This short-term, all-hands-on-deck reaction safeguards the brain because it clears the harmful debris and the inflammation ultimately dies down. That is not the case for those who develop delirium, Inouye says. Persistent inflammation can trigger an acute episode of delirium, and cause neurons and associated cells, such as astrocytes and microglia, to deteriorate, leading to cognitive damage.

The third idea is what's known as the threshold hypothesis. Someone with dementia (even in the earliest stages) has fewer connections between neurons, and can show damage to the insulation that wraps them and helps convey signals – known as white matter. This loss strips the neurological reserves that help the person to cope with inflammation or infection, throwing them over the edge not just into delirium but into a more advanced dementia.

Even though the genesis of delirium and its molecular connections to dementia remain unknown, Inouye has managed to find a way to cut rates of delirium in hospital. She created a programme of simple strategies known as HELP (Hospital Elder Life Programme), which focus on reducing sedation, even during mechanical ventilation, paying close attention to nutrition and hydration, and ensuring the presence of family members to help reassure and orient patients. A 2015 meta-analysis¹⁰ showed that these steps reduced delirium by around 40%. Hospitals around the United States began instituting these simple protocols. Then COVID-19 struck and made this all but impossible.

Dementia surge

As Crosby endured coronavirus-induced delirium in her Boston bedroom, Poloni was treating delirious people with COVID-19 in Lombardy – Italy's ground zero for the coronavirus. Many of Poloni's patients already had dementia and, like many physicians, he was watching for common symptoms of respiratory infections such as fever, cough and difficulty breathing. But some of his patients didn't show those signs at all. Instead, they mostly became "dull and sleepy", Poloni said. Others became restless and agitated – all signs of delirium. It was so prominent that Poloni argued that delirium should be added to the virus's diagnostic criteria. Inouye has



MORTEZA NIKOUBAZL/NURPHOTO/GETTY

Visits from relatives are a source of comfort for people with delirium, a common symptom of COVID-19, but many hospitals have strict no-visitor policies.

made that argument, too, and it is supported by a study she published last month showing that 28% of older adults with COVID-19 have delirium when they present to the emergency department¹¹.

The high numbers of people who developed delirium immediately made Inouye, Price and other researchers worry that the pandemic could lead to a surge in dementia cases in the coming decades, on top of the increase in cases as a result of ageing populations (see 'The cost of delirium'). "Is there going to be an increase in dementia from people who had COVID-19 during adulthood or midlife?" asks Natalie Tronson, a neuropsychologist at the University of

treat coronavirus. An international study is planned to measure the prevalence of delirium in people with COVID-19 in ICUs, as well as identifying factors that predict long-term outcomes. A separate study in Germany and the United Kingdom is also tracking neurocognitive outcomes in people with COVID-19 to determine how delirium affects brain function months later. Another research project led by a team at Vanderbilt University is looking for an alternative to commonly-used sedatives such as benzodiazepines, which are known to increase delirium. The researchers are testing a sedative called dexmedetomidine to see whether it is a safer option for people hospitalized with COVID-19.

Inouye and Tronson hope that the funding of these long-term studies will lead to ongoing scientific interest in the delirium–dementia connection, and provide some insight.

"It's going to be, I think, a little bit frightening and a little bit enlightening, both about how illness affects dementia risk, but also what other lifestyle and genetic protective factors can influence risk as well," Tronson says. "We're learning quickly, but there's still a lot of black boxes."

Carrie Arnold is an independent public-health reporter based in Virginia.

WE DON'T UNDERSTAND THE MECHANISMS OF DELIRIUM AT ALL — WE REALLY DON'T."

Michigan in Ann Arbor. "What happens over the next decades, as the population ages more?"

To begin to find answers, institutes around the world have funded a variety of studies into the long-term cognitive effects of COVID-19, some of which will look at delirium. Already under way in the United States is a study tracking people who have been treated in hospital for COVID-19, many of whom developed delirium during their stay. This study will measure cognitive and psychiatric function in people participating in a trial to assess the safety and efficacy of hydroxychloroquine to

1. Helms, J. et al. *N. Engl. J. Med.* **382**, 2268–2270 (2020).
2. Salluh, J. I. F. et al. *Br. Med. J.* **350**, h2538 (2015).
3. Fong, T. G. et al. *Lancet Neurol.* **14**, 823–832 (2015).
4. Fong, T. G. et al. *Neurology* **72**, 1570–1575 (2009).
5. Fong, T. G., Tulbaev, S. R. & Inouye, S. K. *Nature Rev. Neurol.* **5**, 210–220 (2009).
6. Inouye, S. K. et al. *Alzheimer's Dementia* **12**, 766–775 (2016).
7. Goldberg, T. E. et al. *JAMA Neurol.* **77**, 1373–1381 (2020).
8. Garcez, F. B. et al. *Age Ageing* **48**, 845–851 (2019).
9. Pandharipande, P. P. et al. *N. Engl. J. Med.* **369**, 1306–1316 (2013).
10. Hsieh, T. T. et al. *JAMA Intern. Med.* **175**, 512–520 (2015).
11. Kennedy, M. et al. *JAMA Netw. Open.* **3**, e2029540 (2020).