Source : www.thehindu.com Date : 2023-09-23

THE CURIOUS LINK BETWEEN ALZHEIMER'S DISEASE AND TRAUMA

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

September 22, 2023 05:44 pm | Updated 05:44 pm IST

Image for representational purpose only. File | Photo Credit: Reuters

It is the early 1800s, the French Revolution has just subsided, and Philippe Pinel, a French doctor, proposes a 'radical' humane approach to treating medical illness. He argues that maladies such as Alzheimer's Disease (AD) are better understood as a puzzle of multiple pieces. Why does a person develop a specific illness at a particular time in their life? Each illness, he writes, "represented the intersection of a human being at a specific moment in life with a disease at a particular stage of its development". Take Alzheimer's. Mr. Pinel theorises the condition arises not only due to abnormalities in "plaques and tangles" — proteins in the brain associated with AD — but also from other causes including education, alcohol use, genetics, way of life, even trauma to the head.

Today, science acknowledges all these as risk factors for Alzheimer's, the most common type of dementia that progressively erodes one's memory, thinking and other cognitive abilities. This 'inevitable demise of personhood' has been likened to a 'living death'. India is home to an estimated 53 lakh dementia patients aged 60 and above, a number expected to exceed 120 lakh by 2050, per data collected before the COVID-19 lockdown. The prevalence of dementia among older people is higher in India as compared to the U.S. or U.K., recent evidence also showed. People are living longer, in a country set to become the world's most populous nation. Moving pieces such as diabetes, hypertension, obesity, lifestyle, lack of awareness also contribute to this rise, experts note, as we sit decades away from finding a cure. It is no wonder the theme for this year's World Alzheimer's Day theme is 'never too early, never too late', a clarion call to prevent risk factors where possible.

One association is reiterated in the growing canon of dementia research: that of adversity and cognitive decline, in tune with what Mr. Pinel first observed. Does stress — trauma, of the brain, the mind, the body — erode brain health to a degree that it hastens neurodegeneration, and consequently, the risk of developing AD? The hypothesis has been tested over and over, yielding conflicting and contradictory results. The Alzheimer's question boils down to: We know adversity influences symptoms of AD, but can it increase the risk of *developing* Alzheimer's too?

Evidence connecting traumatic brain injury (TBI) with numerous types of late-onset dementia has strengthened over the last three decades. TBI cases among U.S. veterans were associated with a 60% increase in the risk of developing dementia. Footballers were 50% more likely than

others to develop dementia due to repeated instances of “mild brain trauma”, per a 2023 Scottish study published in the *Lancet Public Health*. The term ‘punch drunk syndrome’ was devised in 1928 to describe syndromes (such as “marked mental deterioration”) contact-sport players presented years after retiring from boxing. Interestingly, the risk of specific brain changes was tied to the number of rounds a player boxed, not the number of times they were knocked out — implying that even injuries that don’t cause physical unconsciousness may slowly build up dementia risk.

The ‘why’ of it all is still inconclusive. A meta-analysis of studies peering into the link between TBI and AD found accumulated *beta-amyloid* (A, a toxic waste protein in the brain). A in excess tends to aggregate and form plaques, which deposit between neurons and disrupt cell function in people with AD. Other causes were vascular damage, white matter degeneration in patients, and deposition of *tau* (a protein that accumulates as neurofibrillary tangles), among other reasons that could lead to neurodegenerative disease. In 2021, researchers looked at MRIs of people with AD and those with TBI to find similarities in neurodegeneration: cortisol thickness — correlated with brain age, healthy memory and attention — had thinned in both. These findings could help “professionals to identify TBI victims who are at greater risk for Alzheimer’s disease”, the researchers said.

Genes could be decisive actors too: people with TBI, who had a specific variant of the gene apolipoprotein E (APOE) called APOE-e4, were more likely to develop dementia, a December 2022 study found, but more research is needed to solidify the genetic link. In some cases, TBI was not linked to AD or dementia at all but to other forms of neurodegeneration such as Parkinson’s Disease. Scientists humbly acknowledge the equivocal nature of data and flagged the need to unearth which pathological mechanisms TBI activate, and how it is linked ot neurodegeneration.

Residents of the conflict-ridden Jammu and Kashmir have the highest prevalence of dementia in India, claimed a research conducted by the University of Southern California and AIIMS-Delhi earlier this year (70% of Kashmir’s population have witnessed a violent death, almost half have undergone some form of mental distress, per the Médecins Sans Frontières). This wasn’t a causal link but a correlation: 11% of people reportedly have dementia, but it is unclearif that group was exposed to trauma or not.

The relationship between PTSD and dementia is complex, but too strong to ignore. A growing body of research has associated post-traumatic stress disorder (PTSD) in American war veterans with AD and dementia risk. Early childhood adversity, due to violence, war or abuse, has also been connected with a later life dementia diagnosis, a 2020 meta-analysis published in the *British Journal of Psychiatry* found. The UCL researchers followed up with patients up to 17 years, people who had gone through both combat and non-combat-related trauma, and found the rate of dementia diagnosis among people with PTSD was almost two times of those without PTSD. “This provides the strongest evidence yet that PTSD is a risk factor for dementia”, says Stefanie Pina Escudero, who is researching the interplay of stress and neurodegeneration at UC San Francisco, and was not involved in the study.

Instead of placing AD and trauma in a ‘cause’ and ‘effect’ equilibrium, think of a two-plate scale. Dementia on one side; protective factors, such as genetics, health conditions, lifestyle sit on the other. “If these factors are negative, they may tilt the balance further towards dementia, while if they are positive, they may help to balance it out,” says Dr. Pina Escudero.

One theory spotlights the role of the hypothalamic-pituitary-adrenal (HPA) axis, the body’s fire alarm: any stressful event activates the HPA axis, alerting us to danger, where cortisol is released to help us cope with stress and it eventually turns off. “However, if there is a constant

fire alarm or one that goes off very easily as in PTSD, it can become very annoying and even harmful," explains Dr. Pina Escudero. The HPA axis is overworked, causing the cortisol levels to remain high and triggering symptoms, "including flashbacks, nightmares, and anxiety, as well as several health problems, including Alzheimer's disease." Moreover, traumatic experiences are also associated with depression, anxiety disorders, sleep disturbances, and substance abuse, and if unaddressed, each of these outcomes "increases the risk of cognitive impairment".

A 2023 study published in *Brain* journal found something similar, where the constant fire alarm eventually had a negative impact on the body, causing inflammation, damage to DNA and cells, and accelerating the ageing process, "which of course can affect the brain and cognition". The researchers examined stress levels in female mice and found *beta-amyloid* proteins released in excess. The authors admitted the need for more evidence, but the finding "demonstrates a direct link between stress and Alzheimer's disease in women at a cellular level." Another paper argued that stress due to traumatic flashbacks and lack of sleep reportedly increases amyloid burden, accelerating cognitive decline prior to AD.

Stress and trauma also often accompany social isolation or depression -- known risk factors that increase the likelihood of developing dementia. A recent John Hopkins study found even a mild hearing loss doubled the risk of dementia. "You may not want to be with people as much, and when you are you may not engage in conversation as much...which could "contribute to a faster rate of atrophy in the brain", researcher Frank Lin explained. The intensity of trauma also adds up: chronic stress (real-life threats like war) distinctly differs from moderate stress (when facing new things). It's like driving a car: "If you press the accelerator to the floor to escape a threat and do so for an hour... then return to driving at a normal speed, the car will continue to function well," explains Dr. Pina Escudero. "However, if you keep the accelerator pressed for days, weeks, months, the entire car will experience wear and tear." One of the regions that may fall to this degradation is the hippocampus, charged with learning and storing new memories.

Genes may play a role too. The Kashmir study found a higher rate of specific DNA variations called the ACE polymorphisms The ACE gene (and its two versions: the I allele and the D allele) instructs the body on making a protein that controls blood pressure. In the study, the people who inherited the I allele from one or both parents had a higher chance of developing Alzheimer's disease. Compared to its other half, the I allele makes a shorter version of the ACE protein, which is not only less effective in disposing of -amyloid in the brain but also contributes to higher blood pressure and threatens the brain's shield -- the blood-brain barrier. Together, they wreak neuronal dysfunction and are hallmarks of AD. However, this connection remains a "matter of debate", says Dr. Pina Escudero. "A person being a carrier of the *ACE* I alleles is not a direct cause of Alzheimer´s disease as maybe other genes are; it is just one more risk factor and may universally apply to all human populations."

The story is "nebulous" when it comes to emotional adversity, says A.B.*, a neuroscientist involved in dementia research in India who wished not to be named. While studies aim to chart pathways between adversity and AD, the precise causality is still unclear.

One way researchers rationalised the 2023 paper on dementia risk in Jammu and Kashmir was that prolonged stress impacts the brain's hippocampus and memory centre. But this theory "makes dementia look so simple", says A.B., because dementia is not just about memory -- there's so much more to the gamut than forgetfulness.

This is an inherent limitation in studying AD and dementia. A.B.* notes that studies that show associations (and not causations), while instructive in guiding research, do not offer "necessary and sufficient" evidence to prove a link. Childhood adversity does impact brain health, and poor brain health may in turn trigger cognitive decline and AD-related symptoms. But it is not wholly

correct to say if A=B, and B=C, so A=C; there are unmapped variables at play. “It’s only a mathematical correlation. It’s like a man and a woman, are walking on the road at the same time. There happen to be other men and women walking who are married. So you conclude that these two are also married,” which is not accurate.

Moreover, the credibility of studies is tied to the composition of datasets, how long were the participants followed, the methodology applied. The Jammu and Kashmir study, for instance, sampled a total of 1,10,000 people from India, but only 1,000 people were surveyed from the Union Territory itself. A.B.* says, “The sampling strategy was not randomised and statistically established, and they had a lot of missing data”. Correlational studies are important, but ‘cherry picking’ symptoms can misrepresent an illness, especially in a landscape marked by limited scientific literacy and lack of data. The threshold of proof to establish scientific causation is justifiably high, but to understand how the brain’s plasticity compensates for stress means exposing people to stress itself. “A rigorous study... would involve randomly assigning two groups of individuals to either experience PTSD or not, and then following them over time to see if they developed dementia,” Dr. Pina Escudero says. “This is not possible for ethical reasons.”

The field is also dominated by research from Western countries sampling a Caucasian population, and may not reflect the socio-economic challenges of low- and middle-income countries. India’s genetic diversity due to migration, coupled with the caste system and resultant endogamy, presents an untapped, unique genetic landscape that will invariably alter the trajectory of dementia among India’s ageing population, argued a 2021 paper in *Nature*.

There are *N* factors that impact brain health and lead to neurodegenerative disorders. One’s age, personality, coping skills, how long the trauma last, the nature of trauma, if one has social support. If their cultural norms create healthy conditions for processing trauma. A paper in *Nature* acknowledged the variability at play, explaining that “past research on the effects of specific adversity shows a fragmentary and somewhat contradictory picture”. Their longitudinal study followed up with patients from 2006 to 2018 and found that adversity did have a bearing on dementia risk (positive and negative). It, however, depended on a) the nature of adversity (did someone’s parents die? did they experience hunger) and b) the period in life when adversity hit.

For now, whether any one of them is “necessary and sufficient” to cause AD is still uncertain, says A.B. Moreover, researchers are still unearthing which brain regions are involved in AD; dementia research is then a lot like flipping pieces to see the full picture of Alzheimer’s, except the box doesn’t specify how many pieces make the puzzle.

The glut of findings interlinking trauma and Alzheimer’s, however, betrays a poignant temptation, to attribute a complex, baffling disease -- which changes the brain, the person and the family -- to one root cause. But as researcher Debomoy K. Lahiri notes in his paper, we need an ‘arsenal’, not a ‘magic bullet’ that targets one region or one cause, for the Alzheimer’s question “requires our understanding the disease as a transformation rather than a state”. Both A.B. and Dr. Pina Escudero propose a 180-degree shift in how we rationalise AD research: “it’s a complex interplay of factors, and we definitely need more studies to look at the impact of adverse events,” says A.B.

As science seeks to demystify the brain, another part of this arsenal is to perhaps utilise research linking trauma to dementia risk, even if observational, into targeting populations “more vulnerable to developing dementia”, improving screening efforts and raising awareness. It could pre-emptively address mental distress, anxiety and trauma in a population who are living through pandemics, conflicts, soaring unemployment and hunger, by investing in a mental health landscape marked by stigma and lack of availability. The route to addressing India’s Alzheimer’s

burden goes beyond immediate medical cure and instead by caring for those who may eventually develop a disease, activists have opined. Dr. Pina Escudero adds that a prerequisite for screening should be to “ensure equal access to screening, follow-up, treatment, and ongoing evaluation for the entire population”. There is no straightforward relationship between trauma, PTSD and dementia; prioritising one trauma over the other for screening creates conditions of inequity.

“It is essential to raise awareness about PTSD and its various health-related consequences, including dementia. People should be encouraged to discuss these concerns with their healthcare professionals,” she says. This, in tandem with healthcare professionals receiving training to identify PTSD and its potential negative outcomes can help them “effectively modify the identified risk factors”. Research linking adversity with AD is then, only discovering newer clues to the puzzle.

“The disease is just too complex in its pathogenesis, which (still) needs to be fully acknowledged. In addition, the exact causes of the disease are still elusive, which still needs to be fully admitted.”Christian Behl, author of “Alzheimer’s Disease Research” (2023)

END