Cold sore viral infection implicated in development of Alzheimer's disease

But people treated with antiviral therapy seem to be at lower risk, large US study finds

Symptomatic infection with the virus responsible for cold sores around the mouth–herpes simplex 1, or HSV-1 for short—may have a key role in the development of Alzheimer's disease, suggests a large pharma industry-funded US study published in the open access journal *BMJ Open*.

But treatment with antiviral therapy seems to be linked to a lower risk of this type of dementia, suggesting that treatment to quell HSV-1 symptoms may be protective, the findings indicate.

Currently, around 35.6 million people worldwide live with dementia, and 7.7 million new cases are diagnosed every year, say the researchers. Alzheimer's disease comprises 60%–80% of all dementias, with total costs for its treatment reaching US\$305 billion in 2020, they add.

Various infectious agents have been implicated in the development of Alzheimer's disease, and the most studied of these is HSV-1, which affected more than two-thirds of under 50s around the globe in 2016 alone.

To shed further light on the mooted role of HSV-1 in Alzheimer's disease and the potential protective effects of antiherpetic drugs, the researchers drew on a large set of US administrative claims data (IQVIA PharMetrics Plus) for the period 2006-21.

People diagnosed with Alzheimer's disease were matched for age, sex, geographical region, database entry year, and number of healthcare visits with those without any history of neurological disease, resulting in a total of 344,628 case–control pairs.

Nearly two thirds (65%) of those with Alzheimer's disease were women. Their average age was 73 and they tended to have more co-existing conditions—all risk factors.

In all, 1507 (just under 0.5%) people with Alzheimer's disease had been diagnosed with HSV-1 (0.44%) compared with 823 (just under 0.25%) of those in the comparison (control) group.

Unsurprisingly, the risk of Alzheimer's disease rose in tandem with age. But, overall, the likelihood of an HSV-1 diagnosis was 80% higher among those with Alzheimer's disease, after adjusting for potentially influential factors.

Among the 2330 people with a history of HSV-1 infection, 931 (40%) used antiherpetic medication after their diagnosis. And they were 17% less likely to develop Alzheimer's disease than those who didn't use these treatments.

The researchers also looked at the potential role of other herpes viruses, including HSV-2, varicella zoster virus, and cytomegalovirus. Both HSV-2 and varicella zoster virus infections were also associated with a heightened risk of Alzheimer's disease.

Exactly how HSV-1 and other neurotropic viruses might heighten the risk of dementia isn't clear, point out the researchers.

"However, studies have shown that inflammatory alterations in the brain caused by HSV infection are pivotal in [Alzheimer's disease] development," they explain.

"It has been reported that $A\beta$ peptides are deposited in response to HSV infection and protect host cells by blocking viral fusion with the plasma membrane, pointing to HSV as a potential risk factor for [Alzheimer's disease]. Consistently, $A\beta$ exhibits antimicrobial properties against various pathogens, including HSV-1," they add.

HSV-1 DNA is also found in the plaques characteristic of Alzheimer's disease, and people carrying the ApoE ϵ 4 allele, the most common genetic risk factor for the disease, are more susceptible to HSV infections, they note.

This is an observational study, and as such, no firm conclusions can be drawn about cause and effect. And the researchers acknowledge that HSV-1 infections before the patient's inclusion in the database weren't known, added to which many people with the infection don't have symptoms, while others might not seek treatment when they do–all factors that might influence the findings.

But their findings are in line with those of other studies. And they suggest: "While the molecular mechanisms remain to be fully elucidated, these results are indicative of a possible role for antiherpetic therapy in mitigating dementia risk."

And they conclude: "These findings place an even greater emphasis on viewing the prevention of herpes viruses as a public health priority.