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Herpes Simplex May Double Alzheimer's Risk

Liam Davenport | October 27, 2014

Herpes simplex virus infection appears to double the risk of developing Alzheimer's disease (AD), claim Swedish researchers in two separate studies.

In a nested case-control study, Hugo Lövheim, MD, PhD, from Umeå University, in Sweden, and colleagues found that the risk for AD was significantly associated with prior herpes simplex virus type 1 (HSV1) infection.

Furthermore, a second investigation by the same team using data from an ongoing prospective cohort study indicated that reactivated HSV1 infection increased the risk for AD two-fold, although the association with the presence of HSV infection was not significant.

Both studies are published in the journal *Alzheimer's and Dementia*.

Strong Link

"Our results clearly show that there is a link between infections of herpes simplex virus and the risk of developing Alzheimer's disease," Dr Lövheim told *Medscape Medical News*.

The concept of a link between HSV and AD is not new — it was proposed initially in 1982. However, the idea fell out of favor.

"When I started looking at this in 2009, I found out that most researchers had discarded the hypothesis," said Dr Lövheim.

"But I didn't think that there had really been nearly enough studies to do so. I think there was a lack of good studies investigating this hypothesis, and especially epidemiological studies of sufficient size.

"I therefore planned to look at this hypothesis.... The exact reason why we did two studies was that I saw the possibility to use these two materials that were available at our university," he added.

In the first study, plasma samples from 360 patients with AD that were stored in the Medical Biobank at Umeå University were matched with samples from 360 age- and sex-matched dementia-free control individuals.

The plasma samples, which were taken an average of 9.6 years before diagnosis, were analyzed for the presence of anti-HSV immunoglobulin (Ig)G and IgM antibodies using enzyme-linked immunosorbent assay (ELISA).

Stop Disease Progression?

There was no significant difference between AD patients and control participants in the proportion of those testing positive for anti-HSV IgG antibodies, at 93.9% vs 90.0% (odds ratio [OR], 1.636; $P = .069$). The results for anti-HSV IgM antibodies were also not significant, at 7.5% vs 5.6% (OR, 1.368; $P = .299$).

However, when the team looked at the time between plasma sampling and AD diagnosis, they found a significant association between the presence of anti-HSV IgG antibodies and AD diagnosis among patients in whom there was at least 6.6 years between sampling and diagnosis, at 95.6% vs 90.0% for control individuals (OR, 2.250; $P = .019$).

In the second investigation, the team used data from the Betula project, an ongoing, longitudinal, prospective cohort study of aging, memory, and dementia among people living in Umeå. Of 3432 individuals who contributed at least one serum sample, 245 (7.1%) developed AD during an average follow-up period of 11.3 years.

Serum anti-HSV IgG antibodies were identified in 88.2% of the participants. Among those with anti-HSV IgG antibodies, 7.6% developed AD, compared with 3.4% of those without such antibodies. Adjusted analysis indicated that anti-HSV IgG antibodies did not increase the risk for AD, at a hazard ratio (HR) of 0.993 (P = .979).

The proportion of individuals with anti-HSV IgM antibodies, which indicate the presence of reactivated HSV1 infection, was 2.9%. AD developed in 15.0% of individuals with anti-HSV IgM antibodies, vs 6.9% of those without the antibodies, and anti-HSV IgM antibodies were significantly associated with the development of AD, at an HR of 1.959 (P = .012).

Dr Lövheim believes that the findings pave the way for studies on whether treating HSV1 infection could slow the development of AD.

"Herpes simplex infection is treatable with antiviral drugs, like acyclovir, so there is at least the possibility that treatment with those drugs might also be able to affect the progression to Alzheimer's disease," he said.

He also raised the possibility that treating HSV1 infection could help patients who have already developed AD to regain function.

"We know that the neurons in the brains of patients with Alzheimer's disease have a rather long phase when they are silent but not yet dead, so I would say there is a possibility that some symptoms might go back, or that one can halt the progression."

Don't Overinterpret

The findings are particularly important, insofar as AD is a considerable and growing healthcare burden.

"There are millions of people across the globe with Alzheimer's disease — 5 million in the United States today – and in the US alone, at least half a million people every year die from Alzheimer's," Keith Fargo, PhD, director of scientific programs and outreach at the Alzheimer's Association, told *Medscape Medical News.*

"It's a major crisis, and it's something that we don't fully understand yet. The Alzheimer's Association is very supportive of any avenue of research that will help us to understand the causes of Alzheimer's disease and, hopefully, potentially a prevention or a cure."

However, Dr Fargo cautioned against overinterpreting the findings.

"I think it's too early at this point to think that these data will necessarily have clinical applications."

Dr Fargo emphasized that the studies show an association of risk, rather than a causal link between infection and the development of AD.

"There could be some third variable, such as a disorder of the immune system, that was conducive of both of those things," he pointed out.

"If that's the case, it would not necessarily be expected that an antiviral would do anything to change the risk at all. Even if there is a causative link between the viral infection or reactivation and the development of Alzheimer's disease, it's not known yet whether the kinds of antiviral therapies that are available today would be effective against the link between the virus and Alzheimer's disease."

Dr Fargo also underlined the fact that in the first article, the sample size was relatively small. In the second study, the number of AD cases was small. Moreover, the association with developing AD was with HSV1 exposure in the first study, but only with HSV1 reactivation in the second.

Nevertheless, Dr Fargo welcomed the study, inasmuch as the Alzheimer's Association, which publishes *Alzheimer's and Dementia*, supports studies that are "a little bit outside the box."

He said the Association is keen to see studies such as these included in the US government's National Plan to Address Alzheimer's Disease. In a recent article, a group of leading scientists called for the plan to be enlarged in scale, expanded in scope, and better coordinated to meet its ambitious goal to "prevent and effectively treat Alzheimer's disease by 2025."

"We think that the scientific community is rightfully calling for additional research into the basic mechanisms of the development of Alzheimer's, and that's one path for getting us an effective prevention or treatment," said Dr Fargo.

The authors report no relevant financial relationships.

Alzheimers Dement. Published online October 7, 2014. Study 1 abstract

Alzheimers Dement. Published online July 17, 2014. Study 2 abstract

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