

# Is Alzheimer's Disease Autoimmune Inflammation of the Brain That Can be Treated With Nasal Nonsteroidal Anti-Inflammatory Drugs?

American Journal of Alzheimer's Disease & Other Dementias®  
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DOI: 10.1177/1533317514545478  
aja.sagepub.com  


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## Abstract

The Alzheimer's Association recently reported that a woman's estimated lifetime risk of developing Alzheimer's at age 65 is 1 in 6, compared to nearly 1 in 11 for a man (ie, female to male ratio 1.8). Based on female to male ratio, Alzheimer's disease could well be an autoimmune disorder. Like Alzheimer's, multiple sclerosis, an autoimmune inflammation of the central nervous system, has a female to male ratio of 2.3. Also based on female to male ratio, Alzheimer's resembles the autoimmune inflammatory disease rheumatoid arthritis, which has a female to male ratio of 2.7. The reasons for the female preponderance in autoimmune disease are unclear, but nonsteroidal anti-inflammatory drugs (NSAIDs) are widely and successfully employed to treat autoimmune anti-inflammatory disease and dramatically relieve symptoms. Moreover, oral NSAIDs consistently reduce the risk of Alzheimer's disease, although they have been totally ineffective as a treatment in multiple failed clinical trials. A basis for this failure might well be that the brain dose after oral administration is too small and not sufficiently early in the pathogenesis of the disorder. But NSAID brain dose could be significantly increased by delivering the NSAIDs intranasally.

## Keywords

autoimmunity, NSAIDs, brain, nasal

The Alzheimer's Association recently reported that a woman's estimated lifetime risk of developing Alzheimer's at age 65 is 1 in 6, compared to nearly 1 in 11 for a man (ie, female to male ratio 1.8). The magnitude of this difference cannot be attributed solely to the fact that women live longer than men.<sup>1</sup> Multiple effects are involved.

## Increased Longevity of Women Effect

Using the Social Security Administration's life expectancy calculator (<http://www.socialsecurity.gov/cgi-bin/longevity.cgi>) yields 21.6 years and 19.5 years for a 65-year-old female and a 65-year-old male, respectively,  $21.6/19.5 = 1.1$ . Assuming the age-specific incidence of Alzheimer's is the same for both sexes, this would also be the expected effect of longevity on the incidence of Alzheimer's. In other words  $(1.1 - 1.0)/(1.8 - 1.0) = 1/8$  or 12.5% of the observed increased Alzheimer's in women is due to the increased longevity of females.

## Cardiovascular Disease Effect

The Framingham Study found that the death of men from cardiovascular disease between ages 45 and 65 was reducing the pool of men at high risk of Alzheimer's disease at later ages. The Framingham Study estimated that this effect explained

20% to 50% of the difference in incidence of Alzheimer's disease among men and women older than 65.<sup>2</sup>

## Autoimmune Inflammation Effect

Biochemical and neuropathological studies of brains from individuals with Alzheimer's disease provide clear evidence for an activation of inflammatory pathways and glial inflammation.<sup>3</sup> Long-term use of anti-inflammatory drugs is linked with reduced risk of developing Alzheimer's disease.<sup>4</sup> Amyloid- $\beta$  plaques and  $\tau$  protein tangles, hallmarks of the pathology, are most likely a nonspecific result of the disease process, rather than a cause.<sup>5</sup>

Based on female to male ratio, Alzheimer's disease could well be an autoimmune disorder. Like Alzheimer's, multiple sclerosis, an autoimmune inflammation of the central nervous system,<sup>6</sup> has a female to male ratio of 2.3.<sup>7</sup> Also based on

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female to male ratio, Alzheimer's resembles the autoimmune inflammatory disease rheumatoid arthritis, which has a female to male ratio of 2.7.<sup>8</sup> In addition, incidence of Alzheimer's disease<sup>1</sup> and autoimmune disease<sup>9</sup> is increasing.

There is other evidence that Alzheimer's disease has an autoimmune component. D'Andrea has suggested that the presence of antineuronal autoantibodies in the serum, whose importance had been previously dismissed, may be without pathological consequence until there is a blood-brain barrier dysfunction, which allows these autoantibodies to access their targets with deleterious effect.<sup>10,11</sup> And there is a relationship between autoimmune thyroid disease and Alzheimer's disease. Genovesi et al report that patients with Alzheimer's disease showed a significant increase in the mean values of antithyroglobulin and antimicrosomal autoantibodies compared to nondemented controls.<sup>12</sup>

Autoimmunity is a factor in cancer regression,<sup>13</sup> and Alzheimer's disease is associated with decreased risk of cancer-specific mortality.<sup>14</sup> Therefore, a predisposition to autoimmunity could predispose to Alzheimer's disease while lowering the risk of cancer.

Features of autoimmunity have been associated with both Alzheimer's disease and diabetes. In both diseases, high levels of advanced glycation end products and their receptor have been detected in tissues and in the circulation.<sup>15</sup>

With 20% to 50% of increased Alzheimer's disease in women due to the effect of death from heart disease in men before age 65<sup>2</sup> and another 12.5% due to the effect of increased longevity of women, the potential role of autoimmunity is reduced. Nevertheless, a significant part of the observed female male incidence difference remains unexplained and may indeed suggest autoimmunity as a factor in the etiology of Alzheimer's.

## Autoimmune Disease Preponderance in Women

Most autoimmune diseases are female sex related. Nearly 75% of the more than 23.5 million Americans who suffer from autoimmune disease are women. The reasons for the female preponderance in autoimmune disease are unclear. Men and women respond similarly to infection and to vaccination, arguing against intrinsic sex differences in immune response. Endogenous hormones could cause sex discrepancy if their effect is a threshold off-on switch rather than quantitatively variable.<sup>16</sup> Moreover, women with autoimmune diseases manifest a higher rate of circulating cells with a single X chromosome. There have been several reports on the role of X chromosome gene dosage through inactivation or duplication in autoimmunity.<sup>17</sup>

Pregnancy appears to increase the risk of autoimmune disease, and the small exchange of cells between mothers and their children during pregnancy may induce autoimmunity.<sup>16</sup> Beeri et al have reported that number of children is associated with neuropathology of Alzheimer's disease in women but not in men. Beeri et al suggest that since the associations between number of children and neuropathology of Alzheimer's disease were found for women only, they might reflect sex-specific

mechanisms (such as variations in estrogen or luteinizing hormone levels) rather than social, economic, biological, or other mechanisms common to both men and women.<sup>18</sup> Also, the association between number of children and neuropathology may be due to increased autoimmunity or the influence of estrogen and different progestins on the development of cognitive decline.<sup>19</sup>

Autoimmune disease, while common in women, is rarely found for the first time in people older than 65 years. In contrast, clinical Alzheimer's disease is much more prevalent in persons older than 65 years. But in Alzheimer's disease, the pre-clinical phase of detectable lowering of cognitive functioning precedes the appearance of clinical disease by many years.<sup>20,21</sup>

## Nonsteroidal Anti-Inflammatory Drugs and Alzheimer's Disease

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely and successfully employed to treat autoimmune anti-inflammatory disease and dramatically relieve symptoms.<sup>22</sup> Moreover, oral NSAIDs consistently reduce the risk of Alzheimer's disease in retrospective<sup>23</sup> and prospective studies,<sup>24</sup> although they have been totally ineffective as a treatment in multiple failed clinical trials.<sup>25</sup> A basis for this failure might well be that the brain dose after oral administration is too small.<sup>26</sup>

Ibuprofen, flurbiprofen, and indomethacin, which are highly lipophilic, readily cross the blood-brain barrier after an oral dose but are poorly distributed.<sup>27</sup> The amount of ibuprofen, flurbiprofen, and indomethacin that reach the brain after an oral dose is small. Most NSAIDs that exhibit good activity against Alzheimer's disease models, such as ibuprofen, flurbiprofen, and indomethacin, distribute poorly to the brain.<sup>28</sup> Plasma protein binding limits brain NSAID uptake by reducing the free fraction of NSAID in the circulation,<sup>27</sup> although the blood-brain barrier is dysfunctional in Alzheimer's disease.<sup>29</sup>

The NSAID brain dose could be significantly increased by delivering the NSAID intranasally. Nasal drug delivery that exploits the olfactory and trigeminal neuronal pathways to convey drugs to the brain is being widely explored by pharmaceutical companies.<sup>30</sup> Low-molecular-weight lipophilic drugs, such as ibuprofen, are readily absorbed into the brain by the intranasal route.<sup>30</sup> Intranasal insulin is already being tested as a treatment for Alzheimer's disease.<sup>31</sup> In addition, Alzheimer's disease starts in the entorhinal cortex, which is connected to the olfactory nerves and spreads outward in an anatomically defined pattern.<sup>32</sup> Therefore, nasal NSAIDs would readily reach the region of the brain where they are most likely to be therapeutic. Indeed, NSAIDs can restore neurogenesis through attenuation of microgliosis.<sup>33</sup> If animal studies can validate the nasal route as a means of delivering a specific NSAID to the entorhinal cortex, then a trial of an intranasal formulation of that NSAID may be justified.

## Authors' Note

Dr Lehrer has filed a patent application for nasal NSAID treatment of Alzheimer's disease.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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