

THE QUEST FOR QUESTIONS

Sex Differences are Emerging

To find the answers in scientific research, you need to be able to ask the right questions. An increasingly important question in the study of dementia and other neurodegenerative diseases is “are there differences in how these diseases affect women and men, and if so, why.”

That was the underlying question of a study conducted by Dr. Mary Tierney, Professor at the University of Toronto and Sunnybrook Health Sciences Centre, along with her colleagues from the Canadian

Consortium on Neurodegeneration in Aging (CCNA). The research, which was published last year in *Neurology*, focused on two neurodegenerative conditions: frontal temporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). FTD is the second leading cause of early onset dementia, characterized by severe behaviour and language disturbances due to neuronal death in the frontal and



temporal parts of the brain. ALS has similar pathological processes as it causes severe motor impairment due to neuronal loss in the spinal cord and motor cortex part of the brain. Although the effects of FTD and ALS on individuals are different, there is one distinct overlap between the two disorders: they both can be caused by the same genetic mutation. An individual who has the mutation will eventually develop one of these diseases, unless that individual passes away at an age younger than when the disease normally reveals itself. There are other genetic mutations that are also known to cause these disorders.

Dr. Tierney and her team wanted to find out whether a person's sex played a role in the prevalence of these genetic mutations amongst patients with ALS and FTD.

"If you get these conditions, you wouldn't expect there to be sex differences in the genetic causes of the disorders. This is because the mutations actually lie on the part of the DNA that is the same for men and women, called the autosome," Dr. Tierney said in an interview with Mind Over Matter®.

Both ALS and FTD can be caused by a variety of factors, not just the genetic mutation examined in this study. If you look at a group of people who have either disease, you may think that the ratios of men and women who have genetic mutations that cause the disorders would be roughly the same. However, that is not what the researchers found.

They surveyed a large number of existing studies of people with the diseases. For ALS alone, they analyzed 32 research papers which reported findings on nearly 13,000 patients who had confirmed diagnoses. In that group, women had a 16% higher prevalence than men of ALS caused by the most common genetic mutation called chromosome 9 open reading frame 72 (C9orf72).

Even greater differences were found among people with FTD. Women had a 33% higher prevalence than men of FTD caused by another genetic mutation (called progranulin or GRN).

"These sex differences are quite high. A big difference," said Dr. Tierney.



"OUR FINDINGS WERE QUITE SURPRISING. IT MAKES YOU WONDER. THERE ARE SEX DIFFERENCES HERE AND WE DIDN'T EXPECT THEM."

In the overall population, men develop ALS at a higher rate from all causes than women. The figures for FTD are less clear - some studies suggest the rates are relatively equal, while others report that men develop FTD more than women.

"You've got a lot more men with ALS [in the overall population], then why are there more women with the most common genetic mutation?" Dr. Tierney queried.

While the research paper does not identify the mechanisms that drive the sex differences, it raises several other crucial questions:



Why are men developing ALS earlier and more aggressively? Is it because they are more likely to be exposed to toxins that could trigger the disease in their work or career environments?



What are the factors protecting women? Could it be estrogen or other sex-related differences?

For Dr. Tierney, the results of the study, and the additional questions it raises, highlight the need to explore why these disparities between the sexes exist.



"WE SHOULD START LOOKING BECAUSE THAT COULD GIVE US CLUES FOR EARLIER INTERVENTIONS... IT COULD LEAD TO INTERVENTIONS THAT ARE TAILORED DIFFERENTLY TO MEN AND WOMEN."

Can we use these findings to improve our understanding of the causes of these diseases and assist in their treatment and management? This study does not provide the answers, but the questions it raises will hopefully point future researchers in the right direction.

This study is only one of a series of research projects examining sex differences in neurodegeneration conducted by members of the CCNA. The following is a brief overview of some of their other work in this field:



A team led by Dr. Roger Dixon from the University of Alberta is investigating why some individuals who are at genetic risk for Alzheimer's disease do not develop it. The researchers are particularly interested in discovering whether there are other risk-reducing or protective factors that shield these genetically at-risk individuals from developing the disease. Dr. Dixon, along with two colleagues from the University of Alberta (Kirstie L. McDermott and G. Peggy

McFall) and two from the Australian National University (Shea J. Andrews and Kaarin J. Anstey), reasoned that these risk-reducing factors could be due to a variety of causes, including vascular health, lifestyle, background, and other biomarkers. Knowing that Alzheimer's disease is more prevalent in women than men, and that recent research has shown that this fact may have some biological and other risk-related underpinnings, they hypothesized that the factors that lead to genetic resilience could also vary by sex. That is exactly what they found. Their work, which was published in 2016 in the *Journal of Gerontology Psychological Sciences*, showed that there was a set of prediction factors in common to both females and males, but there was also a large set that were unique to females. This suggests that

COGNITIVE RESILIENCE TO ALZHEIMER'S GENETIC RISK IS DETERMINED BY MANY FACTORS, PERHAPS ESPECIALLY FOR WOMEN.

It is an important finding, because it could provide a broader set of modifiable targets for interventions that could promote resilience among women at risk for Alzheimer's disease.

Researchers who are studying the effects of vascular illness on a CCNA team led by Dr. JoAnne McLaurin of Sunnybrook Research Institute have been using rodents to explore sex differences related to a variety of conditions and treatments. Their work is in progress, but already has yielded some important findings.

Dr. Shawn Whitehead of Western University is interested in understanding how hypertension (increases in blood pressure) can lead to cognitive impairment. Dr. Whitehead and his colleagues found that, similar to humans, male and female rodents respond differently to stress, as well as medication to reduce stress and hypertension. They want to learn whether these observed sex-dependent differences also lead to differences in the severity of cognitive impairment between men and women.

Dr. McLaurin and her Sunnybrook colleague Bojana Stefanovic found that female rodents respond differently to drug-induced

hypertension, with one drug rendering a more severe disease, while another had no effect.

Dr. Dale Corbett of the University of Ottawa is exploring therapeutic interventions in rodents after a stroke. He found that female rodents with metabolic syndrome are resilient to the benefits of behavioural interventions, whereas male rodents do well.

Dr. Edith Hamel of McGill University found that female rodents fed a high-cholesterol diet performed worse on memory tests compared to males fed the same diet, particularly on tests involving a spatial memory component. However, if the rodents were allowed to exercise, particularly running, they did not show memory impairments, regardless of their sex.

Dr. Dallas Seitz of Queen's University and his colleagues are evaluating how sex and gender may impact physicians' decisions to prescribe psychotropic medications (such as antipsychotics, antidepressants, and benzodiazepines) to older adults with dementia residing in long-term care facilities in Ontario. To date, their study has identified over 56,000 individuals and their preliminary findings suggest that women are more likely than men to be prescribed both antidepressants and benzodiazepines, while they are less likely to be prescribed antipsychotics. This project is now examining whether these patterns continue to be observed once social, medical, and mental health factors are considered.

Dr. Tierney is conducting a meta-analysis, together with Dr. Ashley Curtis, Dr. Mario Masellis, and Dr. Richard Camicioli, examining sex differences in the cognitive profile of non-demented patients with Parkinson's disease. The findings should shed light on whether sex-related factors are important in early disease mechanisms affecting these cognitive abilities, which in turn may inform treatment development.

All of these research findings illustrate the importance of exploring sex differences in neurodegenerative diseases. Women and men are not the same, and researchers are increasingly recognizing that their treatments should not necessarily be the same either. 🧠

