

Sex differences in neurodevelopmental and neurodegenerative disorders: A largely ignored aspect of research.

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Neurological and neuropsychiatric diseases are a complex set of diseases affecting brain health and general well-being of a patient. According to the World Health Organization (WHO), neurological disorders affect up to 1 billion people, whereas 450 million people suffer from a mental or behavioral disorder worldwide. An estimated 6.8 million people die every year as a result of brain-related disorders. Not only is the economic cost for the treatment very high, patients suffering from mental illnesses and neurological diseases are subject to stigma and social exclusion as well as face acute loss of quality of life. Clinicians routinely have observed sex differences in the risk, incidence, and outcome of brain disorders, which makes treatment all the more difficult. However, very few studies investigate the molecular mechanisms behind observed sex differences in neurological disorders.

Autism spectrum disorders (ASD) is a group of neurodevelopmental disorders that are characterized by deficits in social communication and social interaction, low emotional reciprocity, low verbal communication and repetitive behaviors. It is well-documented for its proclivity to affect male children over female children with a diagnosis rate of 4:1 in males vs. females [1]. Attention-deficit/Hyperactivity Disorder (ADHD) is another closely related neurodevelopmental disorder that is diagnosed early in life and affects boys three times as often as girls [2]. In case of neurodegenerative diseases, Alzheimer's disease (AD), Parkinson's diseases and Stroke, are all associated with sex differences in incidence and/or outcome. About 5.4 million Americans have AD of which 5.1 million people are of the age 65 years or older. Of the 5.1 million above 65 years of age, 3.2 million are women and 1.9 million are men [3]. In Parkinson's disease (PD) however, the picture is quite different. PD is more prevalent in men; also the age of onset is much earlier for men. In the case of stroke, women have a less favorable outcome and suffer from a more precipitous drop in health status compared to men. As a result, treatment of such diseases is difficult and yields variable results.

Neuropsychiatric diseases also have a large sex bias associated with them. The most common example is that of depression, where more number of females are affected by it than males [4]. Apart from clinically diagnosed depression, women suffer from subclinical depression and

anxiety symptoms at a much higher rate than men. Women are also more prone to stress-related disorders such as anxiety and post-traumatic stress disorder (PTSD) [5], whereas obsessive compulsive (OCD) is another form of anxiety disorder where more male children are affected by it than female, however in adulthood this sex difference seems to go away [6].

Despite this, sex of the patient is rarely considered when making treatment decisions. Additionally, little research is done to understand the mechanisms underlying sex differences in disease progression. Neuroinflammation is one common pathway that is known to be involved in most diseases mentioned above. However, little is known about the differences in inflammatory pathways in males and females in the CNS during neurological disorders. One other explanation could be differences in basal developmental rates of male and female brains. Brain cortical volume (CV) growth measurement in normal males and females revealed that CV growth in males is slower than females during early life [8]. The findings are interesting as rapid cortical growth has been strongly associated with risk of developing autism [9]. One could also tie in the neuroinflammatory pathway theory to the cortical development theory by hypothesizing that the differences in normal cortical growth in males and females is a reflection of the differences in maturation of glial cells in the brain, such that glial cell maturation in females also takes place at a faster rate than males. It is also possible that to shield against the adverse effects of this increased glial maturity, female brains may possess an innate protective mechanism, but males do not. Hence, exposure to environmental or genetic factors prenatally or early in life may lead to premature activation of glial cells in males leading to widespread inflammation and neuronal cell death due to lack of this protective mechanism. Although speculative, it might be worthwhile to investigate what are the factors that control normal brain development or cortical volume changes, what external or internal stimuli may lead to perturbation of these factors and what are the endogenous pathways that protect one sex (for example females in case of autism) from the adverse effects of the stimuli.

Needless to say, more emphasis needs to be given to the investigating the role of sex in susceptibility and outcomes

of neurological disorders as it may reveal the mechanisms that protect one sex over the other to development of these diseases and point us towards an efficient treatment strategy.

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