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LETTER TO THE EDITOR

Aggression and MAO-A Gene

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Dear Sir,

Aggression encompasses behavioural traits that can result in physical and psychological damage to others. 30–40% of psychiatric patients with Depression, Bipolar disorder, ADHD, Neuropsychiatric and other degenerative disorders do struggle with aggression [1,2]. India State-Level Disease Burden Initiative Mental Disorders Collaborators in their article published in 2020 report that one out of seven people in India had a mental disorder in 2017 itself [3]. Currently with increased urbanisation, the numbers would be much more.

Neural networks, neurotransmitters, hormones, and candidate genes have been associated with antisocial and aggressive behaviour in humans [4]. Highly conserved brain areas, like amygdala, which regulates neuronal pathways activating aggressive, or avoidant behavioural patterns, influence the link between aggression and anxiety [1,5]. A PET study on patients with ASPD showed reduced MAO-A levels compared to controls in brain regions involved in impulse control and aggression [6].

Genetic factors attribute to around 40–50% risk of aggressive behaviour. MAO-A gene, also called "warrior gene" coding Monoamine Oxidase-A enzyme involved in the deamination of neurotransmitters is one of the gene of interest. In the absence of appropriate levels of MAO-A, neurotransmitters may not be degraded appropriately and thereby accumulate in neurons which may lead on to acute aggressive behaviours [1]. Knockout mice models for MAO-A gene, exhibited increased aggressiveness compared to their controls [4]. Many variants in MAO-A gene have been identified which are associated with aggression. These include the SNPs rs6323,

rs909525, rs2064070 associated with outward-expressed anger in male suicidal patients, rs1465108 leading to heightened aggression, rs6609257 altering brain activity in a network of frontal, parietal and occipital cortex, rs2235186 linked to variations in anger control, aggression, and empathy [7], uVNTR in the promoter region with 3 and 3.5 repeats responsible for low activity & 4 and 5 repeats responsible for higher activity of the enzyme [8]. Evolutionary aspects have to be studied as why nature has selectively preserved the low variant of MAO-A despite it being responsible for aggressive behaviour. The effect of MAO-A gene on personality is age and sex dependent. As per a study, low variant of MAO-A results in happiness among women and aggression in men [9]. Many confounding factors like X-inactivation, hormonal differences due to gynaecological conditions and mood swings have to be considered in women. In mice, prenatal suppression of MAO-A leads to increased aggression in adulthood which suggests a potential prenatal sensitization mechanism [4]. Deficiency of Monoamine oxidase in early developmental stages can lead to impaired behavioural aspects manifesting in adulthood.

Recently MAALIN, a novel lncRNA, has been identified which regulates the activity of MAO-A gene in human brain [10]. Use of ARMS/RFLP-PCR, NGS, smMIPS and SGE to detect the common SNPs in targeted exons will ease the diagnosis [7]. Development of molecular techniques to identify individuals who are genetically predestined to aggression can help in early initiation of therapies. Meta-analysis examining the efficacy of different interventions for aggression in patients with dementia showed that behavioural therapy and counselling, were more successful in reducing aggression in adults than pharmacological therapy [4].

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Genetic susceptibility to aggression would be a non-modifiable risk factor and causal association of aggression with MAO-A gene if found to exist would open up a new arena of possibilities in future to be investigated and feasible options towards management and cure pertaining to genetic aspects can be explored. Aggression being the most common symptom in psychiatric disorders definitely requires a deep insight into its genetic pathophysiology.

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