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Commentary

Looking into biological markers of suicidal behaviours

Suicide is now identified as a major public health problem accounting for 1.5 per cent of all deaths globally in 2016[1]. Premature mortality due to suicide affects all age groups but is particularly prevalent among adolescents and young adults. It is the second leading cause of death among those aged 15-29 yr and the third leading cause among those aged 15-39 yr, thus curtailing many young productive lives[2]. Socio-economic and emotional consequences for the surviving family and the society at large are enormously devastating. This has led to public health emphasis on various strategies for risk identification and prevention of suicidal behaviours.

Suicidal behaviour is determined by a complex interaction of various genetic and environmental factors, and includes a spectrum of thoughts (suicidal ideation and planning) and activities ranging from non-suicidal self-injury, suicidal gestures, aborted and non-fatal suicidal attempts to completed suicide. Several risk factors for suicidal behaviour have been identified which include presence of psychiatric illness, substance use, family history of suicide, past history of suicide attempts, physical illness, recent adverse life events, psychosocial crises, access to means of self-harm, genetic and neurochemical abnormalities, traumatic events in early life, personality traits and cognitive styles[3,4].

Clinical risk assessment is largely based on the subjective report of the patient's experience, which has its own limitations with likelihood of under-reporting. Despite the existence of numerous clinical risk factors and refined screening instruments, it is very difficult to predict suicide. Thus, there is a growing need for developing objective measures to supplement clinical data and improve accuracy for risk assessment tools and prevention strategies. With advances in medical research technology, structural and functional brain imaging, molecular genetics and biochemical research, the focus of suicide research has shifted to understanding the neurobiological mechanisms of suicidal behaviour, which might help in reliable prediction of suicide risk. Diverse approaches have been used to identify quantifiable biological correlates, consistently associated with suicide vulnerability. The most prominent biochemical approaches which have yielded valuable information are in the fields of neurotransmitter systems, hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammatory indices, neurotrophic factors and lipoproteins[5].

Among neurotransmitter systems, the role of the serotonergic system has been the most widely implicated in suicide, particularly the violent suicide attempts which may even be independent of its role in depression[5,6]. Low cerebrospinal fluid (CSF) level of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin (5-hydroxytryptamine, 5-HT) has also been found to be consistently associated with suicide and has been suggested to be a specific marker[6]. Genetic polymorphisms of tryptophan hydroxylase (biosynthetic enzyme for serotonin), serotonin receptors (5-HT1A and 5-HT2A) and serotonin transporter (5-HTT) have also been studied and specific alleles identified which confer a higher risk of developing suicidal behaviour[7]. The noradrenergic system has also been implicated with alterations in norepinephrine activity, tyrosine hydroxylase activity, receptor polymorphisms and alpha- and beta-adrenergic binding in the prefrontal cortex and limbic system, being associated with suicidal risk[5-7]. However, the association shown in different studies has been inconsistent, thus precluding any predictive value of these results. Dopaminergic and GABAergic pathways have also been reported to be associated with depression, but studies have not shown enough evidence to connect them with development of suicidal behaviours[6,7].

The role of HPA axis dysregulation in depression and suicidal behaviour has also been extensively researched. HPA axis dysregulation is an apparent indicator of physiological sensitivity to stress which confers increased risk to suicidal behaviours in response to stressful situations[5,8]. Suicidal behaviours have been shown to be associated with lower baseline cortisol levels and exaggerated responses of HPA axis to stress[8]. Studies on suicide completers have indicated hyperreactivity to stress with elevated corticotropin-releasing hormone (CRH) and vasopressin levels in the forebrain, raphe and locus ceruleus, fewer CRH receptors in the frontal cortex, increased pro-opiomelanocortin precursor to adrenocorticotropic hormone (ACTH) in the pituitary and altered glucocorticoid and mineralocorticoid receptor expression and sensitivity[5].

Immune system dysregulation is another pathophysiological mechanism proposed for suicidality, and there is growing evidence in support of the role of neuroinflammation in triggering suicidal behaviours. The potential pathway involves various inflammatory conditions (infections, autoimmune disorders, head injury, *etc*.) causing excessive release of pro-inflammatory cytokines which act as mediators for various neurochemical changes such as dysregulation of tryptophan catabolism (leading to low serotonin levels), hyperactivation of HPA axis and alterations in monoamine metabolism[9]. Studies have focussed both on peripheral (blood and CSF) and central (brain, particularly orbitofrontal cortex) levels of inflammatory markers among suicide attempters. Raised levels of pro-inflammatory cytokines such as interleukins (IL-1β, IL-2, IL-4, IL-6 and IL-13), C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and decreased levels of IL-8 have been reported[5,7,9].

Structural changes in the brain in the form of cortical thinning in the dorsolateral prefrontal cortex, reduced hippocampal volume and reduced dentate gyrus neurons have also been reported in depressed suicide victims, suggestive of accelerated neuron loss and decreased neurogenesis[5]. There have also been reports of reduced brain-derived neurotrophic factor (BDNF) levels associated with suicidal behaviour expression by either genetic polymorphisms or epigenetic mechanisms[5,6,10].

Abnormalities in lipid metabolism as potential biomarkers among suicide attempters and suicide victims have also been a potential area of research[11]. Various novel approaches have been used to explore putative biochemical mediators of interaction between lipid metabolism and complex behaviours such as suicidality. Since the 1990s, proteomics has become an increasingly popular approach for identifying biomarkers for several major physical disorders and has recently been applied in psychiatric disorders such as depression, bipolar disorder and schizophrenia[12]. The volume of proteomic literature in area of suicide is limited and primarily based on post-mortem brain tissue. The study by Mathew *et al*[13] published in this issue describes the application of proteomics to discover a potential peripheral biomarker among survivors of self-harm attempt. Using two-dimensional gel electrophoresis (2D-GE) and matrix-assisted laser desorption ionization mass spectrometry (MALDI MS), the authors found that expression of apolipoprotein (Apo) A-IV (a plasma protein involved in cholesterol metabolism) was reduced among the patients with deliberate self-harm as compared to healthy controls. The authors further validated their findings in a new set of participants using isotope-labelled relative quantification and Western blot analysis. The levels of total, esterified and high-density lipoprotein cholesterol were found to be lower in the self-harm group. The study concluded that downregulation of Apo A-IV was probably the biochemical link between low cholesterol levels and deliberate self-harm. This study has implicated the role of Apo A-IV in suicide, and there is a scarcity of evidence for its role in any other neuropsychiatric conditions. Till now, only one previous proteomic study has found low CSF levels of Apo A-IV in schizophrenia[14] and one genetic study has found association of Apo A-IV codon 360 mutation in patients with Alzheimer's disease[15]. Reduction in plasma and CSF levels of another protein Apo E has also been found to be associated with suicide attempts[16].

This study[13] had several strengths in terms of both biochemical techniques and methodology used. The authors have followed a rigorous approach for identification, validation and quantification of biochemical markers differentially expressed in the target population, using the latest techniques. Discovery of a blood biomarker in close temporal proximity to a suicide attempt can have important management implications. The proteomic approach used here is considered advantageous over genomic approach in exploration of biomarkers[12]. Psychiatric

disorders are multifactorial in origin with involvement of numerous genetic loci and their expression being influenced by various environmental factors over time. Protein expression levels and their post-translational modifications are more closely related to the phenotype or observed behaviour and better reflect underlying dynamic pathophysiological processes[12]. A proteomic approach approach as used in this study is particularly favoured for discovering biomarkers in psychiatric disorders, where experimental evidence for aetiology of such complex phenomena is not easily available[17]. The significant decrease in Apo A-IV expression in the absence of psychiatric disorder in this study population indicates its independent association with suicide attempt.

The study, however, had certain limitations which might restrict the applicability of the results. The term 'deliberate self-harm' has been used to define the target population, as a proxy measure for suicide attempts. Deliberate self-harm is a loose construct encompassing all self-harm behaviours with or without suicidal intent. The results of this study indicate low suicidal intent, high impulsivity and lack of hopelessness or diagnosable psychiatric condition among majority of participants which raises the possibility of non-suicidal self-injury (NSSI) rather than suicidal attempts. It is plausible that more severe attempts may have been excluded due to their inability to participate in the research. Although NSSI is known to be closely related to risk of suicide attempts, some explanation is needed before extrapolating the results to suicidality. As peripheral and central cholesterol metabolisms are independently regulated, it remains to be established to what extent the differences in plasma apoprotein levels correlate with CNS levels. Apo A-IV levels rise soon after feeding although this response may be blunted on chronic ingestion of high fat content diets[18]. This can be a potential confounder which cannot be explained completely by lack of difference in body mass index between the two groups. The study also failed to find significant difference in lecithin-cholesterol acyltransferase activity, the enzyme linking Apo A-IV to esterification of cholesterol, although the authors have commented on the likely causes of such anomaly. Other limitations such as low sample size, low statistical power and observational design of the study are similar to previous proteomic studies in psychiatric disorders highlighting the need for larger cohorts and longitudinal designs for more robust evidence.

Search for biomarkers in psychiatry is continuously expanding with discovery of novel targets based on diverse neurobiological processes. However, this process is particularly challenging for psychiatric disorders due to significant overlap of symptoms between different disorders, heterogeneity of symptoms within the same diagnostic group and lack of precise understanding of exact causation[12,17]. Till date, none of the laboratory findings has been translated to applications in routine clinical practice. Due to multidetermined nature of suicidal behaviour, it is expected that a combination of several biosignatures supplementing clinical, neuroimaging and neuropsychological data may be more useful than a single biomarker alone in predicting suicide.

***Conflicts of Interest*:** None.

Rakesh Kumar Chadda* **& Ankit Gupta**

Department of Psychiatry, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi 110 029, India

**For correspondence*: drrakeshchadda@gmail.com

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