Emergence of PTSD like symptomology in different strata of the society in COVID-19 pandemic-A pathophysiological rationale

Dr. Abhishek Das, Dr. Ankit Halder, Dr. Navna Panchami Ravindran, Dr. Devavrat Harshe,

3rd Year Junior Resident,Department of Pathology ,DY Patil Medical College Hospital and Research Institute,Kolhapur,Maharahstra,India
2nd Year Junior Resident,Department of Psychiatry,DY Patil Medical College Hospital and Research Institute,Kolhapur,Maharasthra,India
1st Year Junior Resident,Department of Psychiatry,DY Patil Medical College Hospital and Research Institute,Kolhapur,Maharashtra
Associate Professor, ,Department of Psychiatry,DY Patil Medical College Hospital and Research Institute,Kolhapur,Maharashtra,India

ABSTRACT: Post-traumatic stress disorder (PTSD) is a marked by increased stress and anxiety that occurs following exposure to a traumatic event.Many functional aetiologies of PTSD are there that included neurotransmitters and endocrine systems.A review of three studies have been done here that includes classes of population from different strata of the society.From this it is quite evident that there is already an emergence of PTSD like symptomology in different strata of the society arising amidst the COVID-19 outbreak all over the globe.This also lays the foundation potential study with detailed inclusion of pathophysiological factors of PTSD and its correlation with mental health of the global population

KEYWORDS: PTSD, SYMPTOMOLOGY, COVID-19, PATHOPHYSIOLOGY.

I. INTRODUCTION

Post-traumatic stress disorder (PTSD) is a common and chronic disorder that can result after exposure to a traumatic event. Despite our understanding the aetiology of PTSD is not complete, many neurobiological systems have been implicated n the pathophysiology and vulnerability towards advent of PTSD after encountering a traumatic event. There are a lot of functional aetiologies in the noradrenergic, serotonergic, endogenous cannabinoid, and opioid systems and the hypothalamic-pituitary adrenal (HPA) axis for development of Post Traumatic Stress Disorder (PTSD).

a) Noradrenegic system

The adrenoreceptors (ARs) are a group of G protein-coupled receptors consisting of three major classifications: α_1, α_2 and β with associated subtypes [1]. CNS activity and sympathetic autonomic responses through cell bodies of locus coeruleus are stimulated by the AR system and these neurons project to the prefrontal cortex and limbic system structures (e.g., amygdala, hypothalamus) [2], which is implicated in selective attention to rewarding and aversive stimuli [3] as well as stress and fear-related responses [4] [5]. Through dysregulation of physiological mechanisms, hyperadrenergic activity has been linked to psychiatric conditions such as major depression [6] [7], traumatic brain injury [8] and anxiety disorders [9-11] [2,12].

The AR system has held a preeminent role in PTSD research, as it influences amygdala functioning and associated fear signalling [5,13,14].

b) Seretonergic system

The serotonergic (5-HT) receptors are a group of G protein-coupled receptors and one identified ligand-gated ion channel ($5\text{-}HT_3$) that encompass seven classifications, ranging from $5\text{-}HT_1$ through $5\text{-}HT_7$ with associated subtypes [15]. The 5-HT system is involved in cognition, emotional processing and behavioural regulation [16]. It has been demonstrated in animal models that serotonin receptor system are involved in the pathophysiology of several psychiatric disorders, including depressive spectrum disorders [17] [18], alcohol use disorders [19, 20] and PTSD [21,22].

c) Endocannabinoid system

Various lines of evidence suggest that the endogenous cannabinoids (eCB), anandamide (AEA) and 2-arachidonolyflycerol (2-AG) which exert much of their actions through the two known cannabinoid (CB) receptors (CB_1, CB_2), play a vital role in the development [23] and functioning of PTSD circuit, specifically in stress responses [24-29]. The CB_1 receptors are of primary interest as

recent studies showed a specific and primary [30] role for the CB_1 receptor in mediating the neurobiological rationale and behavioural consequences of exposure to stress and development of PTSD.

d) Hypothalamo Pituitary Axis and Corticotrophin Releasing Factor

The HPA axis is a stress-responsive neuroendocrine system that ties the CNS to the endocrine system. The HPA axis assists with the adaptation to stress and the maintenance of homeostasis after challenge, yet is also vital in supporting baseline functioning [31]. A dysfunctional HPA axis is associated with numerous psychosomatic and psychiatric disorders [32-40].

Corticotropin-releasing factor (CRF) is a neuronal signalling molecule produced by cells in the hypothalamus in response to physical or psychological stress. Increased levels of CRF in the hypothalamus in response to stress results in the activation of the HPA axis and increased release of cortisol. Patients of PTSD has elevated levels of CRF in cerebrospinal fluid [41,42] and there are many abnormalities in various systems of HPA axis [43].These suggest the role of compounds that has a inhibitory effect on the CRF system or HPA axis hormones in the management scheme of PTSD [44].

e) Opioid system

Many evidences connect opioid systems in the development of PTSD. Relevant to the etiology of PTSD, is the expression pattern of the κ-OR with high receptor levels in a ventral medial, prefrontal, cortex-hippocampal-limbic circuit [45,46] where they mediate anxiety-like behaviours [47].

II. DISCUSSION

During emergence of COVID-19 emerged in China in later part of 2019, in order to stop the spread of virus majority of people were home-quaranted. A study done by Wanjie Tang et al [48] explored the prevalence of post-traumatic stress disorder (PTSD) and depression in a sample of home-quarantined college students to identify the psychological distress risk factors.

Online survey versions of PTSD Checklist Civilian Version and the 9-question Patient Health Questionnaires (PHQ-9) were used among 2485 participants who were from 6 universities to assess the PTSD and depressive symptoms. Various data on durations of sleep,time of home quarantine,exposure and socio demographic variables were collected.[48]

There was prevalence of 2.75 and 9% respectively for PTSD and depression.Coming to psychological distress, feeling extreme fear was its most significant risk factor.It was followed by less sleep durations, being in their graduating year (4th year) and living in areas severely afflicted . Sleep durations was the principal mediator between exposures and mental health problems.[48]

Unlike individual level traumatic events, the COVID-19 pandemic has been a continuing crisis for every member of society. It is well established that stressful events like natural disasters and man-made traumas can have a significant mental health impact and can lead to conditions such as posttraumatic stress disorder (PTSD) and depression [49,50]. The impact of acute, pervasive, and continuing stressors on public and individual psychologies, like those associated with highly infectious and fatal disease outbreaks [51] is not properlyunderstood.Further, little is known about the prevalence and risk factors for mental health problems when faced with such stressors. Studies based on the 2003 SARS epidemic outbreak showed that during the epidemic, all groups of people from the general public to health care workers had many psychological disorders such as fear and worry[52], PTSD. Other than this, in a sample of college students ,stressors related to SARS were the principal predictors of psychological symptoms [53].

During the SARS outbreak, many people suffered from poor sleep because of anxiety and depressive symptoms [54]. Hence, it is reasonable to assume that a higher exposure leads to decreased sleep, which in turn increases the risk of mental illness. And thus it is essential to have a knowledge of the probable association between the COVID-19 pandemic, sleep duration and underlying mental illnesses in the population of college students. Many people chose to remain quarantined when the outbreak was occurred. However, based on a study published from the SARS epidemic, a longer duration of isolation has higher possibility of psychological distress [55].

The COronaVIrus Disease-19 (COVID-19) pandemic has brought into limelight the urgent need to focus on its impact on the mental health of Healthcare Workers (HCWs) who are at the frontline. It has been consistently shown that a high proportion of HCWs is at greater risk for developing Posttraumatic Stress Disorder (PTSD) and Posttraumatic Stress Symptoms (PTSS). [55]

Due to alarming rate of exposure of the highly stressful work-related situations ,the

Healthcare Workers(HCWs) are at high risk of developing PTSD in emergency settings.[55]

The exposers taken into account are: critical care managemrnt, trauma care , frequently witnessing death , operating in crowded settings, disturbance of circadian rhythms due to shift work[56,57]. PTSD rates have been reported to range from 10 to about 20% [58,59,60], with even higher PTSD rates (8% to 30%) among Intensive Care Unit (ICU) staff

Many studies reported a high risk for adverse psychological reactions, particularly PTSS and PTSD among the frontline workers which indicate proximity to "ground zero" as a primary risk factor [61]. HCWs' fear of transmitting th disease to family, friends , stigmatization and rejection in society because of their hospital work were also reported. Studies also reported the reluctance to work and/or considering quitting their job, including high stress levels, symptoms of anxiety spectrum disorders, which could have long-term psychological implications [62,63]. The self-perceived high risk for contagion might be the most crucial aspect in relation to the front-line activities, with for example[64,65]failing to find any significant difference between HCWs in SARS vs. non-SARS units in PTSD prevalence rate. This indicates that not only HCWs working within the SARS units, but also those working outside them and facing uncertainty because of displacement, might develop PTSS during the pandemic.

Now coming to another study done by Cindy et al.[66].

Assessment of factors related to anxiety spectrum disorders and PTSD symptomatology during the pandemic was done .The clinical implications for U.S. young adult mental healthe were also put forward.As previously highlighted, the sense of isolation was an important factor related to PTSS. Consequently, HCWs who had been quarantined were at greater risk [67] as well as HCW survivors from the infection.

The COVID-19 pandemic that has upended the lives of individuals worldwide escalated in the U.S. beginning in March of 2020.It is very difficult to understand the effects of mental health due to COVID-19, as prospective studies on the effects of a pandemic are not widely available till now[61].

Findings of a study done Claudia Carmassi et al.[61]highlight major psychological challenges faced by young adults during the initial weeks of the COVID-19 pandemic. At least one-third of young adults reported having clinically elevated levels of depression (43.3%), anxiety (45.4%), and PTSD symptoms (31.8%). The rates of depression, anxiety, and PTSD werehigh compared to prior studies that had used the same cut points [61].

Surprisingly, maximum respondents reported feeling isolated during the first initial part of the pandemic. They also had low ability to tolerate distress. Despite, maximum reportedthat social support from family, partners, and other well wishers were instrumental during this time.

III. CONCLUSION

Keeping the above three studies in mind,it is fair to conclude upon the fact that there is already an emergence of PTSD like symptomology in different strata of the society arising amidst the COVID-19 pandemic.The future withholds areas of potential study with detailed inclusion of pathophysiological factors of PTSD and its correlation with mental health.

REFERENCES

[1]. Strawn JR, Geracioti TD., Jr. Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. Depress Anxiety. 2008;25(3):260–71.

[2]. Morilak DA, Barrera G, Echevarria DJ, et al. Role of brain norepinephrine in the behavioral response to stress. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(8):1214–24.

[3]. Southwick SM, Bremner JD, Rasmusson A, et al. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biol Psychiatry. 1999;46(9):1192–204.

[4]. O'Donnell T, Hegadoren KM, Coupland NC. Noradrenergic mechanisms in the pathophysiology of post-traumatic stress disorder. Neuropsychobiology. 2004;50(4):273–83.

[5]. Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann N Y Acad Sci. 2006;1071:67–79.

[6]. Wong EH, Sonders MS, Amara SG, et al. Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. Biol Psychiatry. 2000;47(9):818–29.

[7]. Cheok F, Schrader G, Banham D, et al. Identification, course, and treatment of depression after admission for a cardiac condition: rationale and patient characteristics for the Identifying Depression As a Comorbid Condition (IDACC) project. Am Heart J. 2003;146(6):978–84.

[8]. Kobori N, Hu B, Dash PK. Altered adrenergic receptor signaling following traumatic brain injury contributes to working memory dysfunction. Neuroscience. 2011;172:293–302.

[9]. Charney DS, Woods SW, Goodman WK, et al. Neurobiological mechanisms of panic anxiety: biochemical and behavioral correlates of yohimbine-induced panic attacks. Am J Psychiatry. 1987;144(8):1030–6

[10]. Tanaka M, Yoshida M, Emoto H, et al. Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies. Eur J Pharmacol. 2000;405(1-3):397–406

[11]. Geracioti TD, Jr., Baker DG, Ekhator NN, et al. CSF norepinephrine concentrations in posttraumatic stress disorder. Am J Psychiatry. 2001;158(8):1227–30.

[12]. Tanaka Y, Ishitobi Y, Maruyama Y, et al. Salivary alpha-amylase and cortisol responsiveness following electrical stimulation stress in panic disorder patients. Neurosci Res. 2012;73(1):80–4.

[13]. Debiec J, Bush DE, LeDoux JE. Noradrenergic enhancement of reconsolidation in the amygdala impairs extinction of conditioned fear in rats: a possible mechanism for the persistence of traumatic memories in PTSD. Depress Anxiety. 2011;28(3):186–93.

[14]. Onur OA, Walter H, Schlaepfer TE, et al. Noradrenergic enhancement of amygdala responses to fear. Soc Cogn Affect Neurosci. 2009;4(2):119–26.

[15]. Hannon J, Hoyer D. Molecular biology of 5-HT receptors. Behav Brain Res. 2008;195(1):198–213

[16]. Cools R, Roberts AC, Robbins TW. Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci. 2008;12(1):31–40.

[17]. Murrough JW, Neumeister A. The serotonin 1B receptor: a new target for depression therapeutics? Biol Psychiatry. 2011;69(8):714–5.

[18]. Carr GV, Lucki I. The role of serotonin receptor subtypes in treating depression: a review of animal studies. Psychopharmacology (Berl) 2011;213(2-3):265–87.

[19]. Furay AR, Neumaier JF, Mullenix AT, et al. Overexpression of 5-HT(1B) mRNA in nucleus accumbens shell projection neurons differentially affects microarchitecture of initiation and maintenance of ethanol consumption. Alcohol. 2011;45(1):19–32.

[20]. Hu J, Henry S, Gallezot JD, et al. Serotonin 1B receptor imaging in alcohol dependence. Biol Psychiatry. 2010;67(9):800–3

[21]. Murrough JW, Czermak C, Henry S, et al. The effect of early trauma exposure on serotonin type 1B receptor expression revealed by reduced selective radioligand binding. Arch Gen Psychiatry. 2011;68(9):892–900

[22]. Xie P, Kranzler HR, Poling J, et al. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. Arch Gen Psychiatry. 2009;66(11):1201–9.

[23]. Krebs-Kraft DL, Hill MN, Hillard CJ, et al. Sex difference in cell proliferation in developing rat amygdala mediated by endocannabinoids has implications for social behavior. Proc Natl Acad Sci U S A. 107(47):20535–40

[24]. Hill MN, McLaughlin RJ, Bingham B, et al. Endogenous cannabinoid signaling is essential for stress adaptation. Proc Natl Acad Sci U S A. 107(20):9406–11.

[25]. Rademacher DJ, Meier SE, Shi L, et al. Effects of acute and repeated restraint stress on endocannabinoid content in the amygdala, ventral striatum, and medial prefrontal cortex in mice. Neuropharmacology. 2008;54(1):108–16.

[26]. Reich CG, Taylor ME, McCarthy MM. Differential effects of chronic unpredictable stress on hippocampal CB1 receptors in male and female rats. Behav Brain Res. 2009;203(2):264–9.

[27]. Gorzalka BB, Hill MN, Hillard CJ. Regulation of endocannabinoid signaling by stress: implications for stress-related affective disorders. Neurosci Biobehav Rev. 2008;32(6):1152–60

[28]. Hill MN, Miller GE, Carrier EJ, et al. Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social

stress. Psychoneuroendocrinology. 2009;34(8):1257–62

[29]. Hill MN, Miller GE, Ho WS, et al. Serum endocannabinoid content is altered in females with depressive disorders: a preliminary report. Pharmacopsychiatry. 2008;41(2):48–53.

[30]. Hill MN, McLaughlin RJ, Morrish AC, et al. Suppression of amygdalar endocannabinoid signaling by stress contributes to activation of the hypothalamic-pituitary-adrenal axis. Neuropsychopharmacology. 2009;34(1 3):2733–45.

[31]. Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: a review. Biol Psychol. 2005;69(1):113–32.

[32]. Chrousos GP, Gold PW. The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. JAMA. 1992;267(9):1244–52.

[33]. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology. 2000; 25(1):1–35.

[34]. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000;284(5):592–7.

[35]. Holsboer F. Psychiatric implications of altered limbic-hypothalamic-pituitary-adrenocortical activity. Eur Arch Psychiatry Neurol Sci. 1989;238(5-6):302–22.

[36]. Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am J Psychiatry. 2003;160(9):1554–65.

[37]. Stratakis CA, Chrousos GP. Neuroendocrinology and pathophysiology of the stress system. Ann New York Acad Sci. 1995;771:1–18.

[38]. Tsigos C, Chrousos GP. Physiology of the hypothalamic-pituitary-adrenal axis in health and dysregulation in psychiatric and autoimmune disorders. Endocrinol Metab Clin North Am. 1994;23(3):451–66.

[39]. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53(4):865–71.

[40]. Young EA. Sex differences and the HPA axis: implications for psychiatric disease. JGSM. 1998;1(1):21–7.

[41]. Baker DG, West SA, Nicholson WE, et al. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry. 1999;156(4):585–8

[42]. Bremner JD, Licinio J, Darnell A, et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry. 1997;154(5):624–9.

[43]. Ressler KJ, Mercer KB, Bradley B, et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature. 2011;470(7335):492–7.

[44]. Baker DG, Nievergelt CM, Risbrough VB. Post-traumatic stress disorder: emerging concepts of pharmacotherapy. Expert Opin Emerg Drugs. 2009;14(2):251–72

[45]. Hiller JM, Fan LQ. Laminar distribution of the multiple opioid receptors in the human cerebral cortex. Neurochem Res. 1996;21(11):1333–45.

[46]. Simonin F, Gaveriaux-Ruff C, Befort K, et al. kappa-Opioid receptor in humans: cDNA and genomic cloning, chromosomal assignment, functional expression, pharmacology, and expression pattern in the central nervous system. Proc Natl Acad Sci U S A. 1995;92(15):7006–10.

[47]. Bruchas MR, Land BB, Lemos JC, et al. CRF1-R activation of the dynorphin/kappa opioid system in the mouse basolateral amygdala mediates anxiety-like behavior. PLoS One. 2009;4(12):e8528.

[48]. Tang W, Hu T, Hu B, Jin C, Wang G, Xie C, Chen S, Xu J. Prevalence and correlates of PTSD and depressive symptoms one month after the outbreak of the COVID-19 epidemic in a sample of home-quarantined Chinese university students. Journal of affective disorders. 2020 May 13.

[49]. Kopala-Sibley, Daniel C., et al. "Negative emotionality and its facets moderate the effects of exposure to Hurricane Sandy on children's postdisaster depression and anxiety symptoms." Journal of abnormal psychology 125.4 (2016): 471.

[50]. Plexousakis SS, Kourkoutas E, Giovazolias T, Chatira K, Nikolopoulos D. School bullying and post-traumatic stress disorder symptoms: the role of parental bonding. Frontiers in public health. 2019 Apr 9;7:75.

[51]. Leppin A, Aro AR. Risk perceptions related to SARS and avian influenza: theoretical foundations of current empirical research.

International journal of behavioral medicine. 2009 Mar 1;16(1):7-29.

[52]. Mihashi M, Otsubo Y, Yinjuan X, Nagatomi K, Hoshiko M, Ishitake T. Predictive factors of psychological disorder development during recovery following SARS outbreak. Health Psychology. 2009 Jan;28(1):91.

[53]. Main A, Zhou Q, Ma Y, Luecken LJ, Liu X. Relations of SARS-related stressors and coping to Chinese college students' psychological adjustment during the 2003 Beijing SARS epidemic. Journal of counseling psychology. 2011 Jul;58(3):410.

[54]. Johal SS. Psychosocial impacts of quarantine during disease outbreaks and interventions that may help to relieve strain.

[55]. Reynolds DL, Garay JR, Deamond SL, Moran MK, Gold W, Styra R. Understanding, compliance and psychological impact of the SARS quarantine experience. Epidemiology & Infection. 2008 Jul;136(7):997-1007.

[56]. Cieslak R, Shoji K, Douglas A, Melville E, Luszczynska A, Benight CC. A meta-analysis of the relationship between job burnout and secondary traumatic stress among workers with indirect exposure to trauma. Psychological services. 2014 Feb;11(1):75.

[57]. Garbern SC, Ebbeling LG, Bartels SA. A systematic review of health outcomes among disaster and humanitarian responders. Prehospital and disaster medicine. 2016 Dec;31(6):635-42.

[58]. Clohessy S, Ehlers A. PTSD symptoms, response to intrusive memories and coping in ambulance service workers. British journal of clinical psychology. 1999 Sep;38(3):251-65.

[59]. Robertson N, Perry A. Institutionally based health care workers' exposure to traumatogenic events: systematic review of PTSD presentation. Journal of traumatic stress. 2010 Jun;23(3):417-20.

[60]. 60. DeLucia JA, Bitter C, Fitzgerald J, Greenberg M, Dalwari P, Buchanan P. Prevalence of post-traumatic stress disorder in emergency physicians in the United States. Western journal of emergency medicine. 2019 Sep;20(5):740.

[61]. Carmassi C, Foghi C, Dell'Oste V, Cordone A, Bertelloni CA, Bui E, Dell'Osso L. PTSD symptoms in healthcare workers facing the three coronavirus outbreaks: What can we expect after the COVID-19 pandemic. Psychiatry research. 2020 Jul 20:113312.

[62]. Maunder RG, Lancee WJ, Balderson KE, Bennett JP, Borgundvaag B, Evans S, Fernandes CM, Goldbloom DS, Gupta M, Hunter JJ, Hall LM. Long-term psychological and occupational effects of providing hospital healthcare during SARS outbreak. Emerging infectious diseases. 2006 Dec;12(12):1924.

[63]. Wu P, Fang Y, Guan Z, Fan B, Kong J, Yao Z, Liu X, Fuller CJ, Susser E, Lu J, Hoven CW. The psychological impact of the SARS epidemic on hospital employees in China: exposure, risk perception, and altruistic acceptance of risk. The Canadian Journal of Psychiatry. 2009 May;54(5):302-11.

[64]. Spiller TR, Méan M, Ernst J, Sazpinar O, Gehrke S, Paolercio F, Petry H, Pfaltz MC, Morina N, Aebischer O, Gachoud D. Development of health care workers' mental health during the SARS-CoV-2 pandemic in Switzerland: two cross-sectional studies. Psychological Medicine. 2020 Aug 13:1-4.

[65]. Bai Y, Lin CC, Lin CY, Chen JY, Chue CM, Chou P. Survey of stress reactions among health care workers involved with the SARS outbreak. Psychiatric Services. 2004 Sep;55(9):1055-7.

[66]. Liu CH, Zhang E, Wong GT, Hyun S. Factors associated with depression, anxiety, and PTSD symptomatology during the COVID-19 pandemic: Clinical implications for US young adult mental health. Psychiatry Research. 2020 Jun 1:113172.