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A theoretical construct advocating exploration of the converging immunomodulating pathways in suicide and Behçet disease

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Abstract
Suicide is a global public health challenge, with approximately a million people losing their lives to suicide annually. The study of suicide and understanding and the neurobiology of suicide has remained challenging However, focusing on specific illnesses and pathways may aid in providing a better understanding of the neurophysiology of suicide. For example, Postolache *et al*. have extensively reported on *Toxoplasma gandii* and suicidal behaviors. In this paper, we reflect on the role of immunomodulating molecules that play a significant role in neurophysiology that may converge in Behçet disease and suicide. By focusing on a specific illness, it is possible to understand the specific suicide risk factor for that illness as well as garner insight into understanding the pathophysiology of suicide. Behçet disease, an inflammatory disease of the Old Silk Road typically affecting individuals aged 20-50, is associated with significant risk for suicide. Therefore, reflecting on the common pathways involved in both suicidal behaviors and Behçet disease may not only help develop strategies to lower the risk of suicide in Behçet disease but also afford a somewhat less heterogenous population to study suicide in reducing the multitude of confounding factors associated with suicidal behaviors.

Keywords: Immunomodulating pathways, Behçet disease, *Toxoplasma gandii*

Introduction
Suicide is a tremendous global public health challenge [1]. In the United States of America (US), suicide has increased 36% from 2000 to 2021, remaining 9th leading cause of death in age 10-64 years of age It is second leading cause of death in age groups of 10-14 and 25-34 and third leading cause of death in age group of 15-24 with globally almost a million people losing their lives to suicide [2]. In spite of the tremendous global burden of suicidal behaviors, the study of such behaviors, thus, has proven challenging. The reductionist approach may not be able to address this multifaceted challenge. Due to the complex neurobiology of suicidal behaviors, focusing on specific diseases such as Behçet disease (BD) can assist with suicide prevention strategies in specific groups of patients.

Behçet disease (BD), sometimes referred to Old Silk Road disease due to its preferential geographic presentation, is a severe potentially life-threatening condition that is chronic multisystemic inflammatory disorder with undetermined but likely multifactorial etiologies [3]. An increased risk of suicidality has been reported in BD. Since most of the patients in BD are younger, this poses a particular challenge since both suicidality and BD are more prevent in younger people (20-50) particularly in men. In a study of 240 BD patients, Uzunaslan *et al*. 25.4% of patients with multi-system BD had suicidal ideations and suicidal plans [4]. Similar findings were reported by Saygin *et al*., in a study of 303 BD patients, BD patients with active major organ involvement 25.5% of suicidal plan in the past year [4]. BD has been associated with neuropsychiatric disorders [5], known risk factors for suicide. Five to 10 percent of BD show CNS parenchymal involvement and 20% show nonparenchymal involvement (dural sinus thrombi) [6]. It makes logical sense to think of neuroimmunological bases of suicidal behaviors in BD; for decades, Postolache *et al*. have extensively studied

relationship between the immune system, immunological disorders, and suicidality [7]. Similar to Postolache and colleagues' findings, here are common immunological pathways that converge in both DB and suicidal behaviors. In this paper we explore the potential for cytokines and kynurenine pathway as possible mediators of suicidality in BD patients. By focusing on common pathways, it is possible to devise treatment strategies specific to a population such as those living with BD.

Convergence of Inflammatory pathways in suicide and Behçet disease: Immunological mediators associated with suicidal behaviors are poorly understood but well documented [7]. Although the central nervous system (CNS) is often considered a privileged organ due to the existence of the blood-brain barrier (BBB), a large body of evidence suggest that both proinflammatory and anti-inflammatory mediators alter neurophysiology in humans and other animals although the mechanism by which this change is mediated have remained elusive. These immune modulating molecules affect neurophysiology both directly and indirectly. It is well documented that cytokines can affect CNS [8]. Neurons, glial cells, vascular component of the brain tissue can produce cytokines. Cytokine receptors are found on various cellular structures within the CNS [8]. For example, some elements of inflammatory processes directly affect neurotransmission, activating or inhibiting neurotransmitters, as well as other mechanisms such as signaling pathways [9]. The presence of cytokine receptors on neurons underscores their specific functional roles in the normal physiological processes of the CNS. These pathways and inflammatory markers are involved in the neuropsychiatric manifestation of BD.

Type 1 helper T cells (Th1) and related cytokines play an important role in pathophysiology of BD with Th1 cytokines highly elevated in BD [10]. Patients experiencing active BD have been documented to have elevated levels of Th1 cytokines, namely IL-2, IL-12, IL-18, and IFN-γ, in their peripheral blood mononuclear cells (PBMCs)10. In patients diagnosed with Behçet uveitis, there was a notable increase in aqueous levels of interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) compared to individuals without this condition. Specifically, interleukin-15 (IL-15) levels were significantly higher exclusively in the aqueous humor of Behçet uveitis patients. In animal models of intracranial hemorrhage, IL-15 over expression is associated with brain edema and neurological deficit. Moreover, both aqueous and serum levels of interleukin-10 (IL-10) were undetectable in all patients with Behçet uveitis11. IL-10 expression is elevated in most major CNS pathologies promoting cell survival signals [12]. Interleukins 2 (IL-2) has been implicated in regulation of neurotransmission, sleep, hormone release, sleep and arousal regulation, memory function [13]. IL-2 receptor (IL-2R) have been detected in brains of humans and rodents [13, 14]. Zhou *et al*. reported significant improvement in BD patient treated with low dose IL-215. It is documented that IL-12 can reduce inflammation in CNS. IL-12 receptor (IL-12R) found on neurons and oligodendrocytes [16]. Tumor necrosis Factor (TNF) can cause astrocyte to transition to inflammatory state disrupting BBB protection of CNS17. IL-6 receptors are present in several neurons, including those associated with the serotonergic system, although their exact biological functions remain largely uncharacterized [18-20]. Elevated IL-6 is associated with major organ inflammatory response [21]. Similarly, neurons in regions such as the hippocampus, amygdala, and thalamus express IL-1Beta receptors, and IL-1beta is implicated in numerous neurodegenerative diseases [22-24]. IL-1Beta and the tumor necrosis factor-alpha (TNF-alpha) and also stimulating angiogenesis and play a role and pathophysiology of BD [25]. Collectively, such observation potentially can explain some of the increased risk of suicidal behaviors in BD. Therefore, further goal directed and hypotheses driven studies are needed to clarify if these observation that at face value do provide some insight, indeed may be associated with neuropsychiatric phenomena seen in BD.

Kynurenine pathways in BD and suicidal patients

The most interesting observation in regard to neuroimmunological mediators of suicide in patients with BD, arguably, is the increased quinolinic acid in the neuro-Behçet. Kynurenine pathway of tryptophan metabolism has been consistently shown to correlate with neuropsychiatric disorders as well as suicidality [26].

In mammalians, the essential amino acid tryptophan is primarily metabolized in through three different pathways: the kynurenine, serotonin, and indole pathways [27]. Tryptophan, aside from being a building block of host of proteins, is converted to serotonin and melatonin [28]. Although serotonin play important function in the CNS, 90% of serotonin is synthetized in the gastrointestinal tract, however, peripheral serotine cannot cross blood brain barrier (BBB) [28]. Only 10% of serotonin synthesis occurs in the CNS [29, 30]. Tryptophan is transported cross BBB via the L-type amino acid transporter [28, 29, 31]. About 10-15% dietary free tryptophan can cross the blood brain barrier (BBB). In the brain, tryptophan is catabolized to 5-HT by tryptophan hydroxylase 2 (rate limiting enzyme), and in the pineal gland serotonin is further metabolized to melatonin [27]. Kynurenine pathway accounts for 90% of the metabolism where 95% it occurs in the liver [27]. During inflammatory processes more of the tryptophan is shunted to kynurenine pathway where three enzymes i.e. tryptophan 2,3-dioxygenase (TDO) and rate limiting enzymes of indoleamine 2-3-dioxygenase 1 (IDO1-dominent enzyme in the CNS) and IDO2 promote catabolism of tryptophan to kynurenine pathways producing a number of neuroactive products [32-34]. IDO activity is enhanced by pro-inflammatory cytokines and inhibited by anti-inflammatory cytokines with IFN-gamma being a significant stimulator of the pathways. INF-gamma not only enhances IDO1 activity, but it also accelerates gene expression [35].

Kynurenine pathways of tryptophan metabolism result in production of neuroprotective kynurenic acid and picolinic acid as well as neurotoxic quinolinic acid [36]. Kynurenic acid blocks Alpha 7 nicotinic acetylcholine receptor and acts as antagonist at the glycine site of the N-methyl-D-aspartate (NMDA) receptor [37-39]. Quinolinic acid not only has neurotoxic effects via NMDA receptor activation but also can also increase glutamate release and inhibit its reuptake by astrocytes [40]. Neuronal loss associated with effects of quinolinic acid may in part explain pathological findings in brain samples of victims of suicide.

The role kynurenine pathway in BD and suicide seem to need further exploration, however, there are some interesting observations already published. For example, Bruden *et al*. [9] reported a CSF level of quinolinic acid

18.22 nM in control vs 41.94 nM (p<0.001) in patients with suicidal behaviors, an increase of quinolinic acid was observed across all major psychiatric disorders associated with suicidality. Consistent with these findings, Brenden and colleagues reported a higher level of quinolinic acid and higher quotient of quinolinic acid /kynurenic acid in CSF of patients with suicidal behaviors9. In Behçet disease (BD), the rate limiting enzyme of kynurenine pathway, IDO1 is activated. In a sample of 120 patients with BD, Onmaz *et al*. [42]. reported an increase in quinolinic acid in plasma of all patients particularly higher in those with neuro-Behçet. Although they did not measure quinolinic acid in CSF, in plasma there was a significant increase in kynurenine (421.91 ng/mL control vs 236.6 ng/mL BD patient p< 0.001), kynurenic acid (4.14 ng/mL vs 2.56ng/ml p<0.001) and quinolinic acid (18.6 ng/mL control vs 12.6ng/mL BD patients p =0.035). Neuro-Behçet disease (n=106), even higher levels of quinolinic acid in plasma were observed (12.1ng/mL vs 24.1ng/mL p=0.001). It would have been interesting to measure both kynurenic acid and quinolinic acid in CSF of BD patient, nonetheless, since peripheral quinolinic acid can cross BBB43, the increase neurotoxic quinolinic acid associated with suicidal behaviors may in part mediate the increased rate of suicidal behaviors in patients with BD [44, 45].

Conclusion

Suicidal behaviors are complex behaviors and studying the underpinning biological mechanisms have remained challenging, however, there is an accumulating body of research elucidating a strong association between suicidal behaviors and inflammation [7, 9, 46-48]. Behçet disease (BD), a disease of unknown etiology but strong indication of immunological basis has been associated with increased risk of suicide4. The convergence of finding in kynurenine pathway and cytokines between suicidal ideations and BD can prove effective in reducing the risk of suicide in patients with BD. For example, it would have been interesting to measure CSF level of some of these molecules in BD and compare it with that of well documented repository of evidence supporting role of these mediators of inflammation in suicide. BD is a severe potentially life-threatening disease by itself; however, increased risk of suicide and suicidal behaviors add a more complex face to this challenging entity. Furthermore, these data would advocate for screening all patients with BD for suicide risk. Future studies of BD, in our opinion, should utilize more standardized tools such as the Columbia–Suicide Severity Rating Scale [49] can detect suicide risk in a wide range of settings and illnesses [50]. Furthermore, there are treatment modalities that can significantly reduce the risk of suicide as well as improve quality of life, some with very rapid onset of action e.g. ketamine/esketamine use in suicidal patients [51]. By narrowing the study of suicide in a specific population particularly to specific region may reduce the heterogeneity 3of population to a limited degree, and thus, may also aid in developing strategies to cope with this global public health challenge. For example, ground breaking work of Postolache *et al*. [52-54] have extensively reported on possible connection between seropositivity to toxoplasma gandii and suicide resulting in potentially preventative measures in some patients with suicidal behaviors [55]. By applying the same concept, it is possible to better understand the neuropsychiatric findings in BD as well as develop better understanding of pathophysiology of suicidal behaviors in general.

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