

Viewpoint

Life in the flame: Inflammation sounds the alarm for suicide risk

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ARTICLE INFO

Keywords:

Suicide
Inflammation
Cytokines
Psychiatry

ABSTRACT

As suicide became a critical issue in mental healthcare, the World Health Organization (WHO) presented a Mental Health Action Plan in 2013. Particularly, the plan set an explicit goal for suicide prevention, which called for 10% reduction in the suicide rate in member countries by 2020. Now the tough year of 2020 has passed by, many valuable breakthroughs on suicide research have emerged during these recent years. To some extent, a multi-stage system for the prediction and prevention of suicide is taking shape. Inflammatory biomarkers may have a promising future within this field.

As estimated, over 800,000 people died by suicide every year, which meant one suicide death occurred every 40 s. Furthermore, it was indicated that each suicide death was accompanied by more than 20 suicide attempters (Fazel and Runeson, 2020). Owing to its profound impact on public health, suicide became a critical issue in mental healthcare, especially for youngsters and adolescents (Kessler et al., 2020). Therefore, the World Suicide Prevention Day was proposed to be annually held by the International Association for Suicide Prevention (IASP) and WHO on September 10th since 2003. Subsequently in 2013, the first-ever WHO Mental Health Action Plan was adopted by the 66th World Health Assembly, aiming to solve the thorny problem of suicide more efficiently. The plan and its official report entitled "Preventing suicide: a global imperative" set an explicit goal for suicide prevention: reducing suicide rate in member countries by 10% by 2020. During the past few years, the underlying mechanism of suicide has been investigated deeply, and many valuable breakthroughs have emerged in this field.

1. The darkest hour: Suicide and mental disorders

Given the complicated pathogenesis of suicide, a wide spectrum of risk factors containing healthcare system, societal factors like inappropriate media publicity, community factors like disaster and abuse, relationship conflict or loss, as well as individual backgrounds were all considered to associated with suicide within a comprehensive ecological model. To date, individual factors including previous suicide attempts and neuropsychiatric disorders are the most powerful indicators for future suicide risk; family history of suicidal behavior also has a strong

effect on predicting suicide. It was reported that up to 90% of suicide deaths had prior psychiatric diagnoses like depression, bipolar disorder, post-traumatic stress disorder, alcohol dependence, schizophrenia, etc³. Furthermore, comorbidity also increases the suicidal risk. Individuals suffer from more than one mental disorder or accompanied by other physical illnesses are at rather high risk³.

2. The inflamed brain: Mental disorders and inflammation

Early in the 1990s, interferon- α (IFN- α) started to be commonly used in treating hepatitis B/C infection and cancer. Strikingly enough, clinicians noticed that up to 30% of patients receiving IFN- α were included to develop depression (Su et al., 2014) or even suicidal thoughts (Schaefer et al., 2002). Additionally, researches showed that depressed patients usually have higher levels of proinflammatory cytokines in their serum samples, such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), IL-6 and acute phase proteins like C-reactive protein (CRP). Furthermore, a meta-analysis which included 69 original studies confirmed the increase of IL-6 and TNF- α levels in cerebrospinal fluid (CSF) and brain parenchyma, along with the over-activation of cerebral microglia in depression (Enache et al., 2019). It was also reported that patients with autoimmune and infectious diseases are more likely to suffer from depression (Beurel et al., 2020). Meanwhile, nonsteroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors might be conducive to enhancing antidepressant treatment response (Malhi and Mann, 2018).

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Received 21 January 2021; Received in revised form 24 March 2021; Accepted 28 March 2021

Available online 31 March 2021

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3. An elusive connection: Suicide and inflammation

In line with the potential role of inflammation in mental disorders, accumulating researches explored the connection between suicide and inflammation (Fig. 1A). For instance, inflammation was reported to be positively related to the intensity of suicidal ideation in neuropsychiatric patients (Brundin et al., 2015). In a comprehensive meta-analysis, Black and Miller concluded that both IL-1 β and IL-6 levels were highly associated with suicidality, which provided valuable information for distinguishing suicidal from non-suicidal patients (Black and Miller, 2015). Subsequently, Batty and colleagues (Batty et al., 2016) conducted a prospective cohort study and found people with increased inflammation (CRP > 3 mg/L) were up to four times more likely to commit suicide compared with less-inflamed ones (CRP < 1 mg/L). It was also proposed that immunological responses contributed to the connection between the infection of brain-tropic parasite *Toxoplasma gondii* and the elevated risk of self-violence and suicide (Turecki and Brent, 2016). Besides, some other somatic conditions characterized by prolonged immune over-activation, e.g. asthma, allergies, systemic lupus erythematosus (SLE) and multiple sclerosis (MS), were reported to correlate with higher suicide risks (Brundin et al., 2015).

In short, cytokines were speculated to take part in the biomechanism of suicide possibly via activating the kynurenine pathway of tryptophan catabolism, dysregulating the homeostasis of HPA axis, resulting in long-term epigenetic changes and interfering with monoamine metabolism, etc. However, the final decision to act on suicidal ideation should not be simply attributed to either inflammatory activation or an inflammation-induced malaise and haze.

4. A flame in the dark: inflammatory biomarkers for predicting suicide

To our knowledge, suicide is the vicious outcome of a multifaceted pathophysiological process, of which inflammation may be a detectable indicator. Recently, positron emission tomography (PET) imaging of translocator proteins (TSPO) binding, a well-established in vivo biomarker picturing central microglial activation, was suggested as a promising tool for predicting neuroinflammation and suicide. Compared to depressed patients without suicidal thinking, TSPO robustly increased in the anterior cingulate cortex (ACC) of those with suicidal thoughts. Moreover, Attwells and colleagues successfully identified that both natural logarithm of serum PGE₂/CRP and TNF α /CRP correlated with TSPO V_T (total distribution volume) density in brain (Attwells et al., 2020). In a previous study, O'Donovan et al. found suicidal ideation was

significantly associated with an elevated inflammatory index consisting of peripheral CRP, IL-6, IL-10 and TNF- α in depressed patients (O'Donovan et al., 2013). Accordingly, serum biomarkers may be acceptable in the screening step. These findings coincided with the idea of "Cytokines as Suicide Risk Biomarkers" (Pandey, 2015). Recently, hemogram parameters like neutrophil/lymphocyte and monocyte/lymphocyte ratios were also reported predicting adolescent suicide (Ucuz and Kayhan Tetik, 2020).

Combining with prior viewpoints on prediction and prevention of suicide, we firmly believe that suicide is predictable and preventable. In fact, suicide prediction tools have already been designed and applied to help making clinical decisions, especially occurred as items in rating scales for mental assessments. The current strategy for evaluating suicide risk primarily relies on incorporating clinical and socio-demographic data from medical records, insurance information, family/friend/self-reports and major life events, and then collecting detailed information through individual interviews. Despite the putative advantages of such strategy, the process is highly subjective and laborious. To some extent, objective indicators like inflammation-related biomarkers may help developing the multi-stage system for suicide prediction and prevention (Fig. 1B).

5. Where there is a shadow, there is light: Psychoneuroimmunology for fighting COVID-19

In the past tough year of 2020, the Coronavirus Disease-2019 (COVID-19) pandemic led to a worldwide healthcare crisis. Mounting researches reported an unanticipated impact of COVID-19 on mental health of both the infected individuals and general publics. Particularly, the cytokine storm and successive (sub)chronic low-grade inflammation induced by COVID-19 infection might be involved in several psychiatric symptoms (Debnath et al., 2020). Considering there was proof showing deaths by suicide climbed during the 1918-19 influenza pandemic and the 2003 severe acute respiration syndrome (SARS) epidemic, experts warned that suicidal risk needed more attention in this unprecedented time (Gunnell et al., 2020).

Indeed, potential higher suicide vulnerability can be explained by diverse factors which are not directly related to inflammation, specifically isolation, loneliness, bereavement, alcohol consumption, financial stressors, domestic violence, etc. (Moutier, 2020) There is even scarce evidence proving the therapeutic effect of anti-inflammation in reducing suicidal ideation. Still, we believe that our knowledge of the mechanism of suicide is just starting to expand. To some extent, the association between inflammation and suicide could be a meaningful topic to be

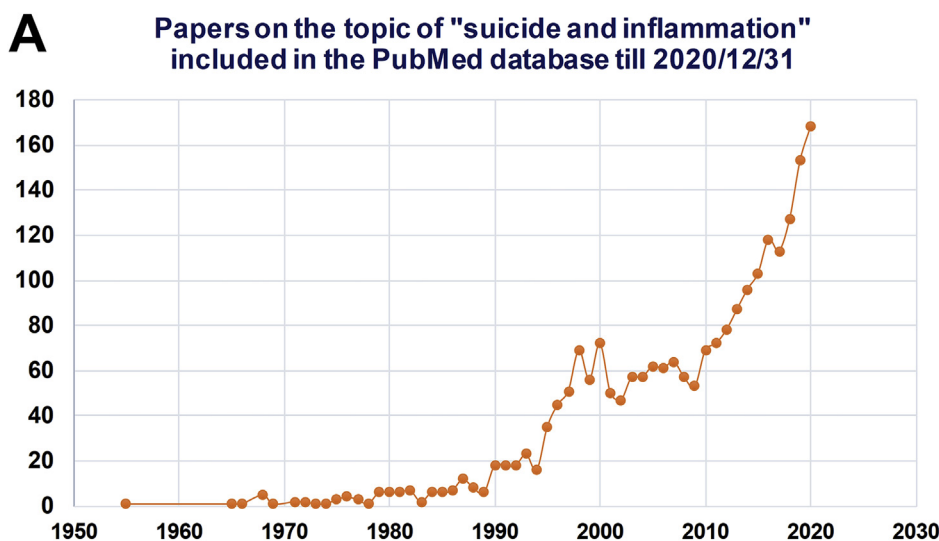


Fig. 1A. Counts of papers on the topic of "suicide and inflammation". Studies investigating suicide and inflammation were thoroughly searched in PubMed database on 2020/12/31. The primary search strategy was "((((((inflammation) OR (inflammatory)) OR (neuroinflammation)) OR (neuroinflammatory)) OR (cytokine) OR (chemokine)) AND (((suicide) OR (suicidal)) OR (suicidality)))". This search yielded 2211 articles in total. As was demonstrated in the figure, the number of papers investigating this topic appeared a blowout growth in recent ten years.

B

Multi-stage System for Suicide Prediction and Prevention

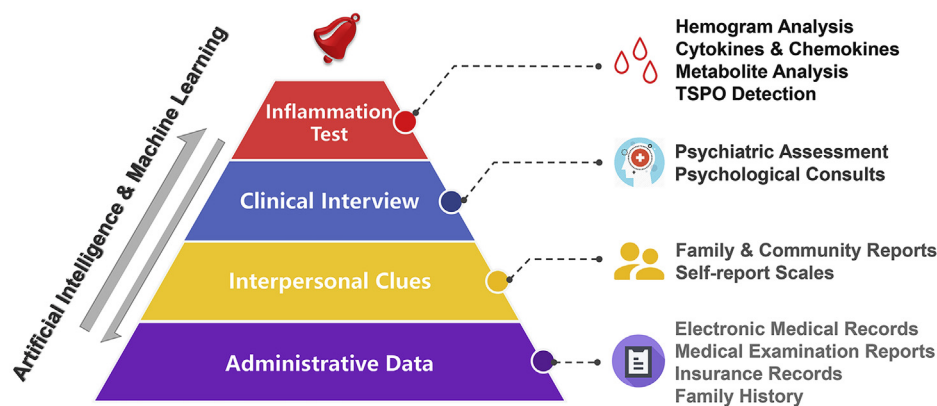


Fig. 1B. The proposed multi-stage system for suicide prediction and prevention. To improve both the positive predictive value (PPV; the incidence of suicide over a prespecified time horizon among patients classified as high-risk) and the Net Benefit (NB) of the prediction and prevention model, the multi-stage system was proposed. Considering previous suicide attempts and psychiatric diagnoses are the most powerful indicators for completed suicide, the administrative data may be the first-stage screening-in and screening-out strategy. Besides, self-rating scales and family- or community-based reports could provide detailed and timely information for predicting suicide or suicide-related behaviors. In the third stage, structured or semi-structured clinical assessments and interviews could guarantee the accuracy of suicide screening and prediction. In the fourth step, blood tests including hemogram analysis, cytokine detection and metabolite measurements, as well as PET imaging of cerebral TSPO are beneficial to quantify the intensity of suicidal ideation and determine the prognosis (risk) in a more objective manner. In addition, innovative methods like artificial intelligence and machine learning can be used to assist both the prediction and management of suicides at the population level.

investigated in-depth. It is necessary to take inflammation into account in future research to improve the prediction and prevention of suicide. Flame light of psychoneuroimmunology may illuminate the dark era of Coronavirus epidemic.

Author contributions

W-J Su and C-L Jiang conceived and designed the paper, W-J Yan and W-J Su drafted the manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work was supported by the Shanghai Sailing Program (Grant No. 20YF1458300 for W-J Su) and National Natural Science Foundation of China (Grant No. 31871171 for C-L Jiang).

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