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Inflammation biomarkers in suicide attempts and their relation to abuse, global functioning and cognition

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ABSTRACT

Objectives: To explore the link between cytokines and suicide attempts and their relationship with the psychological aspects of this complex multifactorial phenomenon.

Methods: 96 participants, including 20 patients with a recent suicide attempt and diagnosis of Major Depression Disorder (MDD), 33 MDD patients with a lifetime history of suicide attempt, 23 non-attempter MDD patients, and 20 healthy controls underwent an assessment on depressive symptoms, global functioning, aggressive behaviour, presence of abuse and attention performance. Additionally, all participants had a blood extraction for IL-2, IL2-R, IL-4, IL-6, and TNF-α plasma levels analysis.

Results: IL-6 levels were significantly different across groups ($F(3,89)=3.690$; $p=0.015$), with higher concentrations in both recent ($p=0.04$) and distant ($p=0.015$) attempt in comparison to MDD non-attempters. IL-6 was associated with adult physical abuse ($B=2.591$; $p=0.021$), lower global functioning score ($B=-0.512$; $p=0.011$), and poorer performance on attention ($B=-0.897$; $p=0.011$).

Conclusions: Recent and distant suicidal behaviour is associated with elevated IL-6 levels, which may be influenced by stressful and traumatic experiences. Elevated concentrations of IL-6 could have a negative impact on attention, increasing suicide risk. More research is needed to clarify the role of cytokines in suicide-related features to explore novel treatments and more effective preventive interventions.

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Introduction

Suicidal behaviour is a global health concern associated with premature mortality, disability, and functional impairment (World Health Organization 2019). Improving the knowledge on its pathophysiology is still limited and determining suicide risk factors remains a challenge for psychiatry (Lindqvist et al. 2011). This has stimulated the study of underlying biological mechanisms and the search for biomarkers in suicide (FDA-NIH Biomarker Working Group, 2016).

Dysregulation of the immune system has been linked to the pathophysiology of suicidal behaviour in which the pro-inflammatory interleukines (IL) IL-1b, IL-2, IL-6, and alfa Tumour Necrosis Factor (TNf-alfa) and the anti-inflammatory IL-4, IL-10 cytokines are unbalanced causing modifications in the function of brain regions related to emotion, motivation and reward causing behavioural changes (Dantzer et al. 2008; Miller et al. 2009; Courtet et al. 2015; Ganança et al. 2016; Vasupanrajit et al. 2021) that may increase

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suicide risk (Dowlati et al. 2010; Serafini et al. 2013; Brundin et al. 2017).

Amongst all cytokines, IL-6 is the most consistently associated with suicide (Ganança et al. 2016; González-Castro et al., 2021). Elevated levels of IL-6 have been reported in the cerebrospinal fluid (Lindqvist et al. 2009, 2011; Bay-Richter et al. 2015; González-Castro et al., 2021), plasma (Janelidze et al. 2011; Isung et al. 2014; Priya et al. 2016; Keaton et al. 2019; Achtyes et al. 2020) and post-mortem tissue of suicide attempters (Pandey et al. 2012; Hoyo-Becerra et al. 2013). Regarding IL-2, some studies (Kim et al. 2008; Janelidze et al. 2011) and a meta-analysis (Ducasse et al. 2015) report increased levels in suicide attempters. In the study of Tonelli et al. (2008) IL-4 levels were elevated in the post-mortem prefrontal cortex of suicide casualties, but Ducasse et al. (2015) found lower IL-4 plasma levels in suicide ideators and attempters in comparison to healthy controls. Concerning TNF-α, higher concentrations were found in plasma of attempters (Janelidze et al. 2011) and in the brain tissue of adolescents who died by suicide (Pandey et al. 2012).

However, the role of cytokines in the complex phenomenon of suicide remains unclear. Some findings in literature do not support the relationship between suicide and IL-6 (Kim et al. 2008; Gabbay et al. 2009; Isung et al. 2012; Su et al. 2020; Ganança et al. 2021), IL-2 (Mendlovic et al. 1999), IL-4 (Mendlovic et al. 1999; Gabbay et al. 2009; Isung et al. 2012) and TNF-α (Lindqvist et al. 2009; O'Donovan et al. 2013; Vargas et al. 2013). Besides, the implication of cytokines in the pathophysiology and severity of the symptoms in MDD without suicide has also been reported (Munkholm et al. 2013; Serafini et al. 2013; Kim et al. 2017; Enache et al. 2019; Beurel et al. 2020; Ting et al. 2020) making it necessary to explore the specific alterations related to suicide to be eligible as a biomarker. Thus, analysing the differences between depressed suicide attempters and depressed non-attempters on their cytokine profile may help our understanding of specific inflammation alterations exclusively implicating suicidal behaviour and differentiate from those realted to depression.

According to the biopsychosocial approach, suicidal behaviour is a multifactorial complex phenomenon involving the interplay of biological, psychological, and social factors (Engel 1978; Turecki et al. 2019; Porter 2020). Some of the psychological variables that have proven to be significantly associated with a higher risk of suicide are cognitive alterations, specifically in the attention domain (Nangle et al. 2006; Keilp et al. 2008, 2014; Richard-Devantoy et al. 2012; Keilp et al., 2013; Olie et al. 2015; Verma et al. 2016; Fernández-Sevillano et al. 2021), child and adult abuse (Björkenstam et al. 2017; Ásgeirsdóttir et al. 2018; Hartley et al. 2018), functional impairment (Jia and Zhang 2012; Fässberg et al. 2016; Lewis et al. 2017; Lutz and Fiske 2018) and lifetime aggressive behaviour (Turecki 2005; McGirr et al. 2008; Buitron et al. 2018; Hartley et al. 2018). However, only a few studies have explored the link between cognition (Huang et al. 2021), abuse (Su et al. 2020), and lifetime aggressive behaviour (Coccaro 2006; Coryell et al. 2018) with inflammation parameters in suicidal behaviour. Thus, the link between biological biomarkers and psychosocial variables in suicide is yet to be explored, as we endavour in this study, which could shed light on the topic and improve its prevention.

The objectives of this study are to analyse the specific inflammatory profile in recent and distant suicide MDD attempters in comparison to MDD non-attempters and healthy controls and to explore its relationship with the psychological variables mentioned. The main hypothesis is that recent suicide attempters will display a more elevated pro-inflammatory cytokine profile than the rest of the groups. Besides, these cytokines would be associated with attention alterations, abuse, lifetime aggressive behaviour, and poorer global functioning, which could increase the risk for suicide.

Materials and methods

Participants

This study was conducted in the Psychiatry Department of the Araba University Hospital – Santiago. 96 participants were classified into the following groups: 20 depressed patients with a suicide attempt within the last 30 days, 33 depressed patients with a distant history of a suicide attempt during their lifetime, 23 depressed patients without suicidal behaviour in their lifetime, and 20 healthy volunteers matched by age, gender, level and years of education with recent attempt group. All patients had been diagnosed with MDD (unipolar or bipolar) according to the 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) before the study and were under psychopharmacological treatment for their condition. Suicide attempts were defined as *self-initiated sequence of behaviours by an individual who, at the time of the initiation, expected that the set of actions would lead to his or her own death* (DSM-5). Patients with substance use disorder (except tobacco),

neurological illness, severe organic disease, systemic autoimmune disease, and under recent (last week) anti-inflammatory treatments were excluded from the study as they can affect inflammatory response and affect the results. Due to their critical health status, patients with suicide attempts involving extremely severe injuries were not recruited in the first month following an attempt and were not included in the recent suicide attempt group.

Healthy controls with either personal or family history of major psychiatric disorders and history of suicide attempts were not included in the study. All participants were between 18 and 65 years old and had signed the Informed Consent. This study was approved by the Ethical Board of the Araba University Hospital and was conducted according to the Declaration of Helsinki (World Medical Association 2013).

Procedure and measures

All participants underwent a clinical and neuropsychological assessment conducted by an experienced psychologist approximately within the first 15 days after reaching mental health services in the case of patients. Healthy volunteers were recruited by a public advertisement in the hospital approved by the Ethics Committee. The severity of depressive symptoms was assessed by the Spanish version of the Hamilton Depression Rating Scale (HDRS) (Hamilton 1967; Bobes et al. 2003) and the Global Assessment of Functioning scale (GAF) was used to measure global functioning (American Psychiatric Association 2014). Lifetime aggressive behaviour was measured by the Lifetime History of Aggression (BGLHA) (Brown et al. 1979) and the presence of the child and adult abuse (physical, sexual, and/or emotional) was evaluated with the suicide attempt assessment protocol developed by García-Nieto et al. (García-Nieto et al., 2012), which includes some items that assess the child and adult abuse. Neuropsychological assessment focussed on attention was measured with the Stroop Test (Golden 2001). Besides, participants had a 10 mL venous blood extraction at 8:30–9:30 after overnight fasting for the analysis of the following inflammation parameters: IL-2, IL2-R, IL-4, IL-6, and TNF-α. After extraction, samples were centrifuged (641xg for 10 min at 4 °C) to obtain plasma which was stored at −80 °C. All the biochemical parameters in plasma were measured using commercially ELISA-based kits available and following the manufacturers' instructions. IL-2 and IL2-Ra were purchased from RayBiotech (USA; ELH-IL2 and ELH-IL2Ra), IL-4 and IL-6 from Diaclone (France; 850.890.096 and 950.035.096), and TNFα from Cloud-clone (USA; HEA133Hu).

Statistical analyses

Comparisons between groups were performed with ANOVA followed by Bonferroni post hoc testing for continuous variables and Chi-Square for categorical variables. Direct scores of the Colour-Word condition of the Stroop test were corrected by age, then converted to Z-scores and gathered into a cognitive dimension labelled as attention. Backward stepwise multiple regressions were performed with two aims: 1) to determine independent variables (adult and child abuse, global functioning, and history of aggressive behaviour) related to inflammatory factors (dependent variables) and 2) to explore the relation of inflammatory factors (independent variables) with attention scores (dependent variable). Regressions were adjusted for possible confounding variables (age, sex, economic status, education, and severity of depressive symptoms according to HDRS), including only significant confounders in each model.

Data statement

Data cannot be shared publicly due to confidential restrictions applicable to health data but could be available under request and prior consent of the CEIC Ethics Committee.

Results

Study groups were not significantly different in terms of demographic variables (Table 1). According to the Bonferroni post hoc test, there were no significant differences in the severity of depressive symptoms between all patients groups (Table 1). Lethality of attempts measured by the Medical Damage Scale was not significantly different between recent and distant attempter groups ($t = -0.503$; $p = 0.24$; $d = -0.36$). Scores of Global Functioning scale ($F(3,81)=22.50$; $p < 0.01$) were significantly lower in recent attempters and non-attempters in comparison to healthy controls ($p < 0.01$ in each comparison).

Out of all subtypes, (physical, sexual, emotional, and negligence) of child and adult abuse analysed, history of child sexual abuse ($F(3,91)=3.35$; $p = 0.02$), child emotional abuse ($F(3,91)=3.12$; $p = 0.03$) and adult emotional abuse ($F(3,91)=3.80$; $p = 0.01$) yielded significant results. According to post hoc analysis,

Table 1. Demographic, clinical, and cognitive variables.

		Recent attempters (1) ($n = 20$) (mean;SD)	Distant attempters (2) ($n = 33$) (mean;SD)	Depressed non-attempters (3) ($n = 23$) (mean;SD)	Healthy controls (4) ($n = 20$) (mean;SD)	Statistical contrast (p)	Effect size	Bonferronic post hoc test
Sex	Female Male	13 (65%) 7 (35%)	26 (78.8%) 7 (21.2%)	18 (78.3%) 5 (21.7%)	14 (70%) 6 (30%)	$\chi^2(3,96)=1.62$; $p = 0.66$	Cramer's $V = 0.13$	
Age		44.70 (8.78)	44.45 (12.76)	50.57 (9.93)	44.58 (9.22)	$F(3,91)= 1.84$; $p = 0.14$	$\eta_p^2=0.0$	$1 = 2 = 3 = 4$
Education (years)		13.95 (5.08)	13.50 (4.25)	13.04 (3.27)	15 (5.07)	$F(3,87)= 0.68$; $p = 0.57$	$\eta_p^2=0.02$	$1 = 2 = 3 = 4$
Marital Status	Single Married Divorced Widow	6 (30%) 10 (50%) 4 (20%) 0 (0%)	10 (31.2%) 14 (43.8%) 7 (21.9%) 1 (3.1%)	0 (0%) 16 (69.57%) 5 (21.7%) 2 (8.7%)	8 (40%) 10 (50%) 2 (10%) 0 (0%)	$\chi^2(3,95)=14.540$; $p = 0.10$	Cramer's $V = 0.23$	
Employement	Inactive Active Retired Other	9 (45%) 7 (35%) 0 (0%) 4 (20%)	6 (20%) 12 (40%) 3 (10%) 9 (30%)	8 (34.8%) 8 (34.8%) 2 (8.7%) 5 (21.7%)	4 (20%) 15 (75%) 0 (0%) 1 (5%)	χ^2 (9,95)=16.061 $p = 0.06$	Cramer's $V = 0.24$	
Economic status	Low Medium High	7 (38.9%) 9 (50%) 2 (11.1%)	10 (37%) 11 (40.7%) 6 (22.3%)	10 (50%) 10 (50%) 0	6 (33.3%) 9 (50%) 3 (16.7%)	χ^2 (6,83)=5.611 $p = 0.46$	Cramer's $V = 0.18$	
Severity of depression (HDRS)		15.50 (7.23)	17.87 (6.54)	14.36 (8.93)	1.60 (2.09)	$F(3,89)= 25.74$; $p < 0.01$*	$\eta_p^2=0.46$	01 > 04 02 > 04 03 > 04
Global functioning (GAF)		7.15 (1.39)	6.88 (1.58)	7.53 (1.65)	9.95 (0.22)	$F(3,81)=22.50$; $p < 0.01$*	$\eta_p^2=0.45$	01 > 04 02 > 04 03 > 04
Child abuse – Physical		0.25 (0.44)	0.25 (0.44)	0.17 (0.39)	0.05 (0.22)	$F(3,91)=1.27$; $p = 0.29$	$\eta_p^2=0.04$	$1 = 2 = 3 = 4$
Child abuse –		0.35 (0.49)	0.31 (0.47)	0.17(0.39)	0 (0)	$F(3,91)=3.35$; $p < 0.05$*	$\eta_p^2=0.1$	01 > 04
Sexual								02 > 04
Child abuse – Emotional		0.35 (0.50)	0.34 (0.48)	0.13 (0.34)	0.05 (0.22)	$F(3,91)=3.12$; $p < 0.05$*	$\eta_p^2=0.09$	01 > 04 02 > 04
Child abuse – Negligence		0.16 (0.37)	0.16 (0.37)	0.87 (0.29)	0.05 (0.22)	$F(3,90)=0.60$; $p = 0.61$	$\eta_p^2=0.02$	$1 = 2 = 3 = 4$
Adult abuse – Physical		0.15 (0.37)	0.13 (0.34)	0.09 (0.29)	0 (0)	$F(3,91)=1.05$; $p = 0.38$	$\eta_p^2=0.03$	$1 = 2 = 3 = 4$
Adult abuse – Sexual		0.2 (0.41)	0.19 (0.40)	0.44 (0.21)	0 (0)	$F(2,33)=2.33$; $p = 0.08$	$\eta_p^2=0.02$	$1 = 2 = 3 = 4$
Adult abuse –Emotional		0.35 (0.49)	0.31 (0.47)	0.13 (0.34)	0 (0)	$F(3,91)=3.80$; $p < 0.01$*	$\eta_p^2=0.11$	01 > 04 02 > 04
BGLHA – Child		1.63 (2.79)	2.16 (3.26)	2.67 (4.00)	0 (0)	$F(3,72)=1.01$; $p = 0.395$	$\eta_p^2=0.04$	$1 = 2 = 3 = 4$
BGLHA – Teen		3.58(4.49)	3.87 (4.54)	2.67 (2.87)	0.60 (1.34)	$F(3,72)=1.17$; $p = 0.326$	$\eta_p^2=0.05$	$1 = 2 = 3 = 4$
BGLHA – Adult		4.21 (3.63)	4.61 (4.36)	3.05 (3.98)	3.80 (4.03)	$F(3,72)=1.99$; $p = 0.123$	$\eta_p^2=0.08$	$1 = 2 = 3 = 4$
BGLHA – Total		9.42 (9.79)	10.65 (9.72)	8.38 (8.91)	1 (2.24)	$F(3,72)=1,61$; $p = 0.194$	$\eta_p^2=0.06$	$1 = 2 = 3 = 4$
Attention		−0.910 (0.77)	−1.025 (0.67)	−0.913 (0.65)	0.046 (0.78)	$F(3,86)=9.83$; $p < 0.001$*	$\eta_p^2=0.25$	01 < 04 02 < 04 03 < 04

HDRS: Hamilton Depression Rating Scale; GAF: Global Assessment of Functioning; BGLHA: Lifetime History of Aggression.

more cases of history of child sexual abuse were reported in recent ($p = 0.04$) and distant ($p = 0.04$) attempters in comparison to healthy controls, respectively. Both child and adult emotional abuse were more frequent in recent (child abuse $p = 0.02$; adult abuse $p = 0.03$) and distant attempters (child abuse $p = 0.01$; adult abuse $p = 0.01$) in contrast to healthy controls and there were no differences between patient groups.

Last, ANOVA comparisons showed no significant differences in BGLHA scores. Attention dimension (Table 1) differed across groups ($F(3,86)=9.83$; $p < 0.001$) with a lower performance in all patient groups ($p < 0.001$ in each post hoc comparison) in contrast to healthy controls. However, attention was not significantly different across patient groups.

Inflammation parameters comparisons are shown in Table 2. ANOVA contrasts showed significant differences in IL-6 levels ($F(3,89)=3.690$; $p = 0.01$) with higher levels in both recent ($p = 0.04$) and distant ($p = 0.015$) suicide attempters in comparison to healthy controls. Although not statistically significant, raw data suggest that numerically IL-6 levels are increasingly higher from healthy controls to recent attempters group (Figure 1).

Backward stepwise multiple regressions revealed that having experienced adult physical abuse ($B = 2.591$; $p = 0.021$) and lower global functioning score ($B = -0.512$; $p = 0.016$) are related to higher levels of IL-6. Besides, higher IL-6 concentrations are linked to lower scores in the attention dimension ($B = -0.897$; $p = 0.011$). Both histories of child physical abuse and history of child aggressive behaviour ($B = 0.25$; $p = 0.05$) are associated with higher levels of IL-4.

Discussion

Our findings suggest that suicide is accompanied by a systemic inflammatory response as IL-6 cytokine plasma concentration was elevated in both recent (last 30 days) and distant depressed suicide attempters. Following our results, several studies described elevated IL-6 in cerebrospinal fluid (Lindqvist et al. 2011; Bay-Richter et al. 2015), plasma (Janelidze et al. 2011; Isung et al. 2014; Priya et al. 2016; Keaton et al. 2019; Amitai et al. 2020) and gene and protein expression related to IL-6 in post-mortem tissue of suicide attempters (Pandey et al. 2012; Hoyo-Becerra et al. 2013). In contrast, Kim et al. (2008) reported elevated levels of IL-6 in non-attempters versus attempters and other studies yielded no differences

Table 2. Inflammation parameters across groups.

	Recent attempters (01) ($n = 20$) (mean;SD)	Distant attempters (02) ($n = 33$) (mean;SD)	Depressed non-attempters (03) ($n = 23$) (mean;SD)	Healthy controls (04) ($n = 20$) (mean;SD)	Statistical contrast (p)	Effect size	Bonferroni post hoc test
IL2	77.66 (70.72)	59.89 (54.46)	52.64 (35.15)	70.52 (48.68)	$F(3,89)=0.91$; $p = 0.44$	0.03	$01 = 02 = 03 = 04$
IL2R	124.11 (30.29)	141.29 (32.32)	136.43 (55.00)	135.00 (40.31)	$F(3,89)=0.71$; $p = 0.55$	0.02	$01 = 02 = 03 = 04$
IL4	1.84 (1.47)	3.73 (7.22)	1.60 (0.68)	2.29 (0.50)	$F(3,89)=1,32$; $p = 0.27$	0.04	$01 = 02 = 03 = 04$
IL6	5.94 (3.49)	5.90 (2.72)	5.41 (2.42)	3.60 (1.64)	$F(3,89)=3.69$; $p = 0.01$	0.11	$01 > 04$ $02 > 04$
TNF-α	43.74 (14.41)	45.74 (20.96)	44.41 (13.09)	39.21 (11.55)	$F(3,89)=0.67$; $p = 0.57$	0.00	$01 = 02 = 03 = 04$

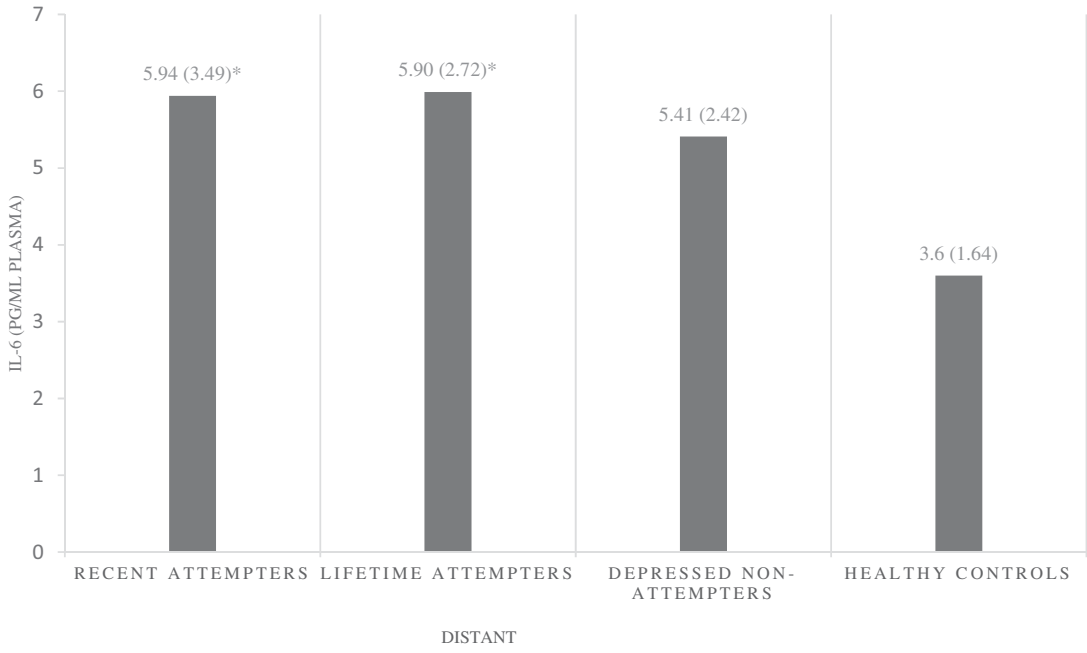

Figure 1. Mean (SD) IL-6 plasma concentrations in each group. *$p < 0.05$ significant differences in comparison to controls.

between groups (Tonelli et al. 2008; Gabbay et al. 2009; Isung et al. 2012; Martinez et al. 2012; Vargas et al. 2013; Ducasse et al. 2015). Thus, although IL-6 is one of the cytokines most frequently associated with suicide (Ganança et al. 2016; Lengvenyte et al. 2019) more studies are needed to clarify its role in suicidal behaviour.

Interestingly, recent suicide attempters had the highest levels of these cytokines and levels decreased in distant attempters, non-attempters, and healthy controls, respectively which may imply a key role of IL-6 in suicidal behaviour. Although not statistically significant, IL-6 concentrations of depressed non-attempters showed a tendency to be higher than healthy controls, in consonance with previous studies that observe more inflammation in depressive patients (Liu et al. 2017; Colasanto et al. 2020; Ting et al. 2020). However, as this study stratifies depressive patients according to their suicidal profile into separate groups, possible differences between non-suicidal depressive patients and healthy subjects might be more subtle than those observed in studies that include depressive patients into the same group regardless of their suicidal history.

The mechanisms by which cytokines influence suicide risk are not clear but there is evidence of their important role in the Central Nervous System (CNS) modulating the synthesis and function of neurotransmissions (Dunn 2006; Borsini et al. 2015; Courtet et al. 2016) which influence emotion, cognition, and behaviour. Areas of the brain that orchestrate and regulate these three psychological processes, such as the hypothalamus, hippocampus, locus coeruleus, and prefrontal cortex, are densely populated with cytokine receptors (Jeon et al. 2019). Hence, dysregulated continual synthesis of IL-6 has a pathological effect on the development of psychiatric conditions (Tanaka et al. 2014) and may increase the risk for suicide (Brundin et al. 2017). According to the prospective study of Batty et al. (Batty et al. 2016) patients with higher levels of inflammation had a three-fold elevated risk of future suicide death, suggesting that inflammation is preceded and implicated in suicide attempts.

Another relevant finding in this study is that higher IL-6 levels were independently associated with lower scores of attention, which may indicate an interesting link between cognition, inflammation, and suicide. As previously mentioned, cytokines can mediate cognition due to their effect on the CNS mechanisms and cognition brain areas (Wilson et al. 2002; Jeon et al. 2019). Alterations in cognitive dimensions like attention, which has been extensively reported for being altered in suicide attempters, result in difficulties interpreting and responding to environmental demands increasing vulnerability to suicide (Lara et al. 2015; Szanto 2017).

Furthermore, our results show that inflammation is also associated with traumatic life experiences which represents a higher risk for suicidal behaviour. In this report presence of adult physical abuse and lower

global functioning scores were independently linked to higher IL-6 concentrations. In addition, a history of child physical abuse and child aggressive behaviour history was significantly linked to higher levels of IL-4. Experiencing adverse life events, namely physical abuse and displaying aggressive behaviour both during childhood and adulthood can dysregulate the immune system as a response to a stressful traumatic stimulus resulting in higher levels of inflammatory parameters (Brundin et al. 2017; Lippard and Nemeroff 2020) as we observed in our study. These higher levels of IL-6 and IL-4 cytokines may suggest a higher vulnerability for suicide as numerous studies have linked suicide and childhood and adult abuse (Hartley et al. 2018; Caravaca Sánchez et al. 2019; Salokangas et al. 2019; Thompson et al. 2019; Coryell et al. 2020) whilst protective variables like resilience, coping styles or safe attachment can mitigate the negative effect of traumatic experiences on mental health (Friedberg and Malefakis 2018; Nehra et al. 2019). A recent study found that the inflammatory response in mood disorders is not uniform and that in those patients, inflammatory phenotypes that include IL-6 were related to suicide risk and childhood adversity (Schiweck et al. 2020).

Apart from IL-6 and IL-4, we also analysed IL-2 and IL2-R concentrations but there were no significant differences between groups. Results regarding these cytokines are contradictory in the literature. Janelidze et al. (2011), Kim et al. (2008) and the meta-analysis of Ducasse et al. (2015) described lower IL-2 concentrations in suicide attempters in comparison to patients without a suicide attempt and healthy controls. Nässberger & Träskman-Bendz (1993) reported increased IL-2 soluble receptor (IL-2R) plasma concentrations in suicide attempters, although Rothenhäusler et al. (2006) did not find these differences.

Concerning TNF-α, in the study of Janelidze et al. (2011), depressed suicide attempters had higher plasma levels than depressed non-attempters and healthy controls. Similarly, Pandey et al. (2012) found more concentration of TNF-α in the prefrontal cortex brain tissue of adolescents who died by suicide. However, there are also contradictory results relating to this inflammation parameter (Huang and Lee 2007; Tonelli et al. 2008; Lindqvist et al. 2009; Isung et al. 2012; Vargas et al. 2013).

Understanding the role of inflammation in suicide and identifying potential factors that can have an influence on this multifactorial phenomenon remains a challenge for psychiatry. Although there is growing evidence for the neuroinflammation hypothesis of suicide, more research is needed to clarify inconsistent data found in the literature. Future studies involving inflammation and suicide should focus on measuring the effectiveness of psychological protective factors and continue the research on the mechanisms involving cytokines. Besides, deeper knowledge on the biological and clinical interplay in MDD patients with suicide attempts would enable novel and personalised treatment options and the development of more effective preventive interventions.

Limitations

This study has some limitations. Although the general sample was not small, each group sample size was not large for cluster comparisons. However, this thorough methodological design composed of four groups that differentiates recent and distant suicide attempters was crucial to obtain specific outcomes of clinically different groups. Recent and distant trauma events were assessed using a standardised protocol but information could be biased when reporting this information. Patients with other psychiatric conditions and substance use disorders were excluded from the study to control significant interactions with inflammation, which may result in a less representative population of at-risk patients. Due to their health status, patients with suicidal attempts involving extremely severe injuries were not recruited during the first month after the attempt. Thus, the sample of recent attempters is less representative regarding this method. Some factors that could potentially influence our results, such as the presence of anxiety, mixed symptoms, BMI and psychopharmacological treatment were not assessed. Individual biomarkers of inflammation were measured instead of full pathways involving receptors and transduction mechanisms.

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