The association between immune markers and recent suicide attempts in patients with serious mental illness: A pilot study

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ABSTRACT

Previous studies have identified elevations in markers of gastrointestinal inflammation in schizophrenia and mood disorders but studies have not measured the association between these markers and recent suicide attempts. We assessed 210 patients receiving treatment for schizophrenia, bipolar disorder, or major depression. We employed the Columbia Suicide Severity Rating Scale to identify recent and lifetime suicide attempts (actual, aborted, and interrupted). Psychiatric participants and a control group of 72 individuals without a psychiatric disorder had a blood sample drawn from which were measured specific markers of gastrointestinal inflammation and also C-Reactive protein (CRP). A total of 20 (10%) of psychiatric participants had a suicide attempt in the previous one month and 95 (45%) an attempt during their lifetime but not in the previous one month. The recent attempters had significantly elevated levels of antibodies to yeast mannan from *Saccharomyces cerevisiae* (ASCA), the food antigen gliadin, and bacterial lipopolysaccharide (LPS) compared with the non-psychiatric group when adjusting for demographic and clinical variables. These markers were not elevated in individuals with a past, but not recent, suicide attempt history. Our study indicates that there is evidence of gastrointestinal inflammation in some individuals who have had a recent suicide attempt.

1. Introduction

Psychological autopsy and epidemiological studies indicate that more than 90% of people who die by suicide have a diagnosable psychiatric illness, particularly major depression, bipolar disorder, or schizophrenia (Cavanagh et al., 2003; Nordentoft et al., 2011). Genetic factors, independent of those associated with psychiatric disorders, may also play a role in suicide but genes of large effect have yet to be identified (Mullins et al., 2014). The ability to predict suicide attempts based on clinical factors remains limited (Zalsman et al., 2016). Currently available biomarkers also have limited predictive value (Oquendo et al., 2014). The identification of blood-based markers would provide for more personalized methods for the assessment and treatment, and ultimately prevention, of suicide attempts.

Many individuals with schizophrenia and mood disorders have evidence of immune activation suggesting that immune dysregulation may be part of the etiopathology of these disorders (Gibney and

Drexhage, 2013; Haapakoski et al., 2016; Leboyer et al., 2016; Severance et al., 2015). Studies by our group and others indicate that the gastrointestinal tract is often the primary source of this immune activation as evidenced by increased levels of markers of gastrointestinal inflammation in individuals with serious mental illness (Kiecolt-Glaser et al., 2015; Petra et al., 2015; Severance et al., 2015). These markers have varying degrees of prevalence and intercorrelations (Severance et al., 2013, 2014). Furthermore, increased rates of suicide and suicide attempts have been found in some populations of individuals with celiac disease (Ludvigsson et al., 2011) or inflammatory bowel diseases (Gradus et al., 2010).

Several of these immune markers have been the focus of our recent investigations. Gliadin is a component of gluten, found in wheat and related cereals. Antibody response to dietary gliadin is associated with celiac disease, an immune-mediated enteropathy, and with non-celiac wheat sensitivity (Uhde et al., 2016) and is thought to indicate intestinal inflammation and/or intestinal barrier dysfunction. We have

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found increased levels of antibodies to gliadin in individuals with schizophrenia (Dickerson et al., 2010) and with bipolar disorder (Dickerson et al., 2011) and in individuals with acute mania during a hospital stay (Dickerson et al., 2012); in the latter study the levels of immune markers were lower 6 months after hospital discharge. We also have studied the antibody response to yeast mannans represented by antibodies to *Saccharomyces cerevisiae* (ASCA), a commensal organism present in some foods and in the intestinal tract of many individuals (Severance et al., 2014). Elevated ASCA levels are associated with increased intestinal inflammation (Kaul et al., 2012). We have previously found increased levels of ASCA in individuals with mood disorders (Severance et al., 2014).

Results from other investigators indicate that inflammation may be associated not only with a proclivity for a psychiatric disorder, but specifically with suicidal behavior. Studies have found an association between a suicide attempt history and the level of cytokines such as IL-6 which are cell signaling molecules involved in the immune response and which can arise from inflammation from many sources, including the gastrointestinal tract (Black and Miller, 2015; Courtet et al., 2016; Gananca et al., 2016; O'Donovan et al., 2013). An association between elevated antibodies to *Toxoplasma gondii*, an apicomplexan parasite, and suicide attempts has also been reported (Arling et al., 2009). In a recent study, we found that individuals with serious mental illness who had a lifetime history of a suicide attempt had elevated levels of IgM class antibodies to *Toxoplasma gondii* and Cytomegalovirus (CMV); we also found an association between the levels of these antibodies and the number of suicide attempts (Dickerson et al., 2016b).

There has been little study of the association between markers of gastrointestinal inflammation and recent suicide attempts. In addition, most studies of biological markers and suicide attempts have focused on a lifetime history of suicide attempts rather than recent attempts; a study of the latter may be more informative about state-based immune dysregulation that could signal an acute period of elevated risk. The purpose of this study was to examine the association between levels of markers of gastrointestinal inflammation and a recent suicide attempt in individuals with schizophrenia, bipolar disorder or major depressive disorder in comparison with non-psychiatric controls.

2. Methods

2.1. Sample

The study sample consisted of individuals with schizophrenia, bipolar disorder, or major depressive disorder as well as non-psychiatric controls who were recruited consecutively in the period May 2014 to November 2016. These individuals were enrolled in ongoing studies of the role of infections and the immune response in individuals with serious psychiatric disorders (Dickerson et al., 2016a). We recently reported on an earlier and smaller version of this cohort in a study of lifetime suicide attempts (Dickerson et al., 2016b).

The inclusion criterion for individuals with schizophrenia was a current diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. The inclusion criterion for individuals with bipolar disorder was a diagnosis of bipolar disorder including bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified, and for major depressive disorder, single or recurrent major depression. Participants were recruited from inpatient, day hospital, and outpatient programs of Sheppard Pratt Health System and from affiliated psychiatric agencies. The diagnosis of each psychiatric participant was established by the research team including a board-certified psychiatrist and based on the Structured Clinical Interview for DSM-IV Axis 1 Disorders and available medical records.

The non-psychiatric controls were recruited from posted announcements in community settings in the same geographic area as the health system where the psychiatric participants were recruited (Dickerson et al., 2014a). These individuals were screened to rule out the presence of a current or past psychiatric disorder with the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-patient Edition (First et al., 1998). Participants were not asked directly if they had a history of a suicide attempt.

All participants met the following additional criteria: age 18–65 (the controls were age 20–60); proficient in English; absence of any history of intravenous substance abuse; absence of intellectual disability; absence of HIV infection; absence of serious medical disorder that would affect cognitive functioning; absence of a primary diagnosis of alcohol or substance use disorder over the past 3 months.

The studies were approved by the Institutional Review Boards of the Sheppard Pratt Health System and the Johns Hopkins Medical Institutions following established guidelines. All participants provided written informed consent after the study procedures were explained.

2.2. Measure of suicide attempt history

All psychiatric participants were assessed by trained raters on the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). Per the C-SSRS, a suicide attempt was defined as a potentially self-injurious act carried out with at least some wish to die as a result of the act: an actual attempt, an aborted attempt, or an interrupted attempt. Participants were assessed as to the occurrence of an attempt over their lifetime and also in the previous one month. Psychiatric participants were categorized into one of three groups: those who had made a suicide attempt in the past one month; those who had made a suicide attempt during their lifetime but not in the past one month, and those who had no lifetime history of a suicide attempt.

2.3. Demographic and clinical variables

All participants were asked about demographic variables including maternal education as a proxy for pre-morbid socioeconomic status, their current cigarette smoking status and were evaluated on a cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998).

Psychiatric participants were interviewed and rated on the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). They were also interviewed about their recent and past use of alcohol and drugs and classified in one of 3 groups: no history, past history only, or recent history (in the last 3 months). Current medications received were recorded from clinical charts and participant self-report and it was noted whether each participant was receiving the following types of medication at the time of the study visit: second generation antipsychotic, lithium, anticonvulsant mood stabilizer, antidepressant medication.

2.4. Plasma collection and measurement of immune markers

Each participant had a blood sample obtained using standard venipuncture methods. Plasma was separated from the blood and was stored at −70 °C until testing. In almost all cases blood samples were collected on the same day that the interview measures were completed.

Levels of IgA antibody to yeast mannan from *Saccharomyces cerevisiae* (ASCA) were determined by the enzyme-linked immunosorbent assay (ELISA), according to the assay kit manufacturer's protocol (IBL America, Minneapolis, MN). IgG antibody to gliadin and levels of C-Reactive protein was measured by ELISA as previously described (Severance et al., 2014). IgA antibody to bacterial lipopolysaccharide (LPS) was measured by ELISA, as follows. Wells of 96-well Maxisorp round-bottom polystyrene plates (Nunc, Roskilde, Denmark) were coated with 50 µL/well of a .01 mg/mL solution of LPS from E. coli O111:B4, Pseudomonas aeruginosa, and Klebsiella pneumoniae (Sigma-Aldrich, St. Louis, MO) in .1 M carbonate buffer (pH 9.6) or left uncoated to serve as controls. After incubation at 37 °C for 1 h, all wells were washed and blocked by incubation with 1% bovine serum

albumin (BSA) in PBS containing .05% Tween-20 (PBST) for 1.5 h at room temperature. Samples were diluted at 1:200, added at 50 μL/well in duplicate, and incubated for 1 h. After washing, the wells were incubated with HRP-conjugated anti-human IgA (MP Biomedicals, Santa Ana, CA) for 50 min. The plates were washed and 50 μL of developing solution, containing 27 mM citric acid, 50 mM Na2HPO4, 5.5 mM o-phenylenediamine, and 0.01% H_2O_2 (pH 5), was added to each well. After incubating the plates at room temperature for 20 min, absorbance was measured at 450 nm. All samples were tested in duplicate. Absorbance values were corrected for non-specific binding by subtraction of the mean absorbance of the associated uncoated wells.

In order to allow for the comparison of different assays, the results were converted to plate adjusted z-scores based on the mean and standard deviation of a control population measured on each assay plate using procedures similar to those which have been previously described (Dickerson et al., 2014b).

2.5. Statistical analysis

The correlations among the markers were determined by the calculation of Pearson correlation coefficients.

The four groups (three groups of psychiatric participants based on suicide attempt history and the control group) were compared on demographic and clinical variables by analysis of variance (ANOVA) for continuous variables or chi-square for dichotomous or categorical variables. For variables obtained in the psychiatric participants only, comparisons were among the three psychiatric groups. Relevant post hoc analyses were performed with the method of Sidak.

The associations between suicide attempt status/timing and the levels of immune markers were analyzed in multinomial logistic regression models using the control group as the reference group. Covariates included in all of the models were age, gender, race; also included were current cigarette smoking and body mass index (BMI) as these factors might alter the levels of inflammatory markers (Liu et al., 2011).

In order to adjust for psychiatric variables not assessed in the control group, we performed additional multinomial regressions using the psychiatric group with no lifetime history of a suicide attempt as the reference group and adjusting also for psychiatric symptom severity (total BPRS score) and receipt of antipsychotic medication.

All statistical analyses were performed using STATA Version 11.0, College Station Texas.

3. Results

3.1. Participant characteristics

The study sample consisted of a total of 282 participants: 90 with schizophrenia, 72 with bipolar disorder, 48 with major depressive disorder, and 72 non-psychiatric controls. As shown in Table 1, a total of 20 (10%) of psychiatric participants had made a suicide attempt in the past one month, 95 (45%) in their lifetime but not in the previous one month, and 95 (45%) had no history of any suicide attempt. Within the group who had an attempt in the past one month, 8 had an actual attempt, 10 had an aborted attempt, and 5 had an interrupted attempt; 3 persons had attempts in more than one category. The groups differed significantly on demographic and clinical variables including age, gender, diagnosis, and BMI. Of note, the psychiatric groups categorized by suicide history did not differ significantly in terms of symptom severity as measured by the BPRS. All psychiatric participants were in psychiatric treatment and receiving at least one psychotropic medication at the time of the study visit; the groups categorized by suicide history differed in terms of current receipt of any antipsychotic medication but not differ in receipt of an antidepressant, lithium, or other mood stabilizer; receipt of any antipsychotic medication was therefore included as a covariate in the analyses within the psychiatric

patients. The specific diagnoses and classes of medications received by participants at the time of the study visit are shown in Supplemental Tables 1 and 2.

3.2. Distributions of and correlations among the markers

Histograms showing the distribution of the markers for each of the study groups are presented in Supplemental Fig. 1a–d. The markers were not significantly correlated with each other except the level of IgA ASCA antibodies and the level of IgA LPS antibodies ($r = 0.34$, $p < 0.001$) suggesting a general increase in IgA antibody production; the level of IgA ASCA antibodies was also modestly correlated with the level of CRP ($r = 0.19$, $p = 0.022$) as has been previously reported (Lakatos et al., 2011).

3.3. Associations between immune markers and suicide attempt history

As depicted in Fig. 1, we found a statistically significant difference between the recent attempters and the control group in levels of IgA ASCA (coefficient = 1.81; 95% CI 0.59, 3.03; $p = 0.004$ adjusted for age, gender, race, smoking status, and BMI); the level in the recent attempt group was significantly higher. We did not find a difference in this marker between either of the other groups (those with no attempt history; those with a lifetime, but not a recent, attempt) and the control group (both $p > 0.05$).

We also found that the level of IgG antibodies to gliadin was significantly higher in the recent attempters vs. the control group (coefficient = 0.79; 95% CI 0.17, 1.40; $p = 0.012$ adjusted for age, gender, race, smoking status, and BMI); there was not a significant difference for either of the other groups ($p > 0.05$).

We also found that the level of IgA antibodies to bacterial lipopolysaccharide (LPS) was significantly higher in the recent attempters vs. the control group (coefficient = 1.16; 95% CI 0.20, 2.13; $p = 0.019$ adjusted for age, gender, race, smoking status, and BMI); there was not a significant difference for either of the other groups ($p > 0.05$).

In the analyses within the psychiatric groups only, we found that one of these markers, levels of IgA ASCA remained significantly higher in the recent attempter group when compared to the never attempter group when adjusting additionally for psychiatric symptom severity and receipt of antipsychotic medication (IgA ASCA, coefficient = 1.99; 95% CI 0.60, 3.38; $p = 0.005$). For the other two markers, anti-gliadin IgA and anti-LPS IgA, the difference between the recent attempter and the no attempter group was not significant when including these covariates.

In terms of CRP, we found that there was a significantly higher level in the past attempter group (coefficient = 0.87, 95% CI 0.25, 1.50, $p = 0.006$) compared with the control group but not in the other two psychiatric groups ($p > 0.05$) when adjusting for age, gender, race, smoking status, and BMI.

4. Discussion

In this study we found elevations in markers of gastrointestinal inflammation in individuals with a psychiatric disorder who had made a recent suicide attempt as compared to control individuals without a psychiatric disorder. On the other hand, these markers were not significantly increased in individuals with a psychiatric disorder who had no history of a suicide attempt or who had a history of an attempt in the past but not in the previous one month. Our findings suggest that gastrointestinal inflammation may be associated with a recent suicide attempt and should be explored as a predictive marker for such attempts. We did not find a specific association between levels of CRP and a recent suicide attempt history. It is of note that increased levels of suicidal thoughts and number of suicide attempts have been found in some populations of individuals with inflammatory bowel diseases

Table 1
Clinical characteristics of study sample (N=282).

	Psychiatric participants (*n* = 210)			Non-psychiatric controls (*n* = 72)
	History of suicide attempt past month (*n* = 20)	History of suicide attempt in lifetime, but not past month (*n* = 95)	No history of any suicide attempt (*n* = 95)	
Age (years)[*]	37.0 ± 14.7	39.3 13.2	35.4 13.4	33.1 ± 11.4
Gender (female)[*]	13 (65%)	44 (46%)	41 (43%)	46 (64%)
Caucasian (white)[*]	14 (70%)	54 (57%)	56 (59%)	24 (33%)
Maternal education (years)	13.2 ± 3.1	13.5 ± 3.1 (n=90)	13.9 ± 3.1 (n=94)	13.8 ± 2.6
Diagnostic group[**]				
1. Schizophrenia	1 (5%)	50 (53%)	39 (41%)	–
2. Bipolar Disorder	6 (30%)	29 (31%)	37 (39%)	
3. Major Depressive Disorder	13 (65%)	16 (17%)	19 (20%)	
BPRS symptoms score[a]	50.8 ± 6.4	50.0 ± 7.9	48.1 ± 8.7	
RBANS cognitive score[b][*]	79.2 ± 12.5	69.9 13.5 (n=94)	71.5 13.2	82.9 ± 11.9
Current smoker[*]	5 (25%)	51 (54%)	31 (33%)	10 (14%)
Body Mass Index BMI[**]	29.2 (± 4.6)	32.1 (± 9.5)	30.7 (± 8.7)	28.1 (± 7.3)
History of alcohol/drug use[**]				
1. No history	6 (30%)	8 (8%)	23 (24%)	–
2. Past history but not recent	7 (35%)	65 (68%)	59 (62%)	
3. Recent misuse	7 (35%)	22 (23%)	13 (14%)	
Care setting[**]				
1. Inpatient	18 (90%)	43 (45%)	43 (45%)	–
2. Day hospital	1 (5%)	10 (11%)	16 (17%)	
3. Outpatient	1 (5%)	42 (53%)	36 (38%)	
Receipt of antipsychotic medication[**]	7 (35%)	84 (88%)	76 (80%)	

[a] Brief Psychiatric Rating Scale (BPRS).

[b] Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

[*] Significant difference among all groups. Age, $F=3.32$, $p=0.020$, post-hoc significant difference -controls vs. past attempt but not last month; Gender, chi2=9.53, $p=0.023$, post-hoc significant difference – controls vs. no attempt history; Caucasian race, chi2=15.4, $p=0.002$, post-hoc significant differences – controls vs. all psychiatric groups; RBANS, $F=16.72$, $p < 0.001$, post-hoc significant differences - controls vs. no attempt history and vs. past attempt but not last month, recent attempt vs. past attempt but not last month; Current cigarette smoking, chi2=30.0, $p < 0.001$, post-hoc significant differences - controls vs. no attempt history and vs. past attempt but not last month; Body mass index, $F=3.23$, $p=0.03$.

[**] Significant difference among psychiatric groups. Diagnosis (chi^2=318.7, $p= < 0.001$); Care setting (chi^2=16.6, $p= < 0.001$); History of drug/alcohol use, chi^2=16.2, $p=0.003$; Receipt of antipsychotic medication, chi^2=29.0, $p < 0.001$, post-hoc significant differences - recent attempt vs. both other groups.
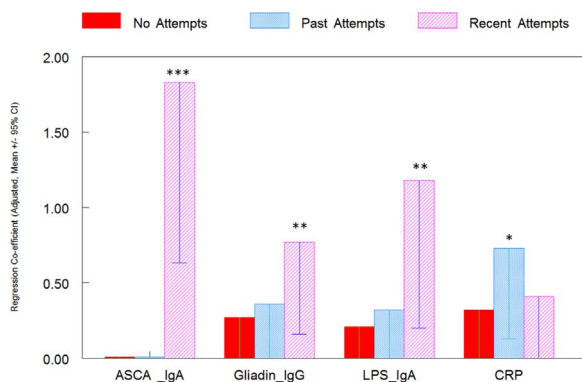

Fig. 1. Association between suicide attempt status and levels of markers of gastrointestinal inflammation and CRP in patients with serious mental illness (N=210). Legend to figure. Reference group is $n=72$ non-psychiatric controls; No attempt group, n=95; Past attempt group, n=95; Recent attempt group, n=20. ASCA= antibodies to Saccharomyces cerevisiae; LPS= lipopolysaccharide; CRP= C-reactive protein; analyses adjusted for age, gender, and race; *** $p < 0.005$, ** $p < 0.02$, * $p < 0.05$. Covariates were age, gender, race, cigarette smoking, and BMI.

([Carson et al., 2014; Fuller-Thomson and Sulman, 2006; Gradus et al., 2010; Triantafillidis et al., 2002](#)).

Whether gastrointestinal inflammation precedes suicide attempts or is signaling a recent suicide attempt needs to be sorted out in future prospective studies. Similarly, whether gastrointestinal inflammation leads to or follows alterations in mood and behavior is not known but may involve the transmission of neuroactive signals though the blood brain barrier or alterations in the gut-brain axis ([Severance et al., 2015](#)). Signaling pathways which have been identified in this context include those involving toll-like receptors, a class of proteins that play a key role in the innate immune system and which respond to microbial products generated in the gastrointestinal tract and can interact with brain pathways and alter the levels of dopamine and other neurotransmitters ([Garcia Bueno et al., 2016](#)).

The markers of gastrointestinal inflammation are of interest because they can be readily measured in blood samples. In addition, some of the markers studied here may be an attractive target for therapeutic intervention since intestinal inflammation can be modulated by dietary interventions as well as the administration of available prebiotic, probiotic, and antibiotic medications.

Our study had a number of limitations. We did not assess all of the clinical factors which may increase the risk for suicide, such as acute and chronic stress exposures and life adversity and we cannot be fully certain that the increased inflammatory markers are indicators of increased risk of suicidal behavior rather than of an underlying condition. In addition, the sample size was too small to calculate predictive values of the measures or to include in our analyses clinical factors which may also be associated with a recent suicide attempt such as drug and alcohol misuse and we cannot rule out the possible confounding effects of psychiatric medications. Also, due to the exploratory nature of our study we did not adjust for multiple comparisons. In our analysis, we combined different types of attempts, not just actual attempts which may be more proximate to death by suicide than aborted or interrupted attempts. We note also that participants with major depressive disorder are disproportionately represented in the recent suicide attempt group; this imbalance may reflect our recruitment procedures which were largely in the inpatient and day hospital setting. Another limitation is that for participants who attempted suicide in the course of their lifetime but not in the previous one month, we do not know the duration of time since their most recent attempt. Strengths of our study include a focus on those who had made

a recent suicide attempt rather than only those with a lifetime attempt history. In addition, we measured blood-based markers that have not been investigated previously in terms of their relationship with suicide behavior.

Suicide, for which a previous suicide attempt is the greatest risk factor, is a major cause of death worldwide and is highly prevalent in patients with serious mental illness. Unfortunately, the ability to predict suicide remains limited and no reliable biological markers are available. The identification of blood-based markers should provide for more personalized methods for the assessment and treatment, and ultimately prevention, of suicide attempts in individuals with serious mental illnesses.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2017.05.005.

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