Research report

Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts

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ABSTRACT

Background: Anecdotal reports of mood disorder following infection with common respiratory viruses with neurotropic potential have been in existence since the last century. Nevertheless, systematic studies on the association between these viruses and mood disorders are lacking.
Methods: Influenza A, B and coronavirus antibody titers were measured in 257 subjects with recurrent unipolar and bipolar disorder and healthy controls, by SCID. Pearson's χ^2 tests and logistic regression models were used to analyze associations between seropositivity for coronaviruses, influenza A and B viruses and the following: a) history of recurrent mood disorders b) having attempted suicide in the past c) uni- vs. bi-polarity and d) presence of psychotic symptoms during mood episodes.
Results: Seropositivity for influenza A ($p = 0.004$), B ($p < 0.0001$) and coronaviruses ($p < 0.0001$) were associated with history of mood disorders but not with the specific diagnosis of unipolar or bipolar depression. Seropositivity for influenza B was significantly associated with a history of suicide attempt ($p = 0.001$) and history of psychotic symptoms ($p = 0.005$).
Limitations: The design was cross-sectional. Socioeconomic factors, inflammatory markers, and axis II psychopathology were not assessed.
Conclusions: The association of seropositivity for influenza and coronaviruses with a history of mood disorders, and influenza B with suicidal behavior require replication in larger longitudinal samples. The need for these studies is additionally supported by the high incidence of these viral infections, the high prevalence of mood disorders, and resilience of suicide epidemics.

1. Introduction

Mood disorders are expected to be the second leading cause of global disease burden by the year 2030 (Lopez and Mathers, 2006). An estimated 20.9 million American adults (representing 9.5% of the population ages 18 and above) suffer from a mood disorder (Kessler et al., 2005). In addition, the risk of attempting suicide is significantly higher in individuals with a diagnosis of a mood disorder (Beautrais et al., 1996; Mann, 2003). Past suicide attempts are the most important predictor of completed suicide (Haukka et al., 2008). Epidemiologically, a highly replicated seasonal peak of suicide in spring (Postolache et al., 2010), with a greater amplitude in individuals with a history of mood disorders, follows or overlaps with seasonal peaks in epidemics

of upper respiratory viruses and related immune responses (Nelson et al., 2005). The development of services to prevent suicide hinges on an understanding of the interplay of factors and agents involved in the pathogenesis of mood disorders and suicidal behavior.

Interest in the potential link between common respiratory viruses and mood disorders dates far back as the late 19th century. For instance, Tuke (1892) in his *Dictionary of Psychological Medicine*, described 18 cases of post-influenza mania and depression–all admitted to the Bethlem Hospital in London. Harrison (1958) described a series of 37 cases of post-influenza depression in Kent, England. Influenza has also been reported to be associated with the onset of a manic episode in individuals with no previous history of mental illness (Steinberg et al., 1972; Maurizi, 1985). These case reports notwithstanding, there is still a need to systematically examine the possible relationship between neurotropic respiratory viruses, mood disorders and suicide attempts.

Coronaviruses are negatively stranded RNA viruses which commonly cause respiratory infection in the United States (Kahn, 2006). Coronaviruses may also be capable of replication within the central nervous system of some individuals, as evident by the presence of RNA in the brains of patients with multiple sclerosis (Arbour et al., 2000; Dessau et al., 2001). The recent development of assays for the measurement of antibodies to prevalent strains of coronaviruses allows for the study of coronavirus exposure and the linkage of this exposure to diseases. Most recently, coronavirus exposure has been implicated in neuropsychiatric diseases including recent onset of psychosis (Severance et al., 2009).

In an attempt to understand the mechanism by which influenza and coronaviruses could be associated with mood disorders, two pathophysiologic mechanisms worth considering are: (a) the viruses directly affect the brain, and/or (b) the immune response to the viruses affects the brain. Furthermore, one could speculate that the viruses or the immune response to the viruses may create a vulnerability to triggers of depression or suicide in some.

It is important to advance the knowledge and understanding of the potential association of neurotropic respiratory viruses with mood disorders considering the high prevalence and functional incapacitation due to mood disorders, and the very high incidence of respiratory infections. For instance, an estimated 5–20% of the US population suffers a new influenza virus infection annually (CDC, 2009). In this current study we evaluated associations between seropositivity for coronaviruses, influenza A and B viruses, and the following: (a) history of mood disorders, (b) having attempted suicide in the past, (c) uni- vs. bi-polarity and (d) presence of psychotic features in mood disorders. We hypothesized that seropositivity will be associated with a history of mood disorders and suicide attempts, as well as the presence of psychotic features during past or current episodes of mood disorders.

2. Methods

2.1. Study participants

The sample included a total of 257 subjects (aged 18 to 65, 95 male, 162 female) for the present study. 39 (15.2%) of these subjects were healthy normal controls. These participants were previously recruited into two primary studies of environmental influences on exacerbation of mood disorders and suicidal behavior. Written informed consent was obtained from all participants. The original studies and the amendment for the current analysis were approved by the Institutional Review Boards of the University of Maryland, Johns Hopkins University and the Sheppard Pratt Health System. All 257 subjects underwent the Structured Clinical Interview for DSM-IV Disorders (SCID) (Basco, 2003). Patients had to meet criteria for major depressive or bipolar disorders and they were excluded if they met criteria for substance dependence, cognitive disorders, or primary psychotic disorders. Suicide attempts were recorded using the Columbia Suicide History Form (Oquendo et al., 2003).

2.2. Serological analysis

IgG class antibodies to influenza A virus H3N2, influenza B virus, and the NL63 strain of human coronaviruses were measured using previously described enzyme immunoassay procedures. Positivity was defined as the generation of a signal greater than that of a standard seropositive sample (Severance et al., 2008).

2.3. Statistical analysis

Statistical analysis was carried out using SAS, version 9.1 (SAS Institute Inc, Cary, NC) and all significance levels reported were two-sided with $p < 0.05$ considered statistically significant. Pearson's χ^2 tests and one-way ANOVA were used to compare groups defined by prior suicide attempts, history of mood disorder without suicide attempt(s), and control. χ^2 tests were used to evaluate relationships between seropositivity for influenza and coronaviruses and the history of mood disorders, suicide attempts, and the presence of psychotic symptoms during mood episodes. Logistic regression models, adjusted for age and gender, were developed to estimate odds ratios with confidence intervals comparing seropositive vs. seronegative subjects on being diagnosed with mood disorders, attempting suicide and experiencing psychotic symptoms.

3. Results

3.1. Demographic and viral seropositivity characteristics

Table 1. depicts demographic and viral seropositivity characteristics of the participants. There were no age, racial or gender differences between participants in the control, history of mood disorder without suicide attempt, and prior suicide attempts groups. A greater percentage of individuals in the mood disorder and suicide attempts groups were seropositive for influenza A ($p = 0.006$), influenza B ($p < 0.0001$) and coronavirus ($p < 0.0001$) in comparison to healthy controls.

3.2. Seropositivity and diagnosis of mood disorders

χ^2 tests revealed statistically significant associations between seropositivity for influenza A ($p = 0.004$), influenza B ($p < 0.0001$), coronaviruses ($p < 0.0001$) and the diagnosis of a major depressive disorder (Table 2). Logistic regression analysis revealed that in this population sample, the odds of

Table 1
Demographic and viral seropositivity characteristics of the study groups ($n = 257$).

Characteristics	Normal controls ($n = 39$)	Major depression ($n = 117$)	Suicide attempted ($n = 99$)	p-value [a]
Age, years (mean ± SD)	42.7 ± 11.0	43.4 ± 10.9	40.3 ± 9.8	0.10
Race white, n (%) vs. other	28 (71.8)	65 (54.6)	60 (60.6)	0.16
Gender male, n (%)	13 (33.3)	43 (36.1)	39 (39.4)	0.78
Influenza A positive, n (%)	25 (64.1)	102 (87.2)	79 (79.8)	0.006
Influenza B positive, n (%)	28 (71.8)	108 (92.3)	96 (97.0)	<0.0001
Coronavirus positive, n (%)	16 (41.0)	98 (86.7)	79 (79.8)	<0.0001

[a] χ^2 test for categorical variables, ANOVA for continuous variables.

having a history of mood disorder were increased with seropositivity for influenza A (OR = 1.71, CI 1.18 to 2.50), influenza B (OR = 2.65, CI 1.65 to 4.25) and coronaviruses (OR = 2.72, CI 1.88 to 3.94) (Table 3).

However the presence of antibodies to these viruses was not associated with the polarity of the mood disorder, i.e. unipolar vs. bipolar (influenza A, $p = 0.30$, influenza B, $p = 0.60$, coronaviruses, $p = 0.80$).

3.3. Seropositivity and suicide attempt

Among individuals with a history of mood disorder, seropositivity for influenza B was significantly associated with a history of suicide attempt(s) ($p = 0.001$) (Table 2), and the odds of having attempted suicide were increased in influenza B seropositive individuals (OR = 2.53, CI 1.33 to 4.80) (Table 3). There was no evidence of an association between seropositivity for influenza A or coronaviruses and a history of suicide attempt(s) ($p = 0.77$, $p = 0.21$).

3.4. Seropositivity and psychotic symptomatology

In addition, seropositivity for influenza B was significantly associated with the presence of a history of psychotic

symptoms in mood disorder patients ($p = 0.005$) (Table 2). The odds of experiencing psychotic symptoms during mood episodes were increased (OR = 2.63, CI 1.23 to 5.64) in influenza B seropositive individuals compared to those that were seronegative. There was no evidence of an association between seropositivity for influenza A or coronaviruses and a history of psychotic symptoms ($p = 0.94$, $p = 0.41$) (Table 2).

4. Discussion

Our study adds to the sparse literature on the association of respiratory neurotropic viruses with mood disorders, and is to our knowledge, the first one to investigate the possible connection between these viruses and suicidal behavior. We confirmed our hypothesis that seropositivity for any of the three respiratory viruses was associated with a history of a mood disorder. However, only influenza B was associated with a history of suicide attempt as well as a lifetime history of psychotic symptoms in patients with mood disorders.

Both influenza and coronaviruses are RNA viruses. The three known types of influenza viruses are designated A, B and C. Types A and B are able to cause an epidemic outbreak while type C only causes mild illness in immunocompetent individuals (Butel, 2007). It has been estimated that up to 20%

Table 2
Associations of influenza and coronavirus seropositivity with patient characteristics.

Characteristic	Influenza A seropositive, n (%)	p [a]	Influenza B seropositive, n (%)	p [a]	Corona virus seropositive, n (%)	p [a]
Gender		0.98		0.003		0.18
Male ($n = 94$)	76 (80.9)		92 (97.9)		77 (81.9)	
Female ($n = 161$)	130 (80.8)		140 (87.0)		117 (74.5)	
Race		0.12		0.31		0.11
Non-white ($n = 103$)	88 (85.4)		96 (93.2)		84 (82.4)	
White ($n = 152$)	118 (77.6)		136 (89.5)		110 (73.8)	
Major depression		0.004		<0.0001		<0.0001
Yes ($n = 216$)	181 (83.8)		204 (94.4)		177 (83.5)	
No (control, $n = 39$)	25 (64.1)		28 (71.8)		16 (41.0)	
Suicide attempt (depressed only)		0.77		0.001		0.21
Yes ($n = 99$)	79 (79.8)		96 (97.0)		79 (79.8)	
No ($n = 124$)	97 (78.2)		104 (83.9)		87 (72.5)	
Diagnosis		0.30		0.60		0.80
Unipolar ($n = 109$)	94 (86.2)		102 (93.6)		90 (84.9)	
Bipolar ($n = 105$)	85 (81.0)		100 (95.2)		87 (83.7)	
Psychotic symptoms		0.94		0.005		0.41
Yes ($n = 74$)	58 (77.3)		73 (97.3)		58 (78.4)	
No ($n = 123$)	98 (77.8)		107 (84.9)		90 (73.2)	

[a] χ^2 test.

Table 3
Adjusted [a] odds ratios for psychiatric characteristics by influenza and corona virus seropositivity, from logistic regression analyses.

Variable	Influenza A			Influenza B			Corona Virus		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Mood dd vs. control	1.71	1.18, 2.50	0.005	2.65	1.65, 4.25	<0.0001	2.72	1.88, 3.94	<0.0001
suicide attempt ≥1 vs <1	1.09	0.77, 1.51	0.65	2.53	1.33, 4.80	0.005	1.25	0.90, 1.73	0.18
Bipolar vs. unipolar	0.82	0.57, 1.20	0.31	1.11	0.61, 2.01	0.74	0.92	0.63, 1.35	0.68
Psychotic symptoms yes vs. no	0.99	0.70, 1.41	0.97	2.63	1.23, 5.64	0.01	1.16	0.81, 1.66	0.40

[a] Adjusted for age and gender.

of children and 5% of adults worldwide experience symptomatic influenza infection annually (Nicholson et al., 2003). Until recently, coronavirus infection mainly presented as the "common cold" and usually had no long term sequelae. However, since 2002, cases have been reported of a severe atypical pneumonia (severe acute respiratory syndrome) due to a novel coronavirus (Levinson, 2008).

The immune response to influenza and coronaviruses involves cell-mediated immunity, antibody-mediated immunity, local production of antibodies, interferon and other host defenses. In addition, systemic symptoms are felt to be related to the production of cytokines including tumor necrosis factor-α, interleukin 6 and 8, and interferon-α (Dolin, 2008; Miura and Holmes, 2009).

At the pathogen-immune system-brain interface, it is important to understand the similarities and differences between sickness behavior (Dantzer, 2001; Dantzer et al., 2008) and clinical depression. Symptoms such as fatigue, sleep disturbance, appetite disturbance, decreased social interaction and loss of interest in usual activities are seen in both clinical depression and sickness behavior related to viral infections (Vollmer-Conna, 2001). Clinically, however, the core psychological symptoms of depression (hopelessness, worthlessness, pessimism and guilt) would be more typical of depression than sickness alone (Gelder et al., 2001).

It is not clear whether the viruses themselves or the immune response to them are the main culprit in potentially leading to mood disorders. In addition to the pathogen-immune–depression connection, it is useful to conceptualize viral infection (with the resulting immune activation) as a form of stress. Some evidence suggests that inappropriate regulation of stress may be involved in the pathogenesis of depressive illness (Gold et al., 1995). Furthermore, the dysregulation of stress linked to the pathogenesis of depressive illness most likely results from a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis (Arborelius et al., 1999; Marques-Deak et al., 2005). An activated HPA axis has also been implicated in individuals who committed suicide–a finding that seems to be further corroborated by the observation of hyperplastic adrenals in suicide victims (Hiroi et al., 2001). Of interest is the fact that interleukins 1 and 6, and TNF-α (cytokines involved in the immune response against influenza) enhance HPA activation (Besedovsky et al., 1986; Besedovsky et al., 1991; Wang and Dunn, 1998; Licinio and Wong, 1999). Interferon-α is also involved in the immune response and a well recognized side effect of this cytokine is the induction of depressive disorder (Capuron et al., 2009).

Cytokines have also been reported to cause a depletion of tryptophan (a precursor amino acid for serotonin synthesis). They stimulate indoleamine 2,3-dioxygenase (IDO) which converts tryptophan to kynurenine (Vollmer-Conna, 2001; Wichers and Maes, 2002) making tryptophan unavailable for serotonin synthesis. There is evidence that reduced tryptophan, and ultimately serotonin, play a role in the pathogenesis of depressive disorders (Dursun et al., 2001).

In exploring the possibility that the viruses could have directly affected the brain to induce a mood disorder, it is worthy to note the fact that both influenza and coronaviruses are potentially neurotropic and have been isolated from the central nervous system (Arbour et al., 2000; Dessau et al., 2001; McCullers et al., 1999; Fujimoto et al., 1998; Xu et al., 2005; Yeh et al., 2004). Maurizi (1985) postulated that direct invasion of the brain (the locus ceruleus) by the influenza virus could have resulted in a manic episode in a 44-year old physician presented in his case report. The study by Zhilinskaya et al. (2002) demonstrated that the M-protein of influenza exerted a depressive effect on the behavior of experimental animals, the effect being observed after a latent period. The authors proposed that the latent period could be the time taken for M-protein to cross the blood-brain barrier. However, both respiratory viruses as well as molecular and cellular mediators of inflammation may take a privileged naso-cortical path that bypasses the blood brain barrier (Tonelli and Postolache, 2010).

Study of cases of influenza encephalitis revealed very little evidence that the neurological complications of influenza are due to the direct effects of the virus (Whitlock, 1982); the evidence supports mediation by immune responses. Perivascular demyelination observed in fatal cases also supports this view (Lishman, 1997). Furthermore, if mood symptoms are due to direct effects of the viruses on the brain, then one would expect that a significant proportion of mood disorder patients would have experienced some symptoms of encephalopathy during the acute CNS invasion phase. This does not appear to be the case in this sample. However, it could be that the individuals with mood disorders were already predisposed, and the presence of the viruses or the immune reaction to them, triggered the mood disorder.

We measured antibodies to the NL63 strain of coronaviruses, which is most commonly associated with respiratory symptoms. A recent serological study documented an increased level of antibodies to this strain of coronaviruses in individuals with the recent onset of psychosis (Severance et al., 2009). This strain also shows substantial cross-reaction with other strains of coronaviruses which can infect the respiratory tract and the central nervous system. It is of note that in the present study a strong association was found with influenza B virus, which has also been associated with decreased cognitive functioning following fetal exposure (Ellman et al., 2009) as well as viral encephalopathy in children (Matsubara et al., 2007).

4.1. Limitations

Our study has a number of limitations that would have to be better addressed in future projects. The first limitation relates to the cross sectional nature of the study. Data collection was carried out at one time point and therefore it is not clear whether influenza or coronavirus infection occurred before, after, or during the onset of the depressive episodes. Consequently, the direction of causality cannot be inferred. Second, possible mediators and confounders such as socioeconomic factors, inflammatory markers, and patients' axis II psychopathology were not assessed. For participants with history of mood disorder, the number of depressive episodes, hospitalizations, age of onset, presence of rapid cycling, comorbid bulimia and cyclothymic temperament (Azorin et al., 2009) were not assessed. In addition, the relatively small sample size makes adjustment for all these potential confounders impractical.

4.2. The implications

If the findings from our study are replicated and an infection-to-mood rather than mood-to-infection causality direction is estimated in future longitudinal studies, a more aggressive prevention and treatment of neurotropic respiratory viruses might be advocated for patients with mood disorders. In addition, individuals with identifiable risk factors for suicidal behavior recovering from these viral infections might have to be monitored more closely. The threshold for intervention (pharmacologic and non-pharmacologic) following the appearance of symptoms of depressive disorder might also be lower for such individuals. The possibility of the use of prophylactic antidepressant medication for a brief time (as in Capuron et al., 2003), or an increase in the standing dose of antidepressants in treated patients at risk might represent a possible logical aim for a future clinical study. Finally, studies designed to elucidate the underlying biological mechanisms of the association between the viruses and mood disorders could lead to the discovery of new treatment targets and agents.

In conclusion, our results suggest an association between seropositivity for influenza and coronaviruses, and a history of mood disorders. In addition, seropositivity for influenza B was associated with suicidal behavior and psychotic features. Replicating our results in larger samples with longitudinal follow-ups may have potential public health relevance, especially in the context of the ongoing flu pandemic.

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