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A commentary revisiting the viral hypothesis of schizophrenia: Onset of a schizophreniform disorder subsequent to SARS CoV-2 infection

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ABSTRACT

The viral hypothesis for schizophrenia has persisted for decades, initially supported by observed increases in psychoses subsequent to the influenza pandemic of the early twentieth century, and then later by evidence of elevated viral antibody titres particularly in schizophrenia patient populations. Several research studies have also focused on maternal infections during the second trimester of pregnancy and their long-term effects on fetal brain development, ultimately leading to schizophrenia. No specific virus has been implicated although a handful have received increasing attention. The current pandemic spreading the SARS CoV-2 corona virus world-wide is now showing anecdotal evidence of psychoses newly developing post viral exposure, implicating neuronal inflammation in crucial areas of the brain that could initiate psychotic symptoms. Time will tell if epidemiological data will, similar to the 1918 influenza pandemic, show that schizophrenia spectrum disorders increase after serious viral infections.

INTRODUCTION

A viral hypothesis for at least some schizophrenia (dementia praecox) has been fiercely debated for almost a century and supporters are divided among those who focused on viruses directly causing the illness and those who focused on prenatal viral infection putting the developing offspring at risk for schizophrenia. Menninger (1994) is known for his observations of an increase in psychoses subsequent to the 1918-1920 influenza pandemic, and many investigators since, most notably EF Torrey and his colleagues (Torrey and Peterson, 1976; reviewed in Torrey et al., 2017), but others as well (reviewed in DeLisi 1996; DeLisi and Crow, 1986), have been strong proponents of this hypothesis in general, often pursuing at great length evidence of vital particles in the brain and antibodies to viruses in blood and even CSF with both negative and positive findings (Taller et al., 1996; Tyrrell et al., 1979; DeLisi and Sarin, 1985; DeLisi et al., 1986; Dickerson et al., 2012, 2019; Yolken et al., 2004; Torrey et al 2006). Over the years maternal infections of a variety of different pathogens during particularly the 2nd trimester of intrauterine growth have been implicated, and include Measles, Herpes, Cytomegalovirus, Toxoplasmosis, and Zika (Brown and Derkits, 2010; Brown et al., 2001; Brown et al., 2012; Joob and Wiwanitkit et al., 2020; Torrey et al., 2006). Postnatal infections of Borna virus, Retroviruses, Herpes and others have been studied as well (e.g.DeLisi and Sarin, 1985; Dickerson et al., 2012, 2019; Taieb et al., 2001; Westergaard et al., 1999; Yolken, 2004). Most recent evidence from research magnetic resonance imaging (MRI) suggests the presence of inflammation in the brains of patients with schizophrenia (reviewed in Pasternak et al., 2016), despite much earlier failures to find evidence of inflammation in post-mortem studies (e.g. Falkai et al., 1999).

SARS CoV-2, the virus causing the COVID-19 current pandemic world-wide is known to cause multiple organ pathology through micro clots and inflammatory reactions along the lining of blood vessels (reviewed in Bikdeli et al., 2020). There is also evidence of its damage extending to the brain (Nath, 2020). Curiously, one of its first, commonly reported symptoms is loss of taste and olfactory sense (Cooper et al., 2020). Since the olfactory pathway connects to temporal lobes, it is not surprising that psychosis, many symptoms of which are related to temporal lobe functions, are being reported. In fact, there are several reports of olfactory deficits long noted in schizophrenia (reviewed in Moberg et al., 2014).

Thus, numerous publications have quickly been circulated of mental health issues as a result of the pandemic and *Psychiatry Research* has published their share of them (https://www.sciencedirect.com/journal/psychiatry-research/special-issue/10XG4HT9L33), but only a few have dealt with the consequences of having acquired the infection. Moreover, there are some case reports and reviews of patients with

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psychotic symptoms post-COVID-19 and others are rapidly being reported as we go to print (Caan et al., 2020; Correa-Palacio et al., 2020; D'Agostino et al., 2020; Hansen et al., 2020; Lim et al., 2020; Palomar-Ciria et al., 2020; Parra et al., 2020, Smith et al., 2020 Troyer et al., 2020). The following adds to these growing number of cases and is an example of one such patient recently admitted to our acute adult inpatient psychiatric unit.

CASE REPORT

Patient X is a 34 year old male Central American immigrant to the USA whose wife began worrying about his behavior shortly after he stayed home in isolation subsequent to having been tested positive for the SARS CoV-2 virus. While he denied having any of the symptoms of the COVID-19 virus, including loss of olfactory function, he did have headaches, and became very anxious for unknown reasons. When he returned to his job as a laborer, he was stigmatized and his colleagues were not willing to work with him. He became quite argumentative and irritable to the point that he was finally fired. He thus remained unemployed for a period of 2 months, beginning to drink heavily, sometimes up to 16 beers a day. At the end of 2 months subsequent to his positive COVID-19 test, he was picked up by police for having stolen a bottle of vodka from a liquor store. After reportedly saying some unusual delusional statements, he was brought to the Emergency Department of our local hospital for evaluation. His wife was called and began to recount a story of an escalating psychosis whereby her husband was seen as becoming excessively religious and telling her that the "world was going to end soon" and that he had a special mission to help God, but he was so scared that he was going to jump off a nearby bridge over the harbor. He admitted to these things and also hearing God speak to him and seeing things appear in the corner of his eyes. He realized that God had given him special powers to heal people and heard God say that "Christ was coming" and he would be saved from the destruction soon to come to earth. While being evaluated in the Emergency Department he requested some water which he felt was "holy" and would help him. However, when the water did not come fast enough, he began banging his head against the wall and became agitated, shouting, and had to be chemically and physically restrained. Several hours later on the psychiatric inpatient unit, he was calm, but had many somatic complaints that changed by the hour. He maintained the same delusions and speech was fast and pressured. During this time he did not have an elevated temperature or any infectious symptoms.

All laboratory evaluations were negative (i.e. Comprehensive Metabolic Panel, CK, IgM and IgG, Herpes antibodies, ANA, Thyroid hormone, SARS-CoV-2 by a nucleic acid amplification test). A CT (Computed Tomography) scan was normal. A clinical MRI scan showed a few punctate nonspecific FLAIR hyperintense foci in the right centrum semiovale, but otherwise normal. Chest X-ray was normal.

He was placed on increasing doses of risperidone up to 4mg with improvement of agitation, but not delusions. While he was no longer desperate, shouting or anxious, he still heard the voice of God and saw things that other people did not see. The patient eventually ceased speaking about God and his beliefs, was calm, scheduled for outpatient follow-up and released.

DISCUSSION

The viral hypothesis for schizophrenia has clearly re-emerged and is worth reconsidering during the current world-wide SARS-CoV-2 pandemic. Since Menninger's reports associating dementia praecox to the influenza epidemic of the early 20th Century, much has been learned about the underlying basis for schizophrenia. An inflammatory process may be associated with the origins of the illness, as highly suggested from brain imaging studies, but it is also now known that many heterogeneous genes of risk may play a role as well as many environmental conditions, such as childhood adversities and heavy marijuana use. How these come together to make people more vulnerable to the effects of a highly contagious virus is unknown. This current pandemic clearly has brought to light many disease disparities among minority and disadvantaged populations. Schizophrenia also has been known to disproportionally affect racial minorities and disadvantaged populations in western countries. Could it be then that the environmental and social determinants of health that have clearly been obvious during this pandemic have interacted with the underlying causes of schizophrenia to exacerbate its incidence? Large scale follow-up studies of the psychiatric consequences of COVID-19 will be important in order to understand whether specific unique treatments are needed for the illness and whether the course of the psychotic illness can be attenuated by specific measures that could alleviate the virus. These accumulating case reports suggest that patients who have suspected COVID-schizophreniform illness should be tested for viral antibodies and load, inflammatory markers, an MRI examining inflammation, and perhaps treated with antiviral medications and steroids to quell the inflammation.

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