

Psychomicrobiology

Viral Infections and Depression

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Introduction

We are living in the Dark Ages of health, where we are surrounded by thousands of contagious viruses, bacteria and other pathogens in the environment that use our bodies as their long-term home. Once these microbes have insinuated themselves into our metabolisms, they frequently remain there for life, where they can slowly (or sometimes rapidly) degrade our physical and mental health. Most of the time this health degradation is subtle and subclinical. We may not realize it, but even in a “healthy” individual, pathogens living in their body’s tissues will subtly reduce that person’s mental and physical faculties, so that they will never reach their complete genetic potential. Other times, the health damage wreaked by these pathogens is overt and severe, precipitating a clinical disease, much suffering, and often an early death.

Pathogenic viruses are quite common in people: Viruses like Epstein Barr virus, HHV-6 virus, Coxsackie B virus, cytomegalovirus, and parvovirus B19 are few examples of this virus. Most of these, once caught, cannot be eliminated. Our bodies are considerably overburdened with persistent viruses which often alter our physiology.

Medical research is discovering that more and more physical and mental disorders, from mild to serious, are linked to chronic low-level infections in the body tissues. It may turn out that the majority of non-genetic diseases are caused by infectious microbes.

Thus it is high time to accept that the human body does not lapse into disease on its own, but rather, the body only tends develop disease when compromised by pathogenic microbes (and of course environmental toxins).

Hence, if we manage to purge all these disease-causing microbes from our bodies, we should be able to eliminate the vast majority of common human diseases, such as clinical depression, anxiety

disorder, nervous breakdowns, burnout at work, personality problems, anorexia, autism, Parkinson’s, Alzheimer’s, bipolar, schizophrenia, multiple sclerosis, heart disease, cancers, diabetes, obesity, etc.

Depression

Depression is a state of low mood and aversion to activity that can affect a person’s thoughts; behaviour, feelings and physical well-being.¹ Depressed people may feel sad, anxious, empty, hopeless, helpless, worthless, guilty, irritable, or restless. They may lose interest in activities that once were pleasurable, experience loss of appetite or begin overeating, or experience problems in concentrating, remembering details or making decisions; and may contemplate or even attempt suicide. Insomnia, excessive sleeping, fatigue, loss of energy, aches, pains or digestive problems that are resistant to treatment may be present.²

Depressed mood is a normal reaction to certain life events, a symptom of some medical conditions (e.g., Addison’s disease, hypothyroidism) and treatments (e.g., hepatitis C drug therapy), and a feature of certain psychiatric syndromes.

Viral Infections

Human immunodeficiency virus (HIV), Hepatitis C virus (HCV), Epstein-Barr virus (EBV), Influenza virus, Herpes Simplex virus (HSV), Hepatitis B virus (HBV), Hepatitis A virus (HAV), Borna disease virus (BDV) and Human T-cell Lymphotropic virus (HTLV) are the common viruses supposed to be related with depression.

Human immunodeficiency virus

Among the psychiatric disorders most commonly seen in HIV-positive individuals, depression is the most prevalent^{3, 4}. Major depression in individuals infected with HIV appears

to be associated with factors such as stigma of the disease, direct effects of the virus and opportunistic infections in the central nervous system (CNS), and the triggering of a depressive episode in vulnerable populations such as injecting drug users (IDUs) and homosexuals.³

Prevalence of depression in HIV-infected individuals

Studies on the prevalence of depression in HIV-positive individuals showed varied results (0% to 45%). This is due to factors such as population (homosexual men, women and IDUs) assessment tool used (diagnostic interview and standardized self-assessment scales), site of the research (community and medical services) and disease stage.⁴⁻⁶ Moreover, the diagnosis of depression in HIV-infected individuals can be difficult due to: the tendency of health professionals to consider depression a normal reaction to the diagnosis of infection, the presence of somatic symptoms that complicate the differential diagnosis, the fear of some patients to express their feelings and psychiatric side effects of some anti-retroviral.

Two studies assessed the prevalence of depression in HIV-positive individuals of both sexes.^{7,8} The first study (1994) was a multicenter, controlled study that included 955 individuals (602 HIV-positive and 353 controls) from five countries (Brazil, Thailand, Zaire, Germany and Kenya). The average prevalence of depression was 7% (range 0% to 21%) in the infected group and 2% (range 0% to 8%) in the control group. The difference between the groups was not significant. The second, an uncontrolled study, showed a prevalence of depression of 29% in HIV-infected men and 35% in HIV-positive women. Both studies, however, included individuals from different populations (heterosexuals, homosexuals and drug users) and were at different stages of virus infection.

Review of studies that compared the prevalence of depression in HIV-positive individuals of both sexes showed that the prevalence in women was higher than that found in men.^{4,5} However, the prevalence of depression is higher in women than in men in the general population, regardless of status for HIV serological status.

With the prevalence of depression in HIV-infected IDUs, three controlled studies^{3,9,10} were analyzed. Two of them approached injecting heroin

users.^{9,10} The first found that the prevalence of depression in this group (11% – 27%) was higher than that found in the general population, regardless of HIV status.⁹ However, the second showed a significantly higher prevalence of depression in HIV-infected individuals compared to seronegative (36% versus 16%, $p < 0.05$).¹⁰ Most HIV-positive patients (56%), however, meet criteria for pre-acquired immunodeficiency syndrome (pre-AIDS) or AIDS clinic.

The prevalence of depression in HIV-infected IDUs (18% -36%) appeared to be higher than in HIV-positive gay men (0% -18%).

Some studies compared the prevalence of depression in different stages of HIV infection.^{7,11} Cross-sectional studies have found significantly higher prevalence of depression in symptomatic HIV-positive patients compared to asymptomatic.^{7,11}

Effects of depression on the progression of HIV infection. Some authors studied the relationship between depression and outcome of infection with HIV.¹² Although the studies were based on diverse populations but they had shown that depression is associated with a worse prognosis of infection.

Hepatitis C virus

The association between HCV and depression began to be studied in the 1990s, soon after the availability of serological tests for the virus. Two lines of evidence support this relationship. One is the fact that patients with psychiatric disorders have a higher prevalence of HCV infection than the general population. The other is the higher prevalence of psychiatric disorders in patients infected with HCV, depression being the most frequent disorder and clinically important.¹³

As in HIV infection, studies on the prevalence of depression in HCV-positive individuals had mixed results. The reasons for this variation were the same as previously reported with HIV in the work, emphasizing the psychiatric side effects of antiviral therapy based on interferon.¹³

A study of patients with terminal liver disease showed a higher prevalence of depression in HCV infection compared to the other.¹⁴ It was also observed that patients with HCV had more somatic symptoms and pain than other patients. The same authors followed a group of patients undergoing liver transplantation and found a higher prevalence of depression in those with recurrent hepatitis C

compared to those negative.¹⁵ As for some other studies on the prevalence of depression in HCV-infected military,¹⁶ it was observed that a higher prevalence of depression is found in HCV-positive military personnel compared to seronegative (49.5% versus 39.1%, $p < 0.0001$). However another study¹⁷ only found a rate of less than 40%.

In summary, existing studies on the prevalence of depression in individuals infected with HCV suggest that this is higher than in the general population. These data reinforce the hypothesis that there is an association between HCV and depression.

Epstein-Barr Virus

The association between EBV and depression was reported in the literature for over 50 years. In a pioneering study, a group of patients with infectious mononucleosis (IM), most commonly caused by EBV, was attended by more than three months, and the presence of depressive symptoms was observed in those with prolonged infection.¹⁸ Other studies reported depressive episodes after IM including severe with suicidal ideation and psychotic symptoms.^{19,21} One study showed a significant increase in the prevalence of depression in women who had IM in the previous year, but not in men. Another Canadian study reported a higher prevalence of depression in those who had IM compared with those who had other upper respiratory tract infections (URTI).²²

Prospective studies on the subject have shown conflicting results. In one uncontrolled study, the prevalence of depression in patients with IM (4.9%) was similar to that found in the general population.²³ In another study, patients with IM, EBV caused tonsillitis or upper respiratory infections were followed for six months, and found that viral infections in general were important triggering depression in the acute phase of infection.²⁴ However, another study found significantly higher prevalence of depression in individuals with IM compared to non-carriers of tonsillitis or upper respiratory tract infections caused by EBV. The average duration of depressive episodes, however, was only three weeks.²⁵

Thus we conclude that there is no study showing a direct correlation between EBV and depression and further studies are required to establish a link.

Influenza virus

The association between influenza virus and depression was first described more than one hundred years ago. A study²⁶ reported 11 cases of postpartum depression early in the influenza epidemic of 1890. Later work emphasized that the depressive episodes after influenza were mild and transient in most cases.²⁷ A study of the 1950s also reported cases of depression after this virus. In none of them, however, influenza was confirmed by serological tests. Despite the weak scientific evidence, an editorial in the *British Medical Journal* (1971) stated that outbreaks of influenza could be followed by intractable depression.

A survey of English after the editorial, however, found no greater number of psychiatric hospitalizations due to depression after influenza epidemics. Additionally, a paper that compared the prevalence of anti-influenza antibodies in depressed patients and patients with other psychiatric disorders, there was no significant difference between groups.²⁸ A survey conducted during the influenza epidemic in a general hospital has not shown a higher prevalence of depressive symptoms in patients with this specific virus compared with those who had other upper respiratory infections. However, a study in adolescents who had high titres of anti-influenza antibody prevalence of depressive symptoms showed significantly higher in patients who had symptomatic infection in the last six months compared to the asymptomatic group.²⁹ Possible explanations for this finding are the known tendency of high levels of anti-influenza antibodies persist for more than one season and the possibility that some asymptomatic individuals have subclinical infection.

In summary, there are few studies on the association between influenza virus and depression, and the results were conflicting.

Herpes simplex virus

The association between HSV and depression was reported in the literature in the 1960s and 1970s, there are no recent studies on the subject.

The first study, conducted in 1969 showed a prevalence of anti-HSV significantly higher in patients with psychotic depression compared to patients with other psychiatric disorders and controls.³⁰ Another study compared the prevalence of HSV antibodies in depressed psychotic controls

and individuals with acute infection with HSV. The psychotic depressed patients had significantly higher prevalence of HSV antibodies compared to controls. Yet individuals with acute viral infection had a higher prevalence of antibodies to HSV-psychotic depressed patients, although the prevalence had fallen six to eight weeks after infection.³¹

In another study, however, there was no significant difference in the prevalence of HSV antibodies in depressed patients compared to patients with other psychiatric disorders and controls.³² Additionally, another study showed a higher prevalence of HSV antibodies in psychiatric patients in general compared to controls.³³ Another study also noted a higher prevalence of HSV antibodies in both psychotic depressed patients and in patients with dementia compared to controls.³⁴

In summary, there are few studies on the association between HSV and depression, and the results were controversial.

Hepatitis B virus

The association between HBV and depression has been little studied so far. As mentioned in the topic Hepatitis C virus in a study that compared the prevalence of depression in individuals infected with HBV or HCV prevalence was found to be higher in HCV-positive.³⁵ In another study, the prevalence of depression was studied in patients with viral hepatitis (B or C) and in healthy controls, there was no significant difference between groups.³⁶

Hepatitis A virus

The association between HAV and depression has been described in literature, but existing jobs are old, dating from the last of 1974. In addition there have been few studies and they have presented conflicting results. A study in 1944 reported cases of soldiers who had post-hepatitis syndrome characterized by emotional instability, fatigue, and discomfort in the upper right quadrant of the abdomen, fat intolerance and malnutrition after hepatitis – A. As for emotional instability specifically, 83% of subjects had evidence of depression and anxiety. Similar findings were found by other authors.³⁷ However, one study did not find the presence of psychiatric symptoms in soldiers with post-hepatitis syndrome. A methodological

weakness common to these studies is the absence of serologic confirmation of HAV infection.

Thus, one can conclude that the association between HAV and depression has been little studied so far.

Borna disease virus

The BDV is a neurotropic virus belonging to the family Bornaviridae. The agent causes a rare type of encephalitis in horses and sheep and is endemic for over 150 years in parts of Germany and Switzerland. After experimental inoculation of BDV in laboratory animals, there was a specific neurobehavioral syndrome similar to bipolar affective disorder in humans. Although there are no reports of human diseases caused by BDV, the association between this virus and depression has been studied for nearly 20 years.

The existing studies were based on research evidence of BDV infection in depressed patients, and the results were conflicting.³⁸

Human T-cell Lymphotropic virus (HTLV)

The association between HTLV and depression has been little studied so far.³⁹⁻⁴¹ Proietti et al⁴⁰ reported the presence of depressive symptoms in individuals infected with HTLV-1, followed in open prevalent cohort of HIV-positive blood donors in a blood centre in Minas Gerais. Preliminary results of a recent study cited in the cohort suggested a higher prevalence of depression in patients with HTLV-1 compared to seronegative blood donors (45.5% versus 18.8%, $p = 0.0543$). These findings were confirmed later.^{40,41}

Correlation Between Depression and Viral Infection – The Immunological Aspect

The burden of Mood Disorders is rising both for the individual, the family, and for the society. Currently, most people who are treated for depression are partially responsive or non-responsive. New tools are needed. One of these tools involves a focus on the inflammation, immune dysfunction, and infections that are often associated with depression.⁴²

Many immunity-inflammation mediated disorders are co-morbid with depression: Heart disease, diabetes, Chron's disease, autoimmune diseases, cancers, HIV, and multiple sclerosis.

The brain and the immune system talk to each other, and the communication is bi-directional. This

means that inflammation (such as that which occurs due to infection) affects the brain. It also means that changes in brain immunity and inflammation affect the body. A meta-analysis of several studies on this issue found that several cytokines (hormones of the immune system) and markers of inflammation (C-reactive protein, interleukin 1 and 6) were positively correlated with depression.⁴³ This means the more depression there is, the more inflammation there is. Cytokines seem to trigger a quick onset of what is called 'sickness behavior'-meaning malaise and fatigue, as well as a delayed onset of depressed mood. Some studies found the same very close correlation between certain cytokines, mood, anxiety and memory.⁴⁴⁻⁴⁸

Reducing inflammation may help alleviate depression: In a randomized placebo controlled trial of a COX-2 inhibitor -celebrex-(celecoxib-blocks pro-inflammatory eicosanoids) with reboxetine (a noradrenergic-reuptake inhibitor antidepressant) augmentation with celecoxib was superior to placebo.⁴⁵

A second randomized double blind placebo controlled study showed that etanercept (a TNF-tumor necrosis factor-blocker) reduced depressive symptoms in people with psoriasis, independent of improvement in the psoriasis. This is consistent with elevated levels of plasma TNF elevations found in depressed patients.⁴⁵

Of further relevance is the fact that the core stress response system in the brain activates and regulates the adrenalin-immune connection in the body (this includes the bone marrow and the thymus gland), as well as secondary immune organs (spleen and lymph nodes). Thus, through this pathway (and there are others), stress affects immune function. On the other hand, not only do the brain stress circuits affect the immune system, but the hormones of the immune system-the cytokines referred to above are known to make the stress circuits of the brain more sensitive.

Another interesting linkage path between the immune system and the brain is the vagus nerve.⁴⁹ This nerve system, when activated, opposes the adrenalin system. When it is activated it stimulates the motivational centres in the brain directly, and through the brain's own immune cells (called microglia) increases nor-adrenalin and serotonin.

Chemicals of inflammation, the cytokines I referred to above, can be released by the brain

microglia, causing a shift in the balance between helping neurons to grow, and putting them to death. When shifted in the wrong direction, this microglia actually stop the brain from making serotonin, and in that case, any medication that works on serotonin-such as fluoxetine, sertraline etc – can not work. (This is part of the reason for 'fluoxetine poop out', and this is why I regularly tell my patients that if an anti-depressant has worked for you for 6 months, and then stops working, something else is going on.) The brain production of serotonin does not return to normal for months after an infection.

Mechanism of Action of Microbial Pathogens Causing Depression

Persistent microbial pathogens are probably major causal factors in many of cases of depression.

One mechanism that explains how such viruses cause depression is through the effects interferon-alpha: Chronic infection with any of these viruses can lead to raised interferon-alpha levels (interferon-alpha is secreted by cells of the immune system as it tries to control the virus), and it is now known that interferon-alpha can significantly affect the serotonin system.^{35,42,43,46,47}

However, this is not the only way that a persistent viral infection can cause depression. Certain types of depression originate in the hypothalamus, which can be dysregulated by viruses such as coxsackie virus B, which have a particular affinity for, and disruptive action on, the hypothalamus.^{35,43}

And another very powerful (but indirect) mechanism through which persistent viruses can cause depression is by raising glutamate and quinolinic acid levels in the brain (high glutamate levels are linked to depression). The excess glutamate/quinolinic acid in this case comes from the activated microglia cells (microglia are specialized macrophages permanently resident in the brain). When the microglia are activated in response to a persistent infection in the brain, these microglia produce lots of glutamate and quinolinic acid, which can then lead to both depression and anxiety disorders as a result of this neurochemical imbalance.^{43,48,49}

Depression can sometimes be caused by low levels of the adrenal hormone cortisol. Viruses like enterovirus often chronically infect the adrenal glands, and in doing so, can alter adrenal function,

leading to low cortisol output, thereby precipitating depression. In addition to depression, a chronic sub-clinical viral infection of the adrenal glands can also cause irregular, sudden spurts of adrenal hormone output, spurts of cortisol and adrenaline for example, and transient high levels of these two hormones can cause tachycardia. This is the probable explanation of the statistically-observed association between depression and tachycardia.⁵⁰

Thus it is quite probable that many cases of depression are ultimately viral in origin, through one or more of these mechanisms. We are just beginning to uncover the complex biochemistry behind the way pathogenic infections cause mental conditions such as depression.

Viruses and Bad Memory

When a person has a persistent viral disease like chronic fatigue syndrome, the working memory and long-term recall is often severely disrupted.^{51,52} But even viruses like the rhinovirus (a common cold virus), which are quickly cleared from the body, can damage the brain while they are active. We are generally accustomed to the idea that memory declines with age. This decline is seen as natural part of aging. But in reality, this memory deficit is likely caused by the numerous chronic and transitory viruses that infect and damage our body over the course of our lives. Again, the realization of this should be a cue to start developing new and ingenious means of eliminating these microbial attacks on our central nervous systems, thereby eliminating the resulting erosion of an individual's cognitive faculties.

Microbial Pathogens and Intelligence

Are the most intelligent, the most emotionally skillful, and mentally well-balanced people those with fewer persistent neurological microbes in their system? This hypothesis could be easily tested. In addition we could see if persistent neurological viruses, bacteria and protozoa were associated with any other undesirable personality traits, such as criminality, anti-social behavior, even extreme shyness, anger and rage problems, and other such anomalies of personality.^{53,54} It may well turn out that many of these mental characteristics have a microbial cause.

It is also worth considering a related hypothesis: that the most intelligent and/or mentally well-balanced people have a more robust immune

response, and so, even though they are exposed to the same gamut of viruses, spread though normal social contact, their central nervous systems are more protected, and thus less affected, by these often nasty pathogens.

Conclusion

Medical research is unearthing increasing evidence that pathogenic viruses, bacteria, fungi and parasites may be the cause of a huge array of serious chronic diseases, as well as being responsible for myriad milder health conditions. So really, given the deterioration in human health that pathogenic microbes likely cause, it is imperative that we find much better means to control or eradicate pathogenic microbes in our bodies.

A substantial investment into a coordinated project is required, to fully understand, control and eliminate the pathogenic microbes in our bodies.

Once we do eliminate pathogenic microbes from our bodies, there will very likely be an astonishing revolution in the human health-span, longevity, sanity, intellectual elevation, morality and happiness for the generations to come.

This should be a primary goal for the 21st century. It is a tough challenge; but human genius relishes in tough challenges.

In recent years, this imperative has also taken on a new urgency, as several factors are currently creating an unprecedented increase in infectious diseases worldwide. These factors include: globalization and cheap air travel, which allows millions to travel and thus carry new pathogens around the globe; mass urbanization, which brings people to live in crowded cities in close contact with each other; human incursion into untouched natural environments and habitats (for example, during the cutting down of rain forests) which brings humans into contact with previously unknown tropical viruses, parasites and other microbes.

Thus we conclude that the most well-informed associations found were those between depression and HIV and HCV. The relationship between depression and other viruses have minimal scientific evidence, and studies with adequate design are needed.

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