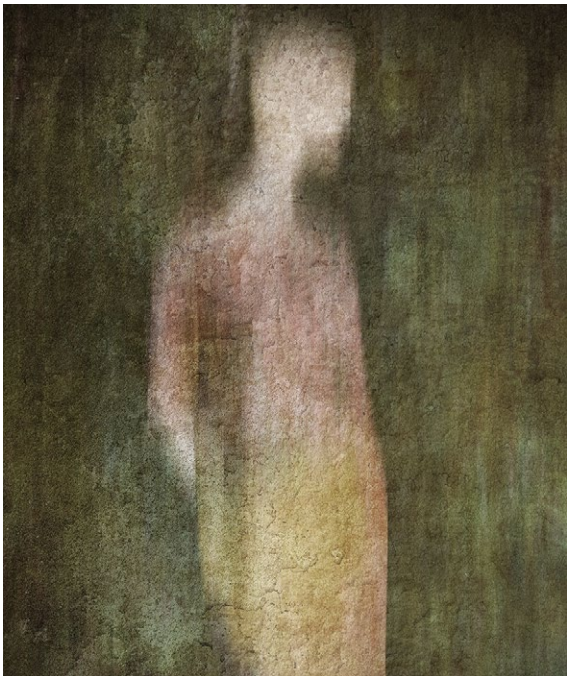
Current PSYCHIATRY

Anorexia nervosa and COVID-19

Understanding the relationship between eating disorders and infections can improve outcomes



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Recent concerns surrounding coronavirus disease 2019 (COVID-19) make it timely to reexamine the complex findings related to eating disorders and the immune system, and the risks for and detection of infection in patients with anorexia nervosa (AN) and similar disorders. To date, there are no published studies evaluating patients with eating disorders and COVID-19. However, it may be helpful to review the data on the infectious process in this patient population to improve patient communication, enhance surveillance and detection, and possibly reduce morbidity and mortality.

The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) issued warnings that individuals who are older, have underlying medical conditions, and/or are immunocompromised face the greatest risk of serious complications and death as a result of COVID-19, the disease process caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Due to malnutrition, patients with eating disorders, especially AN, may be perceived to have an increased risk of medical conditions and infection. Despite many studies on specific changes and differences in the immune system of patients with eating disorders, the consequences of these changes remain controversial and inconclusive.

This article reviews research on eating disorders, focusing on published data regarding the effects of AN on the immune system, susceptibility to infections, infectious detection, and morbidity. We also discuss clinical considerations related to COVID-19 and patients with AN.

continued

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Eating disorders and infections

Clinical Point

Patients with anorexia nervosa have increased rates of morbidity and mortality from infections

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Infection risks: Conflicting data

In a 1981 study that included 9 participants, Golla et al[1] concluded that patients with AN may have "resistance" to infections based on a suggested protective factor within the immune system of these patients. Because this study has been cited repeatedly in multiple articles about AN and cell-mediated immunity,[2-7] some clinicians have accepted this evidence of resistance to infection in patients with AN, which may lower their suspicion for and detection of infections in patients with AN.

However, studies published both before and after Golla et al[1] have shown statistically significant results that contradict those researchers' conclusion. A study that compared the medical records of 68 patients with AN with those who did not have AN found no significant difference, and concluded that the rate of infection among patients with AN is the same as among controls.[8] These researchers noted that infection rates may be higher among patients with later-stage, more severe AN. In a 1986 study of 12 patients with AN, Cason et al[9] concluded that while cellular immunity function is abnormal in patients with AN, their results were not compatible with prior studies that suggested AN patients were more resistant to infection.[1,2,8]

More recently, researchers compared 1,592 patients with eating disorders with 6,368 matched controls; they reviewed prescriptions of antibacterial, antifungal, and antiviral medications as a measure of infection rates.[10] Compared with controls, patients with binge eating disorder (BED), patients with bulimia nervosa (BN), and males with AN more often received prescriptions for antimicrobial medications. There was no statistically significant difference between controls and females with AN, which is consistent with other reports of no increased or decreased risk of infection among females with AN. In terms of antiviral use, this study showed an increased prescription of antivirals only in the BN group.

Several other studies examining the rate of infection in patients with AN concluded that there is neither an increased nor decreased rate of infection in patients with AN, and that the rate of infection in this population is similar to that of the general population.[8,10-12]

Because studies that have included patients with AN have evaluated only symptomatic viral infections, some researchers have proposed that patients with AN may show lower rates of symptomatic viral infection but higher rates of asymptomatic infection, as evidenced by higher viral titers.[6] Further research is required. Despite controversy regarding infection rates, studies have found that patients with AN have increased rates of morbidity and mortality from infections.[6,12-16]

Obstacles to detecting infections

Several factors can complicate the surveillance and detection of infections in patients with eating disorders, especially those with AN. These include:

- an accepted predisposition to infection secondary to malnutrition
- a lack of visual or reported infectious symptoms
- misrepresentation and assumptions from published research.

Clinicians who report fewer observed cases of infections among patients with AN may be overlooking comorbid disease processes due to a bias from the literature and/or a lack of awareness of symptom parameters in patients with AN.

Features of AN include a loss of adipose tissue responsible for pro-inflammatory cytokines, and excessive exercise, which stimulates anti-inflammatory myokines. This can modulate the experience of illness that impacts the core features of disease,[17] possibly reducing symptomatic presentation of infections.

Fever. The presence and intensity of fever may be altered in patients with eating disorders, especially those with AN. In a study of 311 inpatients with AN, researchers found that patients with AN had a significant delay in fever response in AN.[12] Of 23 patients with an active bacterial infection, all but 5 had a fever <37°C, with some as low as 35.5°C. A detectable fever response and unexplained fevers were found in 2 of the 6 patients with a viral infection. A series of case studies found that patients with AN with bacterial infections also had a delayed fever response.[18]

For patients with infections that commonly present with fever, such as COVID-19, a delayed fever response can delay or evade the detection of infection, thus increasing potential complications as well viral exposure to others. Thus, clinicians should use caution when ruling out COVID-19 or other infections because of a lack of significant fever.

Overlapping symptoms. The symptoms of viral infection can mimic the symptoms of AN, which further complicates screening and diagnosis of infection in these patients. Although up to 80% of individuals infected with COVID-19 may be asymptomatic or have a mild presentation, the most common reported symptoms are fever (92.6%), shortness of breath (50.8%), expectoration (41.4%), fatigue (46.4%), dry cough (33.3%), and myalgia (21.4%).[19-21] Gastrointestinal (GI) symptoms have been reported in patients with COVID-19, as well as a loss of taste and smell.

Commonly reported physical symptoms of AN include an intolerance to cold, general fatigue, muscle aches and pains, restlessness, emesis, and a multitude of GI complaints. Patients with AN also have been reported to experience shortness of breath due to conditions such as respiratory muscle weakness,[22] nutritional emphysema,[23] and anxiety and panic attack.[24] These conditions could lead to an increased susceptibility to COVID-19 and increased complications during treatment. Cardiac abnormalities, which are common in patients with AN and BN, may increase the risk of adverse events. While these symptoms may be an important part of screening for diseases such as COVID-19, suspicion of infection also may be lower because of the overlap of AN symptomology, underlying conditions, and a delayed fever response.

Laboratory findings. Laboratory testing results for patients with COVID-19 include lower lymphocyte counts, higher leukocyte counts, elevated levels of infection-related biomarkers and inflammatory cytokines, and significantly decreased T-cell counts.[19] Similar values are also found in patients with AN.

The similar clinical presentations and laboratory values of AN and COVID-19 could lead to delayed diagnosis, increased disease transmission, cross-contamination of facilities, and higher incidences of medical complications and mortality.

The immunology of AN and correlations with COVID-19

Many studies examining the immune system of patients with eating disorders, especially those with AN, have discovered changes and differences in both cell-mediated and humoral response to infections.[1,3,5,7,9,11,16,21,25-27] Whether these differences represent a dysfunctional immune system, an immunocompromised state, or even a protective factor remains unclear.

While some studies have reported that AN represents an immunocompromised state, others describe the immune system of patients with AN as dysfunctional or simply altered.[9,11,22,28] Some studies have found that patients with AN had delayed reactions to pathogen skin exposures compared with healthy controls, which provides evidence of an impaired cell-mediated immune system.[9,27,29]

Some studies have considered the consequences of infection and immunologic findings as markers of or contributing to the onset of AN.[2,30,31] Numerous studies have noted abnormalities in AN with regards to cell-mediated immunity, the humoral system, the lymphoreticular system, and the innate immune system, and potential contributions from increased oxidative stress, a chronically activated sympathetic nervous system and hypothalamic-pituitary-adrenal axis, altered intestinal microbiota, and an abnormal bone marrow microenvironment.[2]

Box 1[19,25,32-34] (***page 26***) describes some of the initial immunologic findings reported in patients with COVID-19. In ***Box 2***[5,8,11,13,14,19,26,28,35-40] (***page 27***), we discuss reports that describe the immunologic overlay of COVID-19 and AN.

Malnutrition and the immune system

Differences in the type of malnutrition observed in low-weight patients with AN may help explain why patients with AN

Clinical Point

Studies of patients with eating disorders have found differences in cell-mediated and humoral response to infections

Eating disorders and infections

Box 1

The immunology of COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new beta-coronavirus that is still being studied for its effects on the immune system. It may take years to fully understand the nature of the pathogen and the response of the human immune system. To better understand COVID-19, researchers have been turning to what they learned from the past outbreaks of severe acute respiratory syndrome (SARS) in 2003-2004 and Middle East respiratory syndrome (MERS) in 2011, both caused by beta-coronaviruses with a zoonotic origin.[25,32]

The proposed pathogenesis for infection of SARS-CoV-2 is similar to SARS and occurs when aerosolized droplets containing the virus enter the host.[32] While currently there is only initial data on the host innate immune status of patients infected with SARS-CoV-2, initial findings of a report on 99 cases in Wuhan, China included increased total neutrophils (38%), reduced total lymphocytes (35%), increased serum interleukin-6 (52%), and increased C-reactive protein (84%).[33] Additional findings were decreased percentages of monocytes, eosinophils, and basophils, as well as significantly decreased levels of cytokines and T-cells in more severe cases.[19] Past research with SARS reported similar T-cell findings, with a more frequent CD8+ response and a greater magnitude of CD4+.[34]

Clinical Point

Keep in mind that the symptoms of eating disorders may mimic an infectious process

can maintain a relatively intact cell-mediated immune system.[1] Protein-energy malnutrition (PEM), which is found in typical states of starvation, consists of deficiencies in multiple vitamins, protein, and energy (caloric content), whereas the dietary habits of patients with AN usually result in a deficiency of carbohydrates and fats.[41] Studies that examined the impact of PEM on immunity to influenza infection have suggested that balanced protein energy replenishment may be a strategy for boosting immunity against influenza viral infections.[42] However, carbohydrates are the primary nutrients for human bone marrow fat cells, which play a crucial role in the maturation of white blood cells. This may account for the leukopenia that is common in patients with AN.[6,43] The protein-sparing aspect of the typical AN diet may account for the immune system changes observed in patients with AN.[44]

Although some studies have proposed that immune deficiencies observed in patients with AN are secondary to malnutrition and return to normal with refeeding,[5,40,45] others have concluded that immune function is not compromised by factors such as nutritional status or body weight in AN.[26,43,46]

Clinical considerations

Neither the CDC nor the WHO have issued a specific protocol for monitoring for and treating COVID-19 in patients with eating disorders; however, the guidelines offered by these organizations for the general population should be followed for patients with eating disorders.

When screening a patient with an eating disorder, keep in mind that the symptoms of eating disorders, such as AN, may mimic an infectious process. Mood symptoms, such as depression or anxiety, could represent physiological responses to infection. Patients with GI symptoms that typically are considered part of the pathology of an eating disorder should be more carefully considered for COVID-19. Monitor a patient's basal body temperature, and be mindful that a patient with AN may exhibit a delayed fever response. Be vigilant for a recent loss of taste or smell, which should raise suspicion for COVID-19. When monitoring vital signs, pay careful attention for any decompensation in a patient's pulse oximetry. Whenever possible, order COVID-19 testing for any patient you suspect may be infected.

Outpatient clinicians should work closely in a collaborative manner with a patient's eating disorder treatment team. Psychiatrists, primary care physicians, psychotherapists, nutritionists, and other clinicians should all follow CDC/WHO guidelines regarding COVID-19, provide surveillance, and communicate any suspicions to the medical team. Eating disorder treatment programs, including residential centers, partial hospital programs (PHP), and intensive outpatient programs (IOP), must enhance monitoring for COVID-19, and exercise caution by

Box 2

The immunologic overlay of COVID-19 and anorexia nervosa

Leukopenia (low leukocyte levels) is a common finding in patients with anorexia nervosa (AN),[8] and often leads clinicians to lower their suspicion for infection. A 2008 Hungarian study that evaluated lymphocyte activation parameters and clinical status in 11 adolescents (10 girls and 1 boy) with AN, 12 obese adolescents, and 10 healthy controls did not find any association between the variables.[35] While many studies have focused on adults, it is important to note that leukopenia is a common finding in adolescents (age 12 to 17) with AN.[36]

Leukocyte counts are elevated in coronavirus disease 2019 (COVID-19), possibly offsetting AN's leukopenia. In addition, neutrophil counts are elevated and monocyte, eosinophil, basophil, and especially lymphocyte counts are significantly decreased. A meta-analysis that included 22 studies and 924 participants (512 with AN and 412 controls) examined common inflammatory cytokine findings in patients with AN.[11] Compared with healthy controls, patients with AN had significantly elevated levels of tumor necrosis factor alpha (TNF-alpha), interleukin (IL)-1, IL-6, and TNF-receptor II, and significantly decreased levels of C-reactive protein and IL-6 receptor. Elevated levels of TNF-alpha and IL-6 also have been reported in patients with COVID-19.[19] These findings may mask suspicion for infection in patients with AN.[19]

In patients with AN and those with bulimia nervosa, CD4+-to-CD8+ ratios also have been found to be low as a result of normal-to-higher levels of CD4+ cells and lower levels of CD8+ cells.[36-39] Researchers have also proposed that the lymphocytosis observed in AN is a result of increased naïve CD4+.[36] In AN, total lymphocyte counts have been found to correlate positively with a patient's body mass index (BMI), while the CD4+ T-lymphocyte correlated negatively with BMI and were critically low in patients with severe malnutrition.[26,40] In patients with COVID-19, CD4+ levels have reported to be within normal range, naïve CD4+ cells were elevated, and CD8+ cells were slightly decreased,[19] which is similar to the findings in AN.

Fewer studies have evaluated humoral immune response in AN, and results have varied. One study (N = 46) found elevated B-cell counts in adolescents with AN-restricting type,[36] while another (N = 40) reported normal levels of B-cells.[5] Specific decreases in immunoglobulin (Ig) G and IgM have also been reported in AN, while IgA, IgG, and IgM usually are normal in COVID-19.[19]

Despite differences in immune system function, cellular immunity appears to remain relatively intact in patients with AN, but can become compromised with severe malnutrition or with advanced weight loss.[28,40] This compromised immunity related to severe AN with a very low BMI likely leads to the increased morbidity and mortality.[8,13,14]

Clinical Point

Anxiety or depression could represent physiological responses to infection in patients with anorexia nervosa

practicing social distancing and providing adequate personal protective equipment for patients and staff. To reduce the spread of COVID-19, many IOPs and PHPs have transitioned to virtual treatment. Residential centers must carefully screen patients before admission to weigh the risks and benefits of inpatient vs outpatient care.

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Clinical Point

Be mindful that a patient with anorexia nervosa may exhibit a delayed fever response

Related Resources

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Bottom Line

Differences in the immune system of patients with an eating disorder do not necessarily confer a higher or lower risk of infection. Symptoms of some infections can mimic the symptoms of anorexia nervosa. Recognizing infections in patients with eating disorders is critical because compared with the general population, they have higher rates of infection-related morbidity and mortality.