

# Advanced Journal of Chemistry-Section B

Natural Products and Medical Chemistry

Journal homepage: http://www.ajchem-b.com/



# Original Research Article

# Symptoms and Complications of Nervous System in Patients with Mucormycosis: A Systematic Review

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#### ARTICLE INFO

#### Article history

Submitted: 2022-10-31 Revised: 2022-11-10 Accepted: 2022-11-30 Available online: 2022-12-15 Manuscript ID: AJCB-2210-1132 **DOI**:10.22034/ajcb.2022.367982.1132

#### KEYWORDS

Mucormycosis Covid-19 Complications Nervous System Symptoms

#### ABSTRACT

**Introduction:** Mucormycosis is a disease that is common in patients with a history of diabetes mellitus who have recently been infected with Covid-19, and it affects the nervous system more than other systems. This study was designed with the aim of examining the symptoms and complications of the nervous system in patients with mucormycosis.

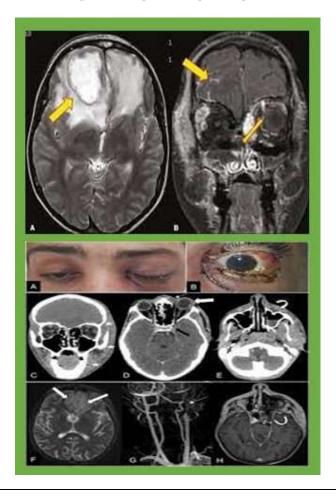
**Method:** Searches were conducted in PubMed, Scopus, Science Direct, and Google Scholar databases between December 2019 and the first five months of 2020. The search terms were: Covid-19, SARS-CoV-2, olfactory disorder, loss of taste, mucormycosis, neurological manifestations, diabetes mellitus, neurological disorder, eye disease, thyroid disease, and diabetes complication.

**Results:** In the initial search, 1259 articles were extracted, after removing the duplicates and evaluating the title and abstract, the articles with the necessary conditions to participate in the present study were selected, and general conclusions were made based on information in the various selected articles.

Conclusion: Whether the findings of this study are sufficient to increase health literacy about mucormycosis and how much this information increases health literacy concerning mucormycosis should be determined in future studies. Given that the Internet is one of the most important sources of health knowledge in our society. Providing the correct information about the contents that are discussed in virtual spaces, especially about topics of interest to people such as traditional medicine and nutrition in the control of mucormycosis disease, can improve people's ability to evaluate the correctness or incorrectness of the information in these spaces.



## GRAPHICAL ABSTRACT



#### 1. Introduction

Coronaviruses are a large family of viruses that are mainly known in humans as the causative agents of respiratory tract infections, ranging from colds to more serious respiratory diseases such as pneumonia, bronchitis, and acute respiratory distress syndrome [1,2]. Of the seven different types of coronavirus that affect humans [3], four of them are very common and most people will experience at least one of them in their lifetime. Three other types of human-infecting coronaviruses under the names of SARS-CoV, MERS-CoV, and SARS-CoV-2 are associated with severe respiratory infections and death. SARS-CoV-2 is a new type of this family that was introduced in the world at the end of

2019 and the disease related to it is named as Covid-19 [4]. This virus is one of the enveloped viruses with a single-stranded ribonucleic acid (RNA) genome and uses the cell receptor "angiotensin-converting enzyme-2" to enter the target cells. This coronavirus, which multiplies efficiently in the upper respiratory tract, tends to the cells located in the lower respiratory tract, and by multiplying in these areas, it leads to lesions in the lower respiratory tract [5]. Approximately, 81% of patients who contract Covid-19 show mild symptoms, and in 14% of cases, the infected person shows severe symptoms, which include pneumonia and shortness of breath. In 5% of cases, the patient's condition has worsened, which is associated with

respiratory failure, infectious shock, and failure in the other body organs [6].

Due to the newness of this virus in the human population, new reports are published daily regarding various aspects of its pathogenesis [7]. Symptoms such as fever, cough, fatigue, muscle pain, joint pain, and shortness of breath have been reported as common and clinically confirmed symptoms caused by the pathogenesis of this virus [8]. However, in addition to these symptoms, SARS-CoV-2 affects different organs of the body, such as the digestive system, nervous system, skin, olfactory system, cardiovascular system, liver, kidney, and eye, and one of these diabetic complications in patients is mucormycosis. Mucormycosis is a disease that is common in patients with a history of diabetes mellitus who have recently been infected with Covid-19, and it affects the nervous system more than other systems [9,10]. This study was designed with the aim of examining the symptoms and complications of the nervous system in patients with mucormycosis.

#### 2. Method

This narrative review study was conducted using relevant articles available in reputable English scientific databases such as PubMed, Scopus, Science Direct, and Google Scholar between December 2019 and the first five months of 2020. The searched words were Covid-19, SARS-CoV-2, olfactory disorder, loss of taste, mucormycosis, neurological manifestations, diabetes mellitus, neurological disorder, eye disease, thyroid disease, and diabetes complication which are equivalent to the Latin databases. The search was conducted by both the main authors of this study and after confirming the titles and abstracts of the articles, the main text of the article was read and included in the present study.

# 3. Results

In the initial search, 1259 articles were extracted, after removing duplicates and evaluating the title

and abstract. 25 articles with the necessary conditions to participate in the present study were selected and general conclusions were made based on the information available in the various selected articles.

#### The main risk factor

There is a bidirectional relationship between mucormycosis and diabetes. On the one hand, diabetes is associated with an increased risk of severe Covid-19, and on the other hand, sudden diabetes and severe metabolic complications of diabetes, such as diabetic ketoacidosis, for which very high doses of insulin are allowed, have been observed in patients with mucormycosis [11]. Based on observations of people who spontaneously developed diabetes after being infected with SARS-CoV-2 or people who presented to the hospital with very high blood sugar and ketones, the researchers suggest that diabetes may only make people more vulnerable to SARS-CoV. 2- It does not make it vulnerable, but this virus may also trigger the occurrence of diabetes in some people [12,13]. This virus can create a severe inflammatory state that disrupts the ability of the pancreas to release insulin and reduces the ability of the liver and muscles to recognize the hormone. However, it is still unclear whether the changes in glucose metabolism remain stable in these patients or disappear during resolution of the infection [14]. In addition, it is not clear whether this is type 1 diabetes, type 2, or a new type of diabetes. Answering these questions is a priority to quickly inform about clinical care, follow-up, and monitoring of affected patients [15].

# A possible mechanism of neurological manifestations of mucormycosis

The causative agent of mucormycosis may cause neurological manifestations by releasing cytokines, viral circulation in the body, or direct virus invasion through multiple ACE2 receptors in the olfactory epithelium [16]. Olfactory

disorder may be caused by damage to the olfactory epithelium. Fever is believed to be caused by cytokines or hypothalamic dysfunction. Seizures may also be due to an excessive increase in cytokines, the severity of the disease, or the involvement of the brain parenchyma; especially the middle temporal lobe [17].

# Nonspecific neurological manifestations

most common symptoms include: consciousness disorder, cognitive disorder, cerebral hemorrhage, stroke, encephalopathy, seizures, ataxia (imbalance), smell disorder, and taste disorder [18]. The initial manifestations of mucormycosis are usually respiratory symptoms. However, doctors have identified neurological symptoms as one of the primary symptoms at the time of diagnosis. Non-specific symptoms when presented alone may make diagnosis difficult. After muscle pain, headache is one of the most common neurological symptoms in patients with mucormycosis [19]. Twenty-one studies have reported headache with a prevalence of 3.5% to 34% among patients with mucormycosis. In general, the prevalence of headache was 10.9% in the population of 6486 people from 21 studies. A review of the previous studies shows that headache is the most common symptom during disease exacerbation in patients mucormycosis. In another study, dizziness was the most common central nervous system manifestation with 16.8%, followed by headache with 13.1%. Dizziness and headache are often seen in early disease as typical symptoms of mucormycosis. Dizziness has been reported in 6 studies with an overall prevalence of 8-77% among 1088 people [20].

Nausea with or without vomiting was reported in 13 studies with prevalence ranging from 1.25 to 8.7%. In general, the overall prevalence of nausea with or without vomiting is 4.6%. Several studies have been conducted during the mucormycosis outbreak. However, the advanced imaging and

diagnostic methods such as magnetic resonance imaging (MRI) and electroencephalography (EEG) have been avoided or their use has been dependent on having specific symptoms of a disease such as bleeding or seizures [20]. Therefore, it is difficult to diagnose the origin of neurological symptoms, either directly through the virus or indirectly through damage to other organs, such as gastrointestinal manifestations [21].

A new study of the neurological symptoms of patients with mucormycosis shows that this disease is a threat to the nervous system [22]. Many hospitalized patients have neurological manifestations that include headache, dizziness, loss of consciousness, difficulty concentrating, smell and taste disorders, seizures, strokes, weakness, and muscle pain [23]. Although the patients with neurological proportion of is small compared with the symptoms the epidemic with respiratory patients, continuation and the fact that a larger part of the world's population may be infected before an effective vaccine is available, the total number of patients with neurological symptoms can increase [24]. Neurological complications, especially encephalitis and stroke, can cause lifelong disability with long-term care needs and increased health, social and economic costs. Now the question is that what are the most common permanent neurological symptoms contracting mucormycosis and what are the recommendations? [25]

**Headache:** Headache is one of the first neurological symptoms of mucormycosis. Especially if there are other symptoms such as pain, fever, and loss of taste, or smell [26].

Light sensitivity and other eye symptoms: Although not nearly as common as headaches, light sensitivity (or so-called photophobia) and the other eye symptoms can occur during an acute mucormycosis infection as well as in the weeks after recovery. Estimates suggest that about 10 to 15 percent of patients develop photophobia, and some researchers have even found that it is the most common ocular symptom of mucormycosis [27] (Figure 1).

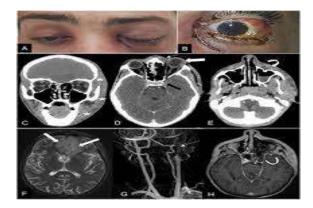


Figure 1. Eye symptoms and mucormycosis

## Olfactory disorder

The loss of the sense of smell in adults following an infection with viruses infecting the upper respiratory tract is called "post-viral anosmia", which accounts for about 40% of anosmia cases. The common coronaviruses are thought to account for 10-15% of cases [28]. Therefore, it is not surprising that SARS-CoV-2 also causes anosmia in patients with Covid-19, but its exact pathogenesis is not known. It is possible that the damage caused by SARS-CoV-2 occurs on the surface of the olfactory neuroepithelium in the roof of the nasal cavity or in the central olfactory pathways [29]. There are several possible scenarios in this regard: In one scenario, SARS-CoV-2 could infect the lining of the nasal cavity and cause local inflammation, and then the inflammation in the nose would prevent odors from reaching the olfactory receptors, as in chronic rhinosinusitis, chronic inflammation of the sinuses and nasal cavity, is one of the main causes of loss of sense of smell. Alternatively, the virus can directly target the olfactory receptor cells inside the nose. If these cells become infected, they are unable to produce signals and the person temporarily loses their sense of smell

[30] because the body replaces the olfactory receptor cells every thirty to sixty days. Likewise, theoretically, viruses can pass through the sieve plate of the ethmoid bone, which is located in the roof of the nose, and infiltrate the olfactory bulb, which is one of the lower structures of the brain and the place where olfactory information is processed, and cause damage to that nerve area and ultimately olfactory disorder [31] (Figure 2).

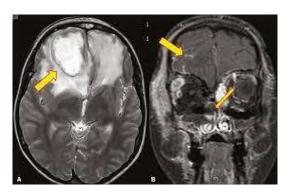


Figure 2. Brain and mucormycosis

The time of onset of olfactory symptoms in mucormycosis patients is different so that in some patients with mucormycosis, it has been reported as one of the initial symptoms in them, and in others, these symptoms develop later in the patients [32]. However, there is insufficient evidence to confirm these hypotheses and more comprehensive research is needed [33].

## Loss of sense of taste

The loss of the smell sense can also be accompanied by the loss of the taste sense. Since the smell sense has a great influence on the ability to detect taste, the loss of the sense of smell can also affect the sense of taste, and people with mucormycosis may experience loss of the sense of taste [34]. Concerning that the chemical receptors for the sense of saltiness, sweetness, sourness, and bitterness of food are located on the tongue, so it seems that people's lack of taste in food is mainly secondary to the loss of their smell sense [35].

#### **Discussion**

According to this study, mucormycosis has a wide range of clinical symptoms, which can be classified into two groups of respiratory and nonrespiratory symptoms, and respiratory symptoms are more common (36). Fever and cough are the most common symptoms. There is also an asymptomatic form, which is an important factor in the spread of the disease in society, especially among children. The chance of infection is not the same for all people in the society. Severe disease usually occurs in susceptible people with underlying disease or in cases where the amount of virus introduced into the body is high. Diagnostic methods are not 100% [37].

Virus antigen measurement in pharynx or nose sample is the most important laboratory criterion and the other laboratory tests are helpful in diagnosing or predicting the disease severity [38]. The risk factors mentioned by most studies for severe disease are male gender, diabetes, high blood pressure, and heart disease. Regarding the other factors, there are contradictions in various studies. There is no age limit for infection. It is debated whether children have equal, less or more susceptibility than adults. In explaining why children are less sensitive to mucormycosis, there are hypotheses related to the immune system and ACE2 receptors [39].

However, they should be included in the transfer cycle. The disease severity is higher in men than in women. Effective treatment, especially for critically ill patients, has not yet been found. In the field of traditional medicine, despite the fact that sometimes strange claims are seen in virtual spaces, no registered study proving the effectiveness of a method, especially in critically ill patients, has been found so far [40]. In Iran, 67 clinical research projects investigating the effectiveness of traditional medicine treatments in mucormycosis have received the executive permission and are being carried out. The recommendations of the Iranian medicine in the

pandemic of respiratory diseases and respiratory drugs that are traditionally used in regions have been collected based on sources. According to the studies in the south of Iran, 99% of people have heard rumors promoted in the name of traditional medicine, and only 6.88% of people disagree with them. Traditional medicine recommendations were only 2.9% [41].

In addition, sometimes recommendations as traditional medicine are published in society, which not only do not exist in the sources of traditional medicine, but also are even theoretically questionable in modern medicine [42]. Traditional fumigation of baking soda to treat Covid-19 is a clear example of these cases [43]. The high level of health literacy, especially in crises, prevents the risk of spreading rumors. Since, according to the current information, close contact with infected people and transmission through the air are the most common methods of transmission of the virus, using a mask and washing hands along with observing physical distance are the most important ways to prevent people from contracting the disease and preventing the spread of the virus in the community [44].

# Conclusion

Whether the findings of this study are sufficient to increase health literacy about mucormycosis and to what extent this information increases health literacy regarding mucormycosis should be determined in future studies. Given that the Internet is one of the most important sources of health knowledge in our society. Providing correct information about the contents that are discussed in virtual spaces, especially about topics of interest to people such as traditional nutrition medicine and in controlling mucormycosis disease, can improve people's ability to evaluate the correctness or incorrectness of the information in these spaces.

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# HOW TO CITE THIS ARTICLE

Saeid Charsouei, Ali Reza Lotfi. Symptoms and Complications of Nervous System in Patients with Mucormycosis: A Systematic Review, Ad. J. Chem. B, 4 (2022) 261-270.

DOI: 10.22034/ajcb.2022.367982.1132

URL: http://www.ajchem-b.com/article\_162967.html