Psychiatr. Pol. 2022; 56(5): 931–944
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/152125

Infections and mental diseases: from tuberculosis to COVID-19

Janusz Rybakowski[1, 2]

[1] Department of Adult Psychiatry, Poznań University of Medical Sciences
[2] Corresponding member of the Polish Academy of Sciences

Summary

The COVID-19 pandemic reactivated interest in the relationship between mental diseases and infectious factors. In this narrative review, such an association for tuberculosis, syphilis, toxoplasmosis, influenza, and COVID-19 was discussed. A connection between tuberculosis and melancholia was postulated for several centuries. In the 1950s, an anti-tuberculosis drug, iproniazid, was found to exert an antidepressant effect. In the 20th century, it was demonstrated that psychiatric disturbances connected with syphilis can be treated by an inoculation of malaria, which initiated immunotherapy. Increased frequency of *Toxoplasma gondii* infections in psychiatric illnesses was found and a higher risk of schizophrenia following infection in pregnancy. A more frequent incidence of schizophrenia in persons born during the influenza pandemic in the second half of the 20th century was evidenced. Mental disturbances can result from an ancient infection of the human genome by retroviruses. Infection during pregnancy can increase their risk in later life. An infection in adult life may also be of pathogenetic significance. COVID-19 causes significant early and late consequences for mental health. Two-year pandemic observations brought data on the therapeutic action of psychotropic drugs on SARS-CoV-2. Despite previous data on the antiviral action of lithium, a significant effect of this ion on the prevalence and course of COVID-19 was not confirmed.

Key words: infections, mental diseases

Introduction

The COVID-19 pandemic and related psychiatric problems have contributed to a rekindling of interest in the association between psychiatric disorders and infec-

Paper presented at the XXVI conference FARMAKOTERAPIA, PSYCHOTERAPIA, REHABILITACJA ZABURZEŃ AFEKTYWNYCH, Kraków, 4-6 November 2021.

tious factors. Interest in the topic already began when the diseases presently known as infectious were not yet associated with specific microorganisms. In the present article, a history of some infectious diseases and various aspects of their connection with psychiatric disorders is discussed, starting with tuberculosis, through syphilis, toxoplasmosis and influenza, up to COVID-19.

Tuberculosis

A relation of tuberculosis (consumption) to the phenomenon of "melancholia" had been postulated at least since the 17th century, long before the discovery of the bacillus *Mycobacterium tuberculosis* by Robert Koch in 1882**.** As an interesting fact from the life of this great scientist, a Nobel laureate in 1905, his association with the Greater Poland voivodeship should be mentioned. In 1872-1880, Koch served as a regional physician in Wolsztyn (Wollstein). Since 1996, there has been a museum dedicated to him, located in the building where he lived and worked.

In the mid-17th century, English physician Gideon Harvey (1640-1700) (do not mistake for William Harvey, the discoverer of blood circulation, living in 1578-1657) in his book "Morbus Anglicus" ascertained that melancholia and black bile (gr. *melaina chole*) are the only causes of tuberculosis (consumption) [1]. Since this time, in medical textbooks, melancholy with accompanying sadness was listed as one of the main causes of consumption. The terms "melancholic" and "consumptive" became synonyms for denoting hypersensitive and artistic individuals, with the strongest expression during the era of Romanticism. According to Susan Sontag, the myth of tuberculosis constituted an episode in the long career of the primeval idea of melancholia. Melancholia, in compliance with the Hippocratic theory of four humors, was an illness of artists. A melancholic (consumptive) character was a feature of higher-order beings: sensitive and creative [2].

Among the prominent artists and creators of the Romantic era who had tuberculosis, worthy of mention are the English poet, John Keats (1795-1821) and the Polish composer, Frederic Chopin (1810-1849). The great writers at the turn of the 20th century, ailing from tuberculosis include Anton Chekhov (1860-1904) and Franz Kafka (1883-1924). In the 20th century, among Poles, the unforgettable Warsaw bard Stanisław Grzesiuk (1918-1963) should be mentioned. As can be noticed, all these persons died prematurely due to the illness at the age of 40 years or even earlier.

The contemporary "buckle" joining together the issue of tuberculosis and melancholy (depression) is the result of the introduction of an antibiotic, iproniazid, for the treatment of tuberculosis in 1952 [3]. In patients receiving this drug, a spectacular euphoric and socializing effect was observed. In popular press, the descriptions of patients appeared, among others of the Staten Island Sea View Hospital, "dancing in the halls tho' there were holes in their lungs". After several years, it was found that iproniazid inhibits the enzyme monoamine oxidase (MAO) which degrades biogenic amines, what results in an increase of these amines in the brain. In 1958, the American psychiatrist Nathan Kline (1916-1983) discovered that iproniazid had an antidepressant effect, making the drug a precursor of antidepressants, categorized as the MAO

inhibitors (MAOIs) [4]. The antidepressant effect of the MAOIs later contributed to the formulation of the catecholaminergic and serotonergic concepts of depression. Among the MAOIs, the most popular became tranylcypromine and phenelzine, appearing shortly, which have been used in some countries (not in Poland) to this day. In 1992, moclobemide, a reversible inhibitor of MAO-A (RIMA) was introduced to psychiatric treatment and has also been used in our country.

Syphilis

The disease is probably an aftermath of Christopher Columbus' expedition to the New World in 1492. Following his return, the illness quickly spread in Europe, from Italy, through France, Germany, Poland and Russia. In the 16th and 17th century, it frequently had a fulminant course with a rash, ulceration of the whole body and concomitant mental disturbances.

The term "syphilis" comes from the poem "Syphilis sive morbus Gallicus" (Syphilis or the French disease) written by the great Italian physician, poet and scholar, Girolamo Fracastoro (1478-1553). Fracastoro was a colleague of Nicolaus Copernicus at the University of Padua, and the first to propose the concept of minute germs transmitting contagious diseases. In the poem "Infectio Syphilis", a shepherd Syphilus was depicted who was punished by Apollin by the disease causing decay of the whole body [5]. The poem of Fracastoro popularized syphilis as the French disease (franca). Another term for syphilis – "lues" comes from the Latin verb *luere* meaning "suffer". In Poland, the first complete description of syphilis was made by Wojciech Oczko (1537-1599), the court physician of Polish kings Stephen Bathory and Sigismund III Vasa. In his elaboration, Oczko defines syphilis as "the court attribute" pointing out the sexual wantonness of the rulers (also Polish) as a possible cause of the illness. Among Polish syphilitic kings, Sigismund II Augustus (1520-1572) and John III Sobieski (1629-1696) should be mentioned, and among the rulers behind the eastern border – tsar Ivan the Terrible (1530-1584) and Vladimir Lenin (1870-1924). However, there were also eminent artists and writers who suffered from syphilis, such as Edouard Manet (1832-1883), Paul Gauguin (1848-1903), Henri Toulouse-Lautrec (1864-1901), Bedřich Smetana (1824-1884), Friedrich Nietzsche (1844-1900) and Pole, Stanisław Wyspianski (1969-1907) [6].

The identification of the pathogenic factor of syphilis i.e., a spirochete bacterium *(Treponema pallidum)* took place in 1905 as a work of the German medics: microbiologist, Fritz Schaudinn (1871-1906) and dermatologist, Erich Hoffmann (1868-1959). The latter was born in Wicimice (Witzmitz), near Gryfice. At that time, psychiatric disorders associated with syphilis of the nervous system (so-called tertiary syphilis) became more and more widespread. The clinical picture of progressive paralysis, the most common form of tertiary syphilis, was dominated by the symptoms of psychosis, depression and dementia. In the first decades of the 20th century, a significant proportion of patients in psychiatric hospitals had mental disorders related to tertiary syphilis.

In the second decade of the 20th century, an Austrian physician, Julius Wagner-Jauregg (1857-1940) attempted to treat the psychiatric disturbances of syphilis by

inducing a "competitive" infectious disease – malaria. After an inoculation of the protozoan parasite causing malaria *(Plasmodium vivax),* the patients had bouts of fever, followed by a significant improvement of their mental status. For the introduction of this method, which can be regarded as the beginning of immunotherapy, Wagner-Jauregg received the Nobel Prize in 1927 [7]. Interestingly, observations on the improvement of psychiatric symptoms after the fever of malaria were made more than a century earlier by the Polish physician Ludwik Perzyna (1742-1800), after whom the Provincial Hospital in Kalisz was named, in his book "Lekarz dla włościan" [8].

Toxoplasmosis

Toxoplasmosis is a disease caused by the protozoan *Toxoplasma gondii.* This microorgamism was identified in 1908 by the French physicians, Charles Nicolle (1866-1936), the Nobel laureate in 1928, and Louis Manceaux (1865-1934), in a rodent, *Ctenodactylus gondii*. *Toxoplasma gondii* is neurotropic: it migrates to brain tissue where it locates in astrocytes, neurons and microglia, forming cysts. The final hosts of the parasite are domestic cats while the intermediate hosts are humans and all other mammals and birds. Despite a great percentage of infected individuals, only a small number show the symptoms of infection, while the rest are carriers. The importance of *Toxoplasma gondii* for psychiatric disorders lies primarily in the increased frequency of the toxoplasmosis infection found in the diseases of the central nervous system and a significantly increased risk of mental illness, mainly schizophrenia, when the infection occurs during pregnancy.

Since the 1950s, studies have shown an increased percentage of toxoplasmosis infection in the population of psychiatric patients, compared with the control group. One of the first in this respect was the paper published in 1953, authored by the eminent Polish parasitologist, Zbigniew Kozar (1918-1972) [9]. In the following years, a higher frequency of the infection in psychiatric illnesses has been confirmed in many investigations and meta-analyses. A recent meta-analysis pertaining to schizophrenia was published in 2012. The assessment of 38 papers investigating the frequency of antibodies against *Toxoplasma gondii* showed that in schizophrenia patients they were three times more prevalent compared to the control group [10]. As to bipolar disorder (BD), the analyses show slightly less than in schizophrenia, but still one and a half times more frequent antibodies than in the control group [11, 12]. Another meta-analysis studied the relationship between *Toxoplasma gondii* infection and depression. The assessment included cross-sectional studies comparing 1,657 patients with depression and 19,565 control persons as well as case-control studies including 1,311 patients with depression and 6,015 control persons. The study did not find a higher risk of depression in subjects infected with this protozoan [13].

In the case of schizophrenia, some researchers postulate a causal relationship between the illness and *Toxoplasma gondii* infection [14]. This is corroborated by a significant association between a positive serological reaction to *Toxoplasma gondii* in pregnancy and the occurrence of schizophrenia, both in adult life as well as the early-

onset form of the illness [15]. On the other hand, a relationship between seropositivity in pregnancy and subsequent BD has not been unequivocally confirmed [16].

There is plenty of evidence suggesting an association between *Toxoplasma gondii* infection and psychiatric illness also on a biochemical and pharmacological level. This protozoan, when present in the brain, can influence the synthesis and metabolism of biogenic amines, especially dopamine and glutamate, playing the role of brain neurotransmitters. It has also been found that the parasite replication can be inhibited by such antipsychotic drugs as haloperidol, fluphenazine, zuclopentixol, risperidone, paliperidone and mood-stabilizing drug, valproic acid. Interestingly, such an effect was not observed for such antipsychotics as clozapine, olanzapine, amisulpride and aripiprazole or for such mood stabilizers as lithium, carbamazepine and lamotrigine [17]. This may indicate that in relation to the pathogenesis of schizophrenia, the contribution of *Toxoplasma gondii* may be underestimated. It seems that in schizophrenia patients, a more detailed diagnostic procedure for the presence of this parasite should be warranted. Given the data presented above, such an approach could also be helpful for the planning of appropriate pharmacological treatment.

Influenza

Influenza pandemics have probably been occurring since antiquity. However, in the history of mankind, the most significant was the influenza pandemic known as the "Spanish flu" occurring more than 100 years ago (1918-1920), resulting in 50 million deaths. In his recent book, Bogusław Chrabota gave it the rightful name of "Influenza Magna", describing as a victim of the illness the brilliant Austrian painter, Egon Schiele, who passed away at 28 years of age [18]. During the Spanish flu, it was believed that the illness was caused by bacteria. It was not until 1933 that the British scientists Wilson Smith (1897-1965), Christopher Andrewes (1896-1988) and Patrick Laidlaw (1881-1940) presented unequivocal evidence that the disease is caused by a virus [19].

However, the implications concerning the relationship between influenza infections and mental illness appeared 30 years after the A2 influenza virus pandemic, which took place in 1957. In 1988, American researchers analyzing the Finnish birth cohort of 1957-1958 demonstrated that the offspring of mothers exposed to influenza, especially during the second trimester of pregnancy, showed an increased risk of hospitalization due to schizophrenia. This pertained to both men and women [20]. Later analyses indicated a simlar relationship in the population of such European countries as Denmark, England and Scotland [21], as well as in Japan [22]. In these countries the strongest association was also observed in the case of the infection occurring during the second trimester of pregnancy; however, women were at a greater risk. Nevertheless, such a phenomenon was not globally confirmed, as it was not found in the Netherlands [23] or Australia [24]. A Dutch investigator, Jean-Paul Selten, the co-author of a negative study, has become the main skeptic in this regard. He was involved in a number of meta-analyses showing that the premises for an association between influenza infection during pregnancy and subsequent schizophrenia are not sufficient. In his recent paper of 2017, he ascertains that this methodological deficiency pertains to both "ecological"

studies, investigating the risk of illness for individuals born after flu epidemics, as well as to "serological" studies, evaluating the presence of antibodies [25].

More recently, Spanish researchers performed an assessment of nearly half a million adults living in Navarra, in the context of influenza pandemics in 1957, 1968, and 1977. Schizophrenia was diagnosed in 2,077 persons, 1.5 times more frequently in men than in women. The logistic regression analysis showed a significantly increased risk of schizophrenia in subjects born in the years of the pandemics, both combined as well as when each influenza pandemic year was analyzed separately [26].

In 1917, the Austrian neurologist Constantin von Economo (1876-1931) described the first case of comatose encephalitis (*encephalitis lethargica*). In the following years, this illness became epidemic. The time coincidence of the Spanish flu and the encephalitis initially suggested that the infectious agent of influenza may play a role in the pathogenesis of the encephalitis. Although this hypothesis has not been confirmed, the treatment of *encephalitis lethargica* served as an illustration for demonstrating the role of the dopaminergic system in the pathogenesis and treatment of disorders of the central nervous system. The treatment of those patients became the basis for the novel "Awakenings" written by the eminent British neurologist, Oliver Sacks (1933-2015), which prompted the famous movie with the same title [27]. In the movie, the physician, portrayed by Robin Williams (1951-2014) uses a dopamine precursor in the patient, a victim of *encephalitis lethargica* from the 1920s, who shows symptoms of catatonia and parkinsonism. The patient, played by Robert de Niro, initially shows a significant improvement in mental and motor activity; however, in the further course of dopaminergic therapy, he develops psychosis.

Infection in various periods of life and psychiatric diseases

Psychiatric disorders may be connected with an infection in various periods of life. They may also be the aftermath of an ancient infection of the human genome by so-called retroviruses (human endogenous retroviruses – HERVs). The retroviruses are the remnants of infections occurring millions of years ago and constitute about 8% of the human genome. In recent decades, hypotheses were put forward postulating the HERVs as the pathogenic factors in some diseases of the central nervous system. The concept of retroviruses being involved in the pathogenesis of schizophrenia (and probably BD) was promoted 35 years ago by a British psychiatrist, Timothy Crow. He suggested that the HERVs are placed in the genome locus responsible for brain lateralization [28]. Recently, French researchers assayed the HERV antigen, showing its presence in 41% of patients with schizophrenia, in 28% with bipolar disorder, and only in 4% of healthy control subjects. The presence of the antigen was related to a higher concentration of pro-inflammatory cytokines and higher indexes of childhood trauma. In schizophrenia, an association was also found with higher doses of antipsychotic drugs, while in BD – with earlier onset of the illness [29].

A large amount of data on the relationship between infection and mental illness concerns infections during pregnancy. In a recent review on this topic, an association between schizophrenia in adult life and infection in pregnancy caused by the protozoan

Toxoplasma gondii and influenza virus was confirmed. Such possible associations with cytomegalovirus and bacterial infections were also indicated. The authors of the review point to the necessity of prospective studies on the impact of Zika virus and SARS-CoV-2 infections during pregnancy on psychiatric disorders [30]. As to bipolar disorder, the paper showing a relationship between influenza infection in pregnancy and psychotic BD deserves mention [31]. In 2019, the results of a Swedish prospective study including 1.8 million children followed for 41 years were presented. It was found that in the offspring of mothers who had an infection during pregnancy, including urinary tract infection, there is a 1.85-fold higher risk of autism and 1.3-fold higher risk of depression in adult life [32].

There are several concepts for the mechanism of mental disorders connected with an infection during pregnancy. A pathogenic factor (microorganism) may act directly on the brain tissue and produce neurodevelopmental disorders. However, likely a more important pathogenic mechanism is an augmentation of the inflammatory reaction of the fetus, thus damaging the brain. Numerous data show that a microorganism can produce placental inflammation and activation of microglia, astrocytes and oligodendrocytes in the fetal brain. This mechanism is enhanced by genetic predisposition (e.g., *DISC-1* gene) and epigenetic factors (excessive DNA methylation) [33].

As already mentioned, in adult patients with schizophrenia and BD, an increased frequency of antibodies to *Toxoplasma gondii* is demonstrated, which indicates a latent infection by this parasite [10-12]. Japanese researchers showed also increased antibodies against cytomegalovirus and herpes simplex virus type 2 (HSV-2) in both these illnesses [34]. Meanwhile, Yolken et al. [35] found that many patients admitted for acute mania were recently treated with antibiotics, which may suggest that the manic episode could have been precipitated by a bacterial infection.

Antiviral effect of lithium

An important discovery related to the connection between mental illness and microorganisms was the detection of an antiviral effect of lithium, a mood-stabilizing drug, currently regarded as the first-line treatment for preventing relapse of bipolar disorder. In 1979, an American psychiatrist, Julian Lieb, described two patients who, during treatment with lithium, had a complete remission of recurrent herpes; in one case – labial herpes, in the other – genital herpes [36]. A year later, researchers from the University of Birmingham showed on a hamster kidney model that lithium at a concentration of 5-30 mmol/l inhibits the replication of type 1 and type 2 HSV [37].

More than 30 years ago, the results of a Polish-American retrospective study of labial herpes caused by HSV-1 in patients taking lithium for prophylactic purposes were presented. The Polish population consisted of 69 patients receiving lithium for an average of eight years under the care of the outpatient clinic at the Department of Psychiatry in Poznań. The overall reduction in the recurrence frequency in 28 patients with labial herpes was 64%, and in a half of them, complete remission was achieved. The American population consisted of two groups of 52 people each. The frequency of labial herpes recurrences, compared to the five-year period before

treatment, decreased in the first group receiving lithium by 73%, while no significant difference was observed in the second group receiving antidepressants [38]. At the same time, researchers from the University of Pennsylvania showed a therapeutic effect of oral lithium on genital herpes, caused by HSV-2 [39]. Several years later, the results of a retrospective study on the frequency of flu-like infections in patients receiving lithium prophylactically were published. They indicate that lithium significantly reduces the frequency of such recurrences, which could suggest that the antiviral effect of lithium also applies to RNA viruses associated with the flu and flu-like infections [40].

Infection with HSV-1 constitutes a pathogenic factor for cognitive deficits in BD [41]. According to recent data, this virus also plays an important role in the pathogenesis of Alzheimer's disease [42]. Thus, the antiviral effect of lithium against HSV-1 can be connected with a favorable influence of lithium on cognitive function in BD as well as its "antidementia" effect.

COVID-19

COVID-19 (coronavirus disease 2019) is a disease caused by a SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. In 2002, a similar virus was the culprit of an outbreak of severe acute respiratory syndrome (SARS), and in 2012 – Middle East respiratory syndrome (MERS). However, it was not until SARS-CoV-2 that a global pandemic was declared, with significant mental health consequences for both infected and non-infected persons. This pandemic is an enormous challenge for psychiatry [43].

SARS-CoV-2 penetrates the organism by binding to ACE-2 (angiotensin-converting enzyme 2) receptors. Once inside the body, the virus causes, among others, inflammatory symptoms (cytokine storm) and damage to small vessels (thromboembolism). The virus enters the central nervous system through the damaged blood-brain barrier, causing inflammatory activation of microglia and astrocytes. Neuropsychiatric symptoms can occur at any stage of the infection. In the initial period, they include, among others, anosmia and cognitive deficits, known as "brain fog". Symptoms that last up to several months after infection are termed "long COVID". Among psychiatric symptoms, the most frequent are cognitive deficits, affecting about 30% of patients. A similar proportion of patients have symptoms of depression and post-traumatic stress disorder [44].

The COVID-19 pandemic causes significant negative consequences for persons with psychiatric disorders and those predisposed to such disorders. An increase in the incidence of depression has been noted across the world. There is an elevated risk of manic episodes in patients with BD. Higher mortality in the course of the infection has been found in patients with schizophrenia and psychosis. Especially spectacular are the *de novo* cases of psychosis, mania, depression, post-traumatic stress disorder and delirium in subjects with no psychiatric history. A case of first-episode mania occurring during COVID-19 treatment in a 44-year-old male patient with no psychiatric history was reported at our center [45].

Psychotropic drugs and COVID-19

During the COVID-19 pandemic, efforts have been primarily made to develop vaccines and antiviral drugs acting specifically against SARS-CoV-2. At the same time, observations on the drugs used in psychiatry that could have a favorable effect on COVID-19 infection appeared. These drugs include antidepressants, antipsychotics, mood stabilizers, as well as other medications. It was found that antidepressants such as selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) can reduce the risk of intubation and death in COVID-19 patients. The SSRI drugs exert an excellent therapeutic effect on post-COVID depression occurring up to six months after recovery from COVID-19. Among antipsychotic drugs, antiviral activity against SARS-CoV-2 was demonstrated for chlorpromazine in experimental conditions but not confirmed in clinical studies. Retrospective analysis seems to suggest a favorable effect on the course of COVID-19 infection in patients with schizophrenia on atypical long-acting injectable (LAI) antipsychotics, such as risperidone, paliperidone and aripiprazole. Among mood-stabilizing drugs, a possible favorable effect has been suggested based on experimental studies for lithium and valproate. Other drugs used in psychiatry, such as amantadine, memantine, melatonin, cannabidiol and disulfiram, also demonstrated a therapeutic effect on COVID-19 infection [46].

Fluvoxamine, an SSRI antidepressant, deserves special mention. Across psychotropic medications, this drug has been one of the most studied in patients with COVID-19. The studies include randomized controlled trials. The results indicate that fluvoxamine prevents deterioration of the clinical status of COVID-19 patients and improves the long-term course of the illness. The agonistic action on sigma-1 receptors is regarded as the main therapeutic mechanism, resulting in a reduction of inflammation and cytokine storm. In April 2021, fluvoxamine was listed as a drug for use in COVID-19 in the recommendation of the American National Institutes of Health (NIH) [47].

Lithium and COVID 19

Shortly after the outbreak of the COVID-19 pandemic, Nowak and Walkowiak [48] quoted the results of experimental studies showing that lithium inhibits the replication of conoraviruses connected with the diseases of pigs, such as the porcine epidemic diarrhea virus, porcine reproductive and respiratory syndrome virus, and porcine transmissible gastroenteritis virus as well as in birds, such as the avian infectious bronchitis virus. They also postulated that the mechanism is due to lithium's inhibition of glycogen synthase kinase 3-beta (GSK-3β) necessary for the production of viral genomic RNA. In the context of available data demonstrating lithium's ability to inhibit RNA viruses and its "anti-inflammatory" properties, suggestions emerged that lithium may modify the course of COVID-19 and, in particular, prevent infection and reduce the severity of the illness [49]. This postulation may be supported by a study conducted by Spanish researchers, who treated six patients with COVID-19

infection with lithium and observed an improvement in inflammatory symptoms and immune response [50].

In 2020, in Polish psychiatric literature, guidelines for patients treated with lithium during the COVID-19 pandemic were listed, according to which those patients should have continuity of direct or telephone contact with the physician, medical clinic or community mental health services providing the care. If a fever develops in a patient treated with lithium, paracetamol and intense hydration are recommended. Non-steroidal anti-inflammatory drugs (ibuprofen, diclofenac) should not be administered because they may increase the concentration of lithium in the blood and cause a risk of toxicity. If a fever greater than 39 °C develops accompanied by symptoms such as vomiting, diarrhea and weakness, lithium should be discontinued until normal food and fluid intake is resumed. If possible, the serum lithium concentration should be determined as soon as possible [51].

Long-term use of lithium does not necessarily protect against the onset and severe course of the illness. We have reported a case of a 58-year-old male patient, living in Lombardy, suffering from BD for over 20 years, who was receiving lithium and valproate prophylactically for a period of 10 years. In February 2020, he became infected with COVID-19 and developed a fever of 40 °C, chest pain, dyspnea and a dry cough. SARS-CoV-2 infection was confirmed by PCR testing. Chest imaging showed pneumonia with changes characteristic of the infection. The patient was treated with antibiotics, oxygen, fluids and antipyretics. An elevated body temperature and dyspnea persisted for 40 days; only after 7 weeks did complete recovery occur [52].

The author of this review presented data on the occurrence and course of COVID-19 infection in 50 patients treated with lithium between March 2020 – March 2021 who had not received vaccination against coronavirus during that time period. The study group was comprised of 23 men and 27 women aged 23-71 (mean 45) years, receiving lithium for 1-45 (mean 7) years. Forty-six subjects had a diagnosis of BD and lithium was used to prevent the recurrence of affective episodes; six of these individuals were on lithium monotherapy. In four patients with a diagnosis of schizophrenia who were treated with clozapine, lithium was used to treat and prevent neutropenia. In the study group, infection with COVID-19 did not develop in 37 patients (74%), including five patients on lithium monotherapy. In eight patients, the infection had a mild course, in two – moderately severe, and one patient died due to COVID-19 pneumonia. Two patients developed lithium toxicity. The observations made on the study group indicate that among the subjects receiving lithium, COVID-19 infection occurred in 25% of patients. In the majority of cases, the infection was mild. The results also indicate that COVID-19 infection and related symptoms such as fever, dehydration and renal insufficiency may be a risk factor for lithium toxicity [53].

Conclusion

As the above review illustrates, the association between infection and mental disorders has a numer of aspects. The most important is the impact of an infection with microorganisms, such as viruses, bacteria and protozoa on triggering mental ill-

ness. This applies not only to infections during pregnancy and later in life but also to "congenital infections", as is the case with retroviruses. The therapeutic context is also interesting. Clinical and experimental observations of this phenomenon have led to treatment approaches that cover both the "infectious" and the "mental" aspect of the illness. This has been the case with tuberculosis, syphilis, toxoplasmosis and recently also COVID-19 infection.

The COVID-19 pandemic, lasting for over two years now, has brought awareness to how important viral infections can be for the general health and mental health of humanity. It is to be hoped that psychiatrists will rise to the enormous challenges brought about by this pandemic.

References

1. Harvey G. *Morbus anglicus: or, The anatomy of consumptions.* London: Nathaniel Brook at the Angel in Cornhil; 1666.
2. Sontag S. *Choroba jako metafora. AIDS i jego metafory.* Kraków: Wydawnictwo Karakter; 2016.
3. Selikoff IJ, Robitzek EH, Ornstein GG. *Treatment of pulmonary tuberculosis with hydrazide derivatives of isonicotinic acid.* J. Am. Med. Assoc. 1952; 150(10): 973–980.
4. Kline N. *Clinical experience with iproniazid (marsilid).* J. Clin. Exp. Psychopathol. 1958; 19 (2, Suppl): 72–78.
5. Kubicki J. *Historia kiły.* Puls Uczelni 2013; 7(3): 37–39.
6. Pesapane F, Marcelli S, Nazzaro G. *Hieronymi Fracastorii: The Italian scientist who described the "French disease".* An. Bras. Dermatol. 2015; 90(5): 684–686.
7. Steinberg H, Kirkby KC, Himmerich H. *The historical development of immunoendocrine concepts of psychiatric disorders and their therapy.* Int. J. Mol. Sci. 2015; 16(12): 28841–28869.
8. Rybakowski J. *Ludwik Perzyna – współczesne odniesienia do jego wiedzy psychiatrycznej.* Neuropsychiatria i Neuropsychologia 2020; 15(3–4): 75–82.
9. Kozar Z. *Badania nad toksoplazmozą wśród umysłowo chorych.* Biuletyn Państwowego Instytutu Medycyny Tropikalnej w Gdańsku 1953; 5: 146–173.
10. Torrey EF, Bartko JJ, Yolken RH. *Toxoplasma gondii and other risk factors for schizophrenia: An update.* Schizophr. Bull. 2012; 38(3): 642–647.
11. Barros de JLVM, Barbosa IG, Salem H, Rocha NP, Kummer A, Okusaga OO et al. *Is there any association between Toxoplasma gondii infection and bipolar disorder? A systematic review and meta-analysis.* J. Affect. Disord. 2017; 209: 59–65.
12. Sutterland AL, Fond G, Kuin A, Koeter MW, Lutter R, Gool van T et al. *Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: Systematic review and meta-analysis.* Acta Psychiatr. Scand. 2015; 132(3): 161–179.
13. Nayeri Chegeni T, Sharif M, Sarvi S, Moosazadeh M, Montazeri M, Aghayan SA et al. *Is there any association between Toxoplasma gondii infection and depression? A systematic review and meta-analysis.* PLoS One 2019; 14(6): e0218524.
14. Burgdorf KS, Trabjerg BB, Pedersen MG, Nissen J, Banasik K, Pedersen OB et al. *Largescale study of Toxoplasma and Cytomegalovirus shows an association between infection and serious psychiatric disorders.* Brain Behav. Immun. 2019; 79: 152–158.

15. Karlsson H, Dalman C. *Epidemiological studies of prenatal and childhood infection and schizophrenia.* Curr. Top. Behav. Neurosci. 2020; 44: 35–47.
16. Del Grande C, Galli L, Schiavi E, Dell'Osso L, Bruschi F. *Is Toxoplasma gondii a trigger of bipolar disorder?* Pathogens 2017; 6(1): 3.
17. Chaudhury A, Ramana BV. *Schizophrenia and bipolar disorders: The Toxoplasma connection.* Trop. Parasitol. 2019; 9(2): 71–76.
18. Chrabota B. *Influenza Magna. U progów wieczności.* Warszawa: Ringier Axel Springer Polska; 2021.
19. Smith W, Andrewes CH, Laidlaw PP. *A virus obtained from influenza patients.* Lancet 1933; 222(5732): 66–68.
20. Mednick SA, Machon RA, Huttunen MO, Bonett D. *Adult schizophrenia following prenatal exposure to an influenza epidemic.* Arch. Gen. Psychiatry 1988; 45(2): 189–192.
21. Adams W, Kendell RE, Hare EH, Munk-Jørgensen P. *Epidemiological evidence that maternal influenza contributes to the aetiology of schizophrenia. An analysis of Scottish, English, and Danish data.* Br. J. Psychiatry 1993; 163: 522–534.
22. Izumoto Y, Inoue S, Yasuda N. *Schizophrenia and the influenza epidemics of 1957 in Japan.* Biol. Psychiatry 1999; 46(1): 119–124.
23. Selten JP, Slaets JP. *Evidence against maternal influenza as a risk factor for schizophrenia.* Br. J. Psychiatry 1994; 164(5): 674–676.
24. Morgan V, Castle D, Page A, Fazio S, Gurrin L, Burton P. *Influenza epidemics and incidence of schizophrenia, affective disorders and mental retardation in Western Australia: No evidence of a major effect.* Schizophr. Res. 1997; 26(1): 25–39.
25. Selten JP, Termorshuizen F. *The serological evidence for maternal influenza as risk factor for psychosis in offspring is insufficient: Critical review and meta-analysis.* Schizophr. Res. 2017; 183: 2–9.
26. Alvarez-Mon MA, Guillen-Aguinaga S, Pereira-Sanchez V, Onambele L, Al-Rahamneh MJ, Brugos-Larumbe A et al. *Being born in winter-spring and at around the time of an influenza pandemic are risk factors for the development of schizophrenia: The Apna study in Navarre, Spain.* J. Clin. Med. 2021; 10(13): 2859.
27. Sacks O. *Awakenings.* Manchester: Duckworth & Co.; 1973.
28. Crow TJ. *Integrated viral genes as potential pathogens in the functional psychoses.* J. Psychiatr. Res. 1987; 21(4): 479–485.
29. Tamouza R, Meyer U, Foiselle M, Richard JR, Wu CL, Boukouaci W et al. *Identification of inflammatory subgroups of schizophrenia and bipolar disorder patients with HERV-W ENV antigenemia by unsupervised cluster analysis.* Transl. Psychiatry 2021; 11(1): 377.
30. Cheslack-Postava K, Brown AS. *Prenatal infection and schizophrenia: A decade of further progress.* Schizophr. Res. 2022: 247: 7–15. doi: 10.1016/j.schres.2021.05.014. Online ahead of print.
31. Canetta SE, Bao Y, Co MD, Ennis FA, Cruz J, Terajima M et al. *Serological documentation of maternal influenza exposure and bipolar disorder in adult offspring.* Am. J. Psychiatry 2014; 171(5): 557–563.
32. Al-Haddad BJS, Jacobsson B, Chabra S, Modzelewska D, Olson EM, Bernier R et al. *Long-term risk of neuropsychiatric disease after exposure to infection in utero.* JAMA Psychiatry 2019; 76(6): 594–602.

33. Al-Haddad BJS, Oler E, Armistead B, Elsayed NA, Weinberger DR, Bernier R et al. *The fetal origins of mental illness.* Am. J. Obstet. Gynecol. 2019; 221(6): 549–562.
34. Tanaka T, Matsuda T, Hayes LN, Yang S, Rodriguez K, Severance EG et al. *Infection and inflammation in schizophrenia and bipolar disorder.* Neurosci. Res. 2017; 115: 59–63.
35. Yolken R, Adamos M, Katsafanas E, Khushalani S, Origoni A, Savage C et al. *Individuals hospitalized with acute mania have increased exposure to antimicrobial medications.* Bipolar Disord. 2016; 18(5): 404–409.
36. Lieb J. *Remission of recurrent herpes infection during therapy with lithium.* N. Eng. J. Med. 1979; 301(17): 942.
37. Skinner GRB, Hartley C, Buchan A, Harper L, Gallimore P. *The effect of lithium chloride on the replication of herpes simplex virus.* Med. Microbiol. Immunol. 1980; 168(2): 258–265.
38. Rybakowski JK, Amsterdam JD. *Lithium prophylaxis and recurrent labial herpes infections.* Lithium 1991; 2: 43–47.
39. Amsterdam J, Maislin G, Potter L, Giuntoli R, Koprowski H. *Suppression of recurrent genital herpes infections with lithium carbonate: A randomized, placebo-controlled trial.* Lithium 1991; 2: 17–25.
40. Amsterdam JD, García-Espańa F, Rybakowski J. *Rates of flu-like infection in patients with affective illness.* J. Affect. Disord. 1998; 47(1–3): 177–182.
41. Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Cole S, Krivogorsky B et al. *Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder.* Biol. Psychiatry 2004; 55(6): 588–593.
42. Itzhaki RF. *Corroboration of a major role for herpes simplex virus type 1 in Alzheimer's disease.* Front. Aging Neurosci. 2018; 10: 324.
43. Szkaradkiewicz A. *Nowe koronawirusy człowieka – SARS-CoV, MERS-CoV i 2019-nCoV (COVID-19).* Zakażenia XXI wieku 2020; 3(1): 1–6.
44. Butler M, Cross B, Hafeez D, Lim MF, Morrin H, Rengasamy ER et al. *Emerging knowledge of the neurobiology of COVID-19.* Psychiatr. Clin. North. Am. 2022; 45(1): 29–43.
45. Kurczewska E, Nawojczyk M, Ferensztajn-Rochowiak E, Jaracz J, Rybakowski F. *Onset of bipolar disorder induced by treated COVID-19 infection in a 44-year-old man with no psychiatric history.* Bipolar Disord. 2022; 24(2): 214–216. doi: 10.1111/bdi.13173.
46. Mueller JK, Riederer P, Müller WE. *Neuropsychiatric drugs against COVID-19: What is the clinical evidence?* Pharmacopsychiatry 2022; 55(1): 7–15.
47. Facente SN, Reiersen AM, Lenze EJ, Boulware DR, Klausner JD. *Fluvoxamine for the early treatment of SARS-CoV-2 infection: A review of current evidence.* Drugs 2021; 81(18): 2081–2089.
48. Nowak JK, Walkowiak J. *Lithium and coronaviral infections. A scoping review.* F1000Res. 2020; 9: 93.
49. Murru A, Manchia M, Hajek T, Nielsen RE, Rybakowski JK, Sani G et al. *Lithium's antiviral effects: A potential drug for CoViD-19 disease?* Int. J. Bipolar Disord. 2020; 8(1): 21.
50. Spuch C, López-García M, Rivera-Baltanás T, Rodrígues-Amorím D, Olivares JM. *Does lithium deserve a place in the treatment against COVID-19? A preliminary observational study in six patients, case report.* Front. Pharmacol. 2020; 11: 557629.
51. Rybakowski J. *Informacja dotycząca stosowania litu w okresie pandemii COVID-19.* Psychiatra 2020; 28: 48–49.

52. Gattner K, Rybakowski J. *A severe course of the COVID-19 in a patient receiving prophylactically lithium.* Farmakoter. Psychiatr. Neurol. 2020; 2(36): 143–148.
53. Rybakowski J. *COVID-19 infection in 50 patients receiving lithium.* Farmakoter. Psychiatr. Neurol. 2021; 2(37): 113–121.

Address: Janusz Rybakowski
Poznan University of Medical Sciences
Department of Adult Psychiatry
60-572 Poznań, Szpitalna Street 27/33
e-mail: janusz.rybakowski@gmail.com