

Letter to the Editor

A FURTHER POSSIBILITY: THE SLEEPING SICKNESS PANDEMIC

Dear Editor,

As a historian of medicine and psychiatry, I would like to draw your attention to an alarming historical possibility and a neuropsychiatric disorder that the COVID-19 pandemic brings to mind. Every report, case presentation, article or news item about the emergence of severe neuropsychiatric conditions in some of the patients recovering from COVID-19 are reminiscent of the significant controversy that occurred a century ago at the time of the Spanish Influenza and warning us of the possibility of facing another dangerous disease, *encephalitis lethargica* (EL), otherwise known as *the sleeping sickness*.

The Spanish Influenza-Encephalitis Relationship

Although COVID-19 has been mostly compared with the Spanish Influenza, the most significant pandemic of the last century, from both clinical and historical points of view, the general impact has been restricted to the practices of “using facial masks” and “the rules of social distancing”. It is noteworthy that very little research has been carried out on the effects of the Spanish Influenza on mental health and the risks of chronic neuropsychiatric outcomes in the long term, despite the ongoing and widespread medical discussion during those years on “encephalitis lethargica”, referred to as the “sleeping sickness epidemic” in Turkey.

The events began towards the end of 1916, before the onset of the Spanish Influenza pandemic, with the observations of Dr Constantin von Economo at the Clinic for Psychiatry and Nervous Diseases at Vienna University of unusual neurological signs in some patients, presenting typically with headache, anhedonia and agitation, leading to a state of drowsiness resembling physiological sleep. Dr Economo noted that this excessively sleepy state comorbid with oculomotor problems resembling partial paralysis of the eye muscles did not clinically fully match any of the neurological disorders known at that time (Lutters *et al.* 2018). In an article published the following year he coined the term *encephalitis lethargica* (EL) to describe this cluster of unusual symptoms. After this initial recognition of the *Sleeping Sickness Pandemic* or *Von Economo's Disease*, further fresh news circulated about this odd disease in Europe and then across the entire world. By 1919, the disease

was spreading in every country in Europe, the USA, Canada and India. Around 1 million people are believed to have been affected by the disease between 1916 and the 1930s (Eghigian 2020, Ravenholt and Foege 1982). By the 1930s, approximately 9,000 articles had been published outside Turkey on the subject of EL (Peng 1993, Foley 2020). However, if a comparative literature review were to be undertaken on the topic of EL during that period, I believe that contribution in the Turkish language would one of the largest.

The Sleeping Sickness Epidemic

We can start with Mazhar Osman, the physician identified with psychiatry in Turkey, in having a name associated with the greatest volume of writing on the subject of EL in the country:

“Encephalitis lethargica, named as sleeping sickness in our country is not the true sleeping sickness written about in medical textbooks. The cause, nature, course and treatment of the sleeping sickness mentioned in these books is completely different. However, we do not have any problems in our country with the naming of Encephalitis Lethargica as Sleeping Sickness, which is more suitable to the language and the understanding of our population (M. Osman 1933).”

Mazhar Osman, in the monthly medical journal, *Istanbul Clinical Practice*, which he published between the years 1920 and 1924, composed a series, consisting of 34 articles, about the Sleeping Sickness. Then, in 1925 he published a book which contained these articles, entitled *The Sleeping Sickness Epidemic* (M. Osman 1925). The book referred to is one of several concerned with EL published across the world in the early years. Mazhar Osman was exceedingly busy dealing with the sleeping sickness at this period, indeed he even claimed that the Spanish Influenza was actually the same entity as EL:

“There is no doubt that the absolutely calamitous epidemic in 1918-1919 in Istanbul, whether called the flu, Spanish flu or the ‘rag disease’, that continues to produce so many victims, is Encephalitis Lethargica.” (M. Osman 1933).

One of the doctors who also wrote about the disease was Nazım Şakir, the student and later colleague of Mazhar Osman. Having remarked that encephalitis did not arrive in Turkey prior to the Spanish Influenza, Nazım Şakir described the first case of EL he detected in Istanbul in the winter of 1918-19 as follows:

“I had seen the first case in Beşiktaş. This patient was a young woman who had come to Istanbul after becoming ill in Gallipoli.

Sleeping continuously, she could be woken up easily to fall asleep again after eating and speaking (...) I saw the patient again one day later and declared the possibility of her having encephalitis lethargica. This possibility induced in me the suspicion that we were facing an outbreak of encephalitis lethargica in Istanbul which till then had been unknown to me. Indeed, after January 1919, the cases gradually began to increase with the numbers diagnosed each day exceeding those made the day before. However, since encephalitis lethargica was a novel disease in our country, our colleagues, other than those who were particularly able or expert, were unable to diagnose the condition and hence a large number of cases remained unknown.” (N. Şakir 1933).

As for the disease symptoms according to Mazhar Osman, sleeping sickness began with chills, shaking, a general state of malaise and aches and pains. In one or two days most of the patients presented with three basic symptoms of sleeping, double vision and pyrexia. The patients began to sleep both day and night; but some, who were unable to sleep just lied down with their eyes closed (M. Osman 1928; M. Osman 1925). The course of Sleeping sickness did not only follow neurological signs, but also involved psychiatric symptoms emerging some time later. The mood of some patients was more severely affected by development of apathy, avolition, avoidance of work or pleasure and not wanting to leave home or even looking out of the window. It is possible that some people who had read, at the time of their publication, the stigmatising remarks and harsh ascriptions about the illness and the patients made by Mazhar Osman, to draw attention to the increase in mental health problems during severe episodes, were so seized with fear that they would “prefer to die rather than to contract this illness”. The few lines below, which are less terrifying and drastic while describing the mental symptoms of the severe episodes, may give a sufficient impression:

“Mental symptoms may be extremely severe during extreme attacks, closely resembling delirium tremens and severe confusional psychoses. Patients become extraordinarily excited and aroused, completely bewildered and in a daze, unaware of time or place; experiencing many visual hallucinations and delusions about their occupations.

(The patient, if a trader, talks about his job; the ticket-seller prepares the account for his takings, the lover sings pathetic songs for his beloved, the young girl combs her hair in front of a mirror, the soldier hears the sound of the bugle and runs to grab his rifle from the wall). In times of an epidemic, however, this is called encephalitis lethargica. In other sporadic cases without nervous symptoms, encephalitis lethargica cannot be predicted.” (M. Osman 1925).

What is beyond dispute for Mazhar Osman is that “*Sleeping sickness is transmissible, so there must be some pathogen. So far this pathogen has not been discovered.*” (M. Osman 1933).

Awakening and Oblivion

Despite the intervening passage of a century, the aetiology of EL remains unknown. Broadly speaking, there are two theories: the environmental theory and the infective theory. However, a third theory may be autoimmunity. Economo, who evaluated the parallel increase in the cases of this sickness

with the Spanish Influenza pandemic, stressed the possibility that sleeping sickness could be a type of influenza associated encephalitis. Relying on the findings in the brain tissue taken during autopsy, he reached the conclusion that this was an infection of viral origin. Interestingly, EL disappeared in the years when the effects of the Spanish Influenza completely disappeared. The hypothesis of new studies made in 2004 was the possibility of EL being a post-infective autoimmune disorder. The increase in the cases of narcolepsy in some European countries during the 2009 H1N1 influenza pandemic raised again the issue of the connection between the Spanish Influenza and EL (Hoffman and Vilensky 2017).

EL became the subject of the book, “Awakenings”, by Oliver Sacks, published in 1973 (Sacks 2003) and the script of a Hollywood made film shot in 1990, when a long forgotten event was watched with interest. The film, describing the re-awakening of post-encephalitis patients by L-Dopa in a New York care home, showed how encephalitis darkened the lives of humans while brightening the careers of the stars Robin Williams and Robert De Niro.

The relationship between Spanish influenza, neurological disorders and EL has not been the subject of historical research for many years. One exceptional study in this field was by Mamelund (2003), who investigated mental hospital admissions in Norway during the years 1872-1929. He noted that the mean annual incidence of first time hospitalisation for mental disorder cases attributed to influenza increased some 7.2 times over the six years following the Spanish Flu pandemic. He demonstrated that the complaints of the surviving Spanish Flu patients included sleep disorders, depression, mental confusion, dizziness and difficulties in coping with work. Another noteworthy research reported that cases of EL peaked exactly four years after the appearance of the Spanish Influenza epidemic, demonstrating the remarkable concurrence of these events (Foley 2009).

The COVID-19-Encephalitis Relationship

Various investigations made in the past years on the possible effects of human coronavirus on the central nervous system. The study tested the hypothesis that an infective respiratory pathogen can penetrate the central nervous system and cause inflammation of the brain. One study testing the human coronavirus strain OC43 on the animal model reported occurrence of acute encephalitis and neuronal degeneration linked to the infection particularly in susceptible mice injected with the virus. After complete clearance of the virus from the bloodstream, the viral RNA persisted for a number of months in the mouse (Jacomy *et al.* 2006).

As the COVID-19 pandemic took hold, the first published articles were on the possible entry by the SARS-CoV-2 into central nervous system and its effects. Subsequently the first actual case of encephalitis followed by further novel cases of encephalitis were reported (Ye *et al.* 2020, Wu *et al.* 2020). One of the earliest studies carried out in the city of Wuhan in China reported incidences of neurological symptoms of

varying severity, mainly consisting of headaches and dizziness, in 36.4% of the 214 patients admitted to the hospital (Mao et al. 2020). The first case of viral encephalitis due to SARS-CoV-2 was reported on 4th March 2020 at the Ditan Hospital in Beijing. It drew attention to the potential of the virus to cause damage to the central nervous system (Xiang et al. 2020). Autopsies on COVID-19 infected patients demonstrated cerebral oedema (Xu et al. 2020).

Considerable literature had already accumulated before the end of the first 6 months of the COVID-19 pandemic by the increasing number of published articles on the neurological signs and disorders due to the viral infection, which, on the basis of a systematic review, include hyposmia, headache, weakness, altered states of consciousness, encephalitis, demyelination, neuropathy and stroke (Montalvan et al. 2020, Whittaker et al. 2020).

Two brief articles drawing direct attention to the historical possibility mentioned above have recently been published. That by Giordano et al. (2020) draws attention to the fact that the spread of the virus within the central nervous system may overlap with Economo's hypothesis, reminding us that it is still unknown whether the infection, starting in the olfactory bulbs, triggers off neurodegenerative changes in the patients and that the potential of this virus to create neurological sequelae after a long interval must not be underestimated. The article by Badrfam R and Zandifar A (2020), titled "*From encephalitis lethargica to COVID-19: Is there another epidemic ahead?*" points to the ability of the virus to produce persistent neurological lesions, explaining that, just as it had happened a century ago, symptoms of Parkinson Disease can develop over the years following encephalitis.

CONCLUSION

The general history of medicine in the twentieth century may well be called the century of "forgetting" or "not remembering" especially from the point of view of historical epidemics. The medical historian Snowden (2019) describes this situation as *historical amnesia* and *social amnesia*. The "fear" and "danger" of the COVID-19 pandemic has reminded us of the Spanish influenza pandemic of the previous century. Despite knowing the agent causing the disease, we still do not have complete knowledge of the mechanisms behind the pathogenesis and progress of the disease and its physical and mental effects.

The uncertainty on the Spanish influenza being the cause of EL may be resolved through new historical research on the relationship between these events. At present, we do not know whether COVID-19 will give rise to similar clinical scenes of encephalitis in the years to come. However, in comparison the situation one century ago, we have the advantage of paying attention to historical evidence and keeping in mind,

while evaluating the neuropsychiatric findings generally and encephalitis cases in particular during the current pandemic, that long-term follow-up of the patients will be required even after recovery.

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