Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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From encephalitis lethargica to COVID-19: Is there another epidemic ahead?

Historically, we have seen the only epidemic of encephalitis lethargica, about 100 years ago [1]. A syndrome that was identified in 1916–1917 and about 10 years later, a large number of patients were diagnosed with it [2]. It is estimated that about one million people develop the syndrome at that time [3]. In addition to the risk of death in a relatively large number of patients, other manifestations of post-encephalitic Parkinsonism may have developed over time, which could have been years later [4].

Encephalitis lethargica manifests itself with symptoms such as extrapyramidal movement deficit and other symptoms of profound sleep impairment and neuro-psychiatric manifestations [5]. About six years after the initial report, its peak was recorded in the United States with 2000 deaths [6]. The total number of people who lost their lives during that 6-year period was more than 150,000 around the world [7]. The point of attention was the relative synchronicity of encephalitis lethargica with the influenza pandemic in 1918, although the peak of encephalitis lethargica was about 4 years after the influenza peak [8]. Since then, various studies have been conducted on the causes of the disease and its epidemic but many researchers, despite the coincidence of the disease with the influenza pandemic, did not consider the direct role of influenza in the development of this disease [3].

In 2003, Dale et al. reported that about 20 patients with suspected manifestations of encephalitis lethargica, such as sleep disorders, lethargy, Parkinsonism, dyskinesia, and neuropsychiatric symptoms, increased protein and oligo-clonal bands in their spinal fluid [9]. They considered the condition to be related to post infectious autoimmune disorder. They reported an increase in anti-streptolysin-O in 60 % of cases and active autoantibodies against human basal ganglia antigens in 95 % of these patients. According to their report, these antibodies bind to neurons more than glial populations. They concluded that, in their view, encephalitis lethargica -like syndrome was still common, and that the syndrome may be secondary to autoimmune against deep gray matter neurons.

Following the COVID-19 pandemic, cases of encephalitis have been reported that could indicate a possible involvement of the central nervous system in COVID-19 [10]. The formation of neurological manifestations of COVID-19 has raised serious concerns about the development of chronic neurological disorders associated with the disease [11]. However, conclusions in this area need further and more accurate assessments [12].

In 2006, the assessment of the likelihood of damage to the central nervous system and related neurological disease was investigated using the OC43 strain of human coronavirus in animal models [13]. In the laboratory, neurons degenerated during infection. Also, following intracerebral inoculation of HCoV-OC43, acute encephalitis was seen with neuronal cell death and apoptosis. In the samples tested, although the virus was completely cleared of blood, viral RNA remained for several months. Some mice showed motor manifestations several months after the initial infection. These results showed that in susceptible groups, coronaviruses could be associated with increased neurogenic degeneration followed by neuropathology and motor deficits.

Also, according to laboratory models, after acute infection of human neurons by Human coronavirus OC43, it is possible for the infection to persist in human neural cell lines following spot mutations in infected cell lines [14]. In addition, some point mutations were seen in a group of molecular clones that indicate the evolutionary course of the viral population.

In the field of autoimmune induction by various organisms, a report was published on the experimental model of retinopathy by the murine coronavirus. (Experimental Coronavirus Retinopathy-ECOR) [15]. The report described the phenomenon as a function of induction, duration, and intensity of innate immune reactivity. This model is based on the interaction between the viral component, the genetic and immunological component, and was formed during the chronic stage of the disease (between 10 and 120 days later) and among some species.

The above characteristics can be indicative of the ability of coronaviruses to produce persistent neurological lesions. Acute COVID-19-related encephalitis, along with the potentially long-term worrying consequences of the disease, underscore the need for clinicians to pay attention to the suspected cases of encephalitis in this regard. The use of appropriate diagnostic methods in clinically suspicious cases and follow-up of acute cases of encephalitis after recovery can be effective in identifying probable cases with chronic manifestations.

Declaration of Competing Interest

There is no conflict of interest.

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