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Letter to the Editor

Encephalitis lethargica. What is still wrong?

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A Di Vito[1], A Donato[2], J Bria[1], F Donato[3,4] and G Donato[2]

Abstract

Encephalitis lethargica developed in epidemic from 1919 to 1926 in Europe and throughout the world. From the clinical point of view, the disturbances of consciousness and alertness and the possible outcomes of a postencephalitic Parkinsonism has attracted much attention. For a long time, it was thought that such a disease may still occur sporadically. In this review, the authors examined historical and current pictures of epidemics that may be related to *Encephalitis lethargica*. The previous *Nona* and *Russian Influenza* exhibited frequent neurological symptoms. The *Spanish flu*, formerly related to *Encephalitis lethargica*, would appear an epidemic that had its development in a partially overlapping period. The current pandemic linked to *COVID-19* sometimes has aspects that can resemble *Encephalitis lethargica*. Based on historical analysis and the more recent immunological data, it could be suggested that *Encephalitis lethargica* was an autoimmune encephalitis that arose in a secondary form to the action of a viral agent. It cannot be ruled out that this agent was a coronavirus. From the nosological point of view, the term *Encephalitis lethargica* should be abolished in designating autoimmune encephalitis pictures that run sporadically.

Keywords

Encephalitis lethargica, autoimmune encephalitis, virus, *Russian influenza*, *Spanish influenza*, COVID-19, pandemics, history of medicine

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Introduction

Jean-René Cruchet first described *Encephalitis Lethargica* (EL) in the winter of 1915–16 in French soldiers in Verdun, but other cases have been previously described in the spring of 1915 in Rumania and Bulgaria.[1] EL spread in a pandemic form in Europe, North America, and the Soviet Union between 1916 and 1930 and it was estimated that more than one million people have been affected.[2,3] Although Jean-René Cruchet was the first to present cases of EL, he did not report detailed description of the patients until 1928. Conversely, Constantin von Economo on April 17, 1917, presented a detailed clinical picture of EL which also bears his name, to the Psychiatric Society of Vienna.[4] The fact that Jean-René Cruchet did not report any anatomopathological data, as well as his doubts on the infectious nature of the disease have strongly led to a lower consideration of his theories in the following years.[5] Von Economo's theories were instead less discussed and still find greater consensus today.

[1]Department of Experimental and Clinical Medicine, University Magna Graecia of Catanzaro, Catanzaro, Italy
[2]Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy
[3]CeRPS Foundation (Research Center on Psychiatry and Social Sciences), Nocera Inferiore, Italy
[4]Giuda Lab, Department of Mechanical, Energy and Management Engineering, University of Calabria, Arcavacata di Rende, Cosenza

Corresponding author:
A Di Vito, Department of Experimental and Clinical Medicine, University Magna Graecia of Catanzaro, Viale Europa, Catanzaro 88100, Italy.
Email: divito@unicz.it

Von Economo was born in 1876 in Romania into a Greek aristocratic family. He spent his childhood and adolescence in Trieste, which belonged to the Austro-Hungarian Empire. He attended the Medical School at the University of Vienna, where he held the position of professor of Psychiatry and Neurology from 1921 until his death in 1931. Certainly, such noble of Greek origin was endowed with a lively mind and serendipity, as evidenced by his initial reflection on the new pathology: "Since Christmas we have been able to observe in the psychiatric clinic a series of cases that do not meet the criteria of our usual diagnoses. Despite this, they show a similarity in the form of onset and in their symptoms that force us to group them into a single clinical entity."[4] EL was originally classified into three clinical forms: somnolent-ophthalmoplegic, hyperkinetic, and amyostatic-akinetic, demonstrating a heterogeneity that could be linked to a different distribution of subcortical anatomical damages.[6] The "delirious somnolence" described by Von Economo was preceded by meningeal signs and fever and could lead to death or sequelae, among which the postencephalitic Parkinsonism will prove to be of extreme importance.

From the neuropathological point of view the clinical picture was described in this way: "Therefore we have the histological picture of a *polioencephalitis cerebri*, *pontis* et *medullae oblongatae*, with a slight poliomyelitis of a perivascular, inflammatory and diffusely infiltrative but not haemorrhagic and only slightly neuronophagic character."[2,4,7] After the first outbreak, only rare cases have been reported. The histopathological picture of the sporadic cases appeared like that of EL described by von Economo: presence in the acute phase of perivascular infiltrates of lymphocytes and plasma cells in the basal ganglia and in the midbrain; persistence of infiltrates in the chronic phase, even for many years after the acute episode; activation of microglia; neuronal loss and astrocytic gliosis in *substatia nigra*.[8]

The etiology of EL is far to be elucidated. While the historical reports of EL seem to suggest a viral origin, no elements to confirm or exclude this theory have been reported. Similarly, "alternative" hypotheses such as that of autoimmune encephalitis still appear poorly supported by scientific data.[9] Although the most recent data have ruled out the old hypotheses of links to the Spanish flu that broke out in 1918,[9,10] we believe that a careful analysis of history, through the current acquisitions in the field of immunology and neuroscience can suggest interesting hypotheses on the pathogenesis of EL. In this article, the authors reviewed some salient features of the pandemic that occurred in the last century, highlighting the neuropathological and clinical picture where available. Attention has been directed to the epidemic suggestive of EL and the analysis has been conducted from a historical and scientific perspectives to shed new light on the mystery of EL.

Lessons from historical and contemporary epidemics

During the last one hundred and 30 years, some major epidemics from infectious agents showed the involvement of the central nervous system (CNS) at different extent, accompanied by neuropsychiatric symptoms.[11] Some of these epidemics have been directly or indirectly related to EL. Below, in this paragraph, we have discussed the main types.

The Nona

From a review of old and recent literature, it appeared that in past centuries flu-like epidemics were characterized by the loss of consciousness.[12] An interesting first event in the history of epidemics of the last century is the spreading of a pathology called "Nona." On PubMed, it's possible to find a short paragraph concerning this subject, which appeared in the magazine Hospital on April 12, 1890, entitled "The New Disease *Nona*." We can read: "On interviewing the Medical Superintendent of the Ospedale Maggiore at Milan, an institution with accommodation for from two to three thousand patients coming from all parts of Lombardy, a member of our staff learns that nothing is known of '*Nona*' there. No cases had been reported in the strictly medical journals, and no cases had been brought into hospital. The cases described in the papers were probably ordinary examples of trance presenting no features not already well understood."[13] The *nona* was firstly described in northern Italy and central Europe in the winter of 1889/90, although similar cases were reported in Portsmouth and New York. The origin of the term *nona* ("ninth" in italian) is not clear; some authors suggested that it referred to the number of days its victims could hope to survive. Also, some authors have referred to it as "nonna" ("grandmother"), but it could simply refer to the year 1890.[12] After 1890, the *nona* survived only in the memories of patients who experienced it. Interestingly, von Economo remembered his grandmother's tales about the *nona*, observing the first cases of EL. Despite the lack of solid scientific evidence, Von Economo also suggested that it represented an earlier EL epidemic.[14] However, very little was known about the *nona*. The published medical literature was limited to a few cases. Moreover, both the causative agent and neuropathological pattern were unknown. The potential link between such a disease and EL was the deep somnolence reported in both conditions.[12] Based on these considerations, we can conclude that the parallels between EL and "*nona*" do not provide useful information for understanding the etiopathogenesis of EL. In the same period of *nona*, a new epidemic called *Russian Influenza* broke out.

The Russian influenza

The *Russian Influenza* (RI) pandemic spread between 1889 and 1894. It was not only the first epidemic in the industrial era but also the first in the era of bacteriology and one of the widely reported in daily press. Such a disease came from the East, probably from Kazakhstan through Russia, and then spread to Europe, America, and the whole world. In St. Petersburg, the first cases of influenza occurred in October 1889 and the epidemic spread in November reaching a very large scale; indeed, about 150,000 people developed the disease.[15] Despite the low mortality (between 0.10% and 0.28%) the epidemic caused one million deaths in various waves. RI presented itself as an influenza-like syndrome in which neurological alterations such as lethargy could be present; moreover, neuralgia, neurasthenia, neuritis, nerve exhaustion, grippe catalepsy, psychosis, prostration, inertia, anxiety, and paranoia have also been described.[16,17]

Serological investigations on subjects born before or during the epidemic, suggested that the RI was due to a flu virus and precisely to the H3N2 virus, subsequently associated to the Hong Kong flu in 1968.[18] Later, other observations suggested that the agent of the Russian flu was the H3N8 virus.[19] However, clinical and laboratory data also suggest a coronavirus as a possible cause of the RI. A reconstruction of the evolutionary relationships of three species-specific group 2 coronaviruses (Betacoronavirus, which also include SARS-CoV and SARS-CoV-2) and, namely, bovine coronavirus (BCoV), human coronavirus OC43 (HCoV-OC43), and porcine hemagglutinating encephalomyelitis virus (PHEV), highlighted the possibility that they shared a recent common ancestor.[20] The estimate timing of the most recent common ancestor of HCoV-OC43 and BCoV was from 1873 to 1891; however, examination of the molecular clock data led to a more precise estimate around 1890.[21] Using such a molecular dating to investigate the origin of viral epidemics, HCoV-OC43 has been suggested as the most likely for RI pandemic, proposing a potential bovine trans-species infection.[22]

The clinical picture of the Russian was very interesting. Some authors stressed that the main form of presentation was "nervous influenza."[23,24] Severe headache, severe fatigue, and fever forced the patient to bed, and in a short time the patient developed depression, psychosis, and delirium which could resolve in a short time or persist for weeks without interruption. This status strongly resembled the "delirious somnolence" described by Von Economo, further reinforcing the idea of a common trigger.

These clinical aspects, together with the ability to affect different organs and tissues, the frequency of relapses and the presence of neurological symptoms including anosmia, recall those of COVID-19.[16] In summary, the causative agent of the RI has not yet been definitively established, but its discovery could be useful in understanding the origin of later epidemics such as EL and possibly even the current pandemic.

The Spanish influenza

The denomination of *Spanish Influenza* (SI) found its roots in socio-political context. Iberian Peninsula was neutral in the period of the First World War and the information was not confidential, so that Spanish doctors could describe the characteristic of the flu epidemic in April 1918. Even if the start of the pandemic was not clearly defined, one theory suggested that the pandemic began in the Fort Riley military camp in Kansas in March 1918 with a major flu epidemic among the recruits arriving from the Middle West leaving for Europe.[25,26]

The influenza pandemic of 1918–1919, called "*Spanish influenza*" or "Spanish flu," was caused by an extremely virulent virus (H1N1 influenza A virus) and had three fundamental characteristics: a high mortality, a rapid death after the appearance of the first symptoms and most victims from young adults.[27] The pandemic was divided into three major waves. The first wave in the spring of 1918 was moderate but rapidly progressive. The second wave in the autumn of 1918 was severe and destructive. The third, in the spring of 1919, had intermediate characteristics between the first two. Between the spring of 1918 and the winter of 1919, at least 50 million people worldwide died from the SI. However, it's important to underlie that high mortality could not be a direct consequence of viral infection; indeed, most of the victims showed a secondary bacterial pneumonia.[26]

The complete genomic structure of the 1918 SI virus was published in a paper by Taubenberg and coll. in 2005. The genetic material was extracted from lung samples from a corpse of an Alaskan Inuit woman found frozen in a mass grave under the permafrost, and from autopsy samples from American soldiers. The virus, classified as "avian-like" viruses, could have passed through intermediate hosts such as pigs; however, a direct jump from birds to humans has also been suggested.[26,28–32] The subsequent recovery of the virus using reverse genetic techniques also confirmed its virulence in mice and embryonated chicken eggs.[33]

Given the apparent temporal overlap and based on epidemiological data, it was believed until recently that the SI virus could also be the causative agent of EL.[34] However, most deaths were pulmonary, and many patients succumbed to secondary bacterial pneumonia, as we have previously mentioned. Other patients died within a few days of the onset of respiratory symptoms from either acute pulmonary hemorrhage or massive pulmonary

edema. At death, pathological lesions other than pulmonary were almost absent.[35,36] Furthermore, the failure to find the viral RNA H1N1 in the autopsy pieces of patients who died of EL also rebutted the hypothesis that EL derived from the Spanish flu virus.[10]

COVID-19

Coronaviruses are widely distributed between humans and animals and cause respiratory, enteric, liver, and neurological diseases. They are a group of enveloped and positive-sense single-stranded RNA viruses, with large genomes around 30 kb in size. SARS-CoV-2 is the seventh member of the coronavirus family known to have infected humans. Prior to the SARS-CoV-2 outbreak, the 21st century experienced major outbreaks caused by two other coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Such epidemics resulted from two zoonotic coronavirus that crossed the species barrier and caused high morbidity and mortality in human populations. SARS-CoV-2, SARS-CoV, and MERS-CoV show several similarities related to clinical presentations, which can range from asymptomatic infection to severe disease with severe acute respiratory syndrome. Genetic sequence analysis revealed that SARS-CoV-2 belongs to the β-coronavirus genus, with nucleotide identity of 79.0% with SARS-CoV and identity of 51.8% with MERS-CoV.[37] Interestingly, SARS-CoV-2 is 96% genome-wide identical to a bat coronavirus.[37] Autopsy studies on patients died from COVID-19 have shown that lung lesions are predominant with a picture of diffuse alveolar damage and consequent organized pneumonia. Furthermore, a probable renal tropism and widespread pictures of endothelitis have been described.[38] The endothelial damage and general alterations in coagulation parameters have also been reported in COVID-19 patients classified as severe. Accordingly, in these patients, a hypercoagulable state with widespread thrombosis and fibrinolysis can be observed, along with abnormal findings of biomarkers such as D-dimer, von Willebrand factor (vWF), factor VIII, prothrombin time, platelet count, ADAMTS13, Interleukin 6 (IL-6), fibrinogen, and antiphospholipid antibodies. The inflammatory state associated to the so-called "cytokine storm" found in the course of the disease, is also a determining factor in the widespread phenomena of arterial and venous thrombosis.[39]

Since the onset of the pandemic, more than one third of patients have been observed to have symptoms attributable to the central nervous system such as cerebrovascular disease or impaired consciousness.[40] Neuropathological picture suggested at least three different mechanisms of brain damage by SARS-CoV-2 infection. In a first hypothesis, brain damage could be determined by the presence of the virus in the brain.[41] Accordingly, viral particles can be found in brain tissue or olfactory bulbs by immunohistochemistry, in situ hybridization, transmission electron microscopy or molecular methods such as RT-PCR.[42] Alternatively, clinical manifestations such as hypoxic state, coagulopathy, general metabolic alterations, and cytokines could explain all brain dysfunctions.[41] Indeed, in autopsy cases, the neuropathological picture may include acute cerebrovascular accidents, lacunar infarcts, small hemorrhages, but also evident encephalitic pictures or signs of activation of microglia and perivascular lymphocytic infiltration. A third proposed mechanism was autoimmune encephalitis, characterized by the development of host antibodies that cross-reacted and identified self-antigens as foreign. Indeed, a broad spectrum of autoimmune encephalitis is associated with the development of antineuronal antibodies (such as antibodies to the N-methyl-d-Aspartate receptor (NMDA-R)), anti-gangliosides antibody (such as anti-GAD antibody), and onconeural antibody (such as anti-amphiphysin antibody).[43–46] From a clinical point of view, during COVID-19, disturbances of the sleep-wake cycle and psychiatric signs have been described and some authors have pointed out a state of permanent clouding of the sensory over time in patients who have passed the acute phase, the so-called "brain fog."[17,47] These psychiatric disorders are reminiscent of those reported during the EL, further corroborating the idea to explore for a coronavirus as etiological agent of the EL.

Discussion

The first recognized outbreak of "Encephalitis Lethargic" took place in the period between 1915 and 1926. Clinical manifestations included disturbances of alertness and consciousness with frequent involvement of the extrapyramidal system, months, or years after the infection. In the following decades, in scientific literature, it was suggested that this disease is still present in a sporadic form or in an apparently low endemic rate. Such a disease was recently included in immune-mediated extrapyramidal movement disorders and in autoimmune encephalitis.[48] The triggers of this class of disorders could be unknown environmental or genetic causes, or in most cases viral or bacterial infections and tumors.[48,49] It's remarkable that autoimmune encephalitis may be as common as infective encephalitis.[50] Autoimmune encephalitis are disorders in which the immune system targets self-antigens expressed in the central nervous system by the production of autoantibodies. Many viruses capable of epidemic spread in humans can give rise to autoimmune encephalitis through different mechanisms, such as molecular mimicry, epitope spreading, bystander activation and persistent infection and polyclonal expansion.[51]

Interestingly, general clinical features seem to suggest a similarity between the symptoms of pediatric patients

affected by EL (predominantly psychiatric, sometimes with striking behavioral changes) and current autoimmune encephalitis.[52,53]

Based on clinical, neuropathological data and the epidemic course of EL, the infectious and autoimmune hypothesis appears to be the most accredited. The fact that the causative agent has not yet been found may be related to its clearance in the examined tissues, in the phase in which the autoimmune response was triggered.[54]

In our opinion, the historical information of EL plays a key role in the establishment of epidemic origin. As pointed out by some authors in the last decades, no hypothesis can be excluded: viruses, bacteria, toxins, secondary effects of infectious agents, or other degenerative conditions could all be considered as etiologic factor in EL. While the infectious hypothesis appears the most probable, the fact that the EL epidemic began in 1915 is the most important proof allowing us to exclude any association with SI and its virus. Moreover, the current pandemic has also made us reflect on the possibility that two viruses can spread in epidemic form at the same time. Indeed, as observed during COVID pandemic, coinfection may account for overall higher mortality and worse patient outcome.[55] In the history of EL, many viruses have been suggested as causative agent for EL. The arboviruses, included in the families *Togaviridae* and *Flaviviridae*, the poliovirus, the coxsackieviruses and echoviruses, belonging to the Enterovirus group (*Picornaviridae*), and *Orthomyxoviridae* represent just some of the viruses suggested as responsible for EL development.[56] The SARS-CoV-2 pandemic has focused the attention on the *Coronaviridae* family. As previously mentioned, in the past some authors speculated on the potential role of coronaviruses in long-lasting pandemics such as the so-called "Russian Influenza." Overall, the available data regarding viral and autoimmune encephalitis suggest that the encephalitis described by von Economo was caused by the spread in epidemic form of a viral infection which in turn triggered a picture of autoimmune encephalitis.

Conclusions

Based on the above considerations, we believe that the identification of the causative agent of EL needs further investigations. For example, archival tissues derived from patients died from this disease could be further checked for specific virus. Given the lack of solid evidence on the etiopathogenesis of EL, we would like to suggest a nosological consideration. Even though clinical pictures characterized by lethargy can be associated with almost all types of viral or autoimmune encephalitis (including the epidemic encephalitis reported in this paper), we suggest that the term "*Encephalitis lethargica*" is not used for similar clinical picture currently present in sporadic form, until the causes of the pandemic form described by von Economo will be definitively clarified.

Author contributions

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ORCID iD

A Di Vito https://orcid.org/0000-0002-8294-8684

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