

## DORSAL COLUMN

### Grey Matter

# Encephalitis lethargica: 100 years after the epidemic

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Encephalitis lethargica is a neurological syndrome that spread across Europe and then the world beginning in the winter of 1916–17, and continuing into the 1930s. Although the exact number of people afflicted with encephalitis lethargica during the epidemic period is unknown, it is estimated to be more than one million worldwide (Ravenholt and Foege, 1982). Those who survived were sometimes left with lingering and permanent neurological sequelae that rendered them nearly akinetic. Although 100 years have elapsed since the beginning of the epidemic period, many questions remain about this mysterious illness: What causes it? How is it transmitted? Could an epidemic happen again?

## History of encephalitis lethargica

In late 1916, while treating patients in the Psychiatric-Neurological Clinic of the University of Vienna, Dr Constantin von Economo examined several patients who presented with unusual neurological symptoms. The patients had been admitted with varying diagnoses such as meningitis, multiple sclerosis, and delirium; however, none of them matched well into any known diagnostic scheme. In particular, many of the patients presented with marked lethargy. Von Economo considered the uniqueness of this set of symptoms as a distinct disease entity, which he described in a 1917 manuscript entitled *Encephalitis Lethargica*.

Contemporaneous to von Economo, a French physician, René Cruchet was treating similar patients in a military hospital for neuropsychiatric disorders. Cruchet, too, believed that these cases differed from previous cases of encephalomyelitis, and his own description of the disease was published within a few days of von Economo's. Cruchet and von Economo's papers were followed by many more articles as the disease spread across Europe and then around the world. During the epidemic period, approximately 9000 papers were published about this perplexing illness (Peng, 1993).

Although encephalitis lethargica was first officially recognized as a separate disease entity in 1917, Crookshank (1918) identified several historical epidemics that resembled encephalitis lethargica, including the English sweats (England, 1529), *mal mazzuco* (Italy, 1597), *Kriebelkrankheit* (Germany, 1672–75), *Rafania* (Sweden, 1754–57), and *nona* (Italy, 1890–91). Further, in 1921 Urechia proposed that the initial appearance of encephalitis lethargica during the epidemic period was in early 1915 rather than 1916, and most likely in Romania. The movement of troops across Europe during World War I likely facilitated the spread of encephalitis lethargica, which reached epidemic status in Vienna in 1917, followed by France and England in 1918. By 1919, the epidemic had overrun most of Europe, the USA, Canada, Central America, and India. During the epidemic period, peaks of encephalitis lethargica occurred in 1920 and 1924. Subsequently, acute cases became less common, although many patients suffered chronic neurological

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sequelae that persisted long after the epidemic period. There has been no epidemic recurrence of encephalitis lethargica since the early 20th century, but putative sporadic cases continue to occur.

## Clinical presentation

Encephalitis lethargica was classically characterized by acute and chronic phases, although the two often blended together. During the acute phase, patients typically experienced excessive sleepiness, disorders of ocular motility, fever, and movement disorders, although virtually any neurological sign or symptom could be exhibited, with day-to-day, and even hour-by-hour shifts in symptomatology. The chronic phase could occur months to years later and was most commonly characterized by parkinsonian-like signs.

Acute encephalitis lethargica often presented as a gradual onset of non-descript flu-like symptoms, including malaise, low-grade fever, pharyngitis, shivering, headache, vertigo, and vomiting. Neurological symptoms followed and could present very quickly, as in the case of a girl who experienced a sudden hemiplegia while walking home from a concert. Within half an hour she was asleep, and died 12 days later.

To facilitate diagnosis among the vast array of symptoms, von Economo classified acute encephalitis lethargica into three forms: somnolent-ophthalmoplegic, hyperkinetic, and amyostatic-akinetic; although many other types were described during the epidemic period.

The somnolent-ophthalmoplegic form was the most common and typically developed soon after onset of prodromal symptoms. Patients became dazed, confused, and delirious, and often exhibited features of mild meningeal irritation. Cranial nerve palsies were also a common feature, particularly affecting nerves III, IV and VI, resulting in ophthalmoplegia and pupillary abnormalities. Most notably, patients experienced an overwhelming desire to sleep and would sleep for abnormally long periods of time, but were easily awakened and often aware of everything that had transpired around them while in this state of pseudo-somnolence. The mortality rate for the somnolent-ophthalmoplegic form was higher than that of other forms of encephalitis lethargica, exceeding 50%; however, a greater number of survivors experienced few or no long-term sequelae than in the other forms.

The hyperkinetic form presented with an initial manic phase during which the patient experienced chorea, vocalizations, myoclonic twitches, and myorhythmia of the ocular and masticatory muscles. (Oculomasticatory myorhythmia is also indicative of Whipple's disease, but it is not known whether the movement disorder seen in the hyperkinetic form of encephalitis lethargica is the same or different from that seen in Whipple's disease). The manic phase was followed by generalized restlessness, weakness, and fatigue that persisted for days. During this hypomanic phase, patients experienced neuralgic pain in the face and

limbs, visual and tactile hallucinations, and day-night sleep cycle reversal.

The amyostatic-akinetic form was the least common form of acute encephalitis lethargica proposed by von Economo. With this form, patients experienced rigidity and lack of movement with no noticeable weakness. Patients were very slow to alter their posture, and any such movements were minimal. Patients often exhibited *flexibilitas cerea*, or waxy flexibility. In this state, patients remained rigid and immobile for long periods of time, but the rigidity could be overcome with slight external force. Patients with the amyostatic-akinetic form remained mentally intact, but emotions were hardly noticeable on masked faces. Recovery could be slow or rapid, with the condition sometimes lasting several months.

The chronic phase of encephalitis lethargica typically developed 1 to 5 years after the acute phase, but it could also follow immediately, or more than a decade later. One patient developed a postencephalitic syndrome 45 years after initial infection (Sacks, 1990). The chronic phase was characterized by parkinsonism, but sleep disturbances, oculomotor abnormalities, involuntary movements, speech and respiratory abnormalities, and psychiatric disorders were also common features. In the decades following the epidemic, it was estimated that as many as 50% of parkinsonism cases were postencephalitic (Krusz *et al.*, 1987).

Postencephalitic parkinsonism typically presented with stiffness and bradykinesia that affected the upper limbs more than the lower limbs. Unlike idiopathic Parkinson's disease, patients who suffered from postencephalitic parkinsonism frequently displayed *kinesia paradoxical*—a condition in which the patient was akinetic one moment, and perfectly mobile the next. Movement was typically triggered by some external stimulus, such as a ball being thrown. Chronic encephalitis lethargica was also associated with other movement disorders including chorea, torsion spasms, myoclonus, and tics affecting the jaw, lips, tongue, and palate.

Oculogyric crisis was a common feature of chronic encephalitis lethargica, occurring in 15–20% of patients at the height of the epidemic, and ~30% of postencephalitic patients in the following decades (Sacks, 1990). Oculogyric crisis is an involuntary upward deviation of the eyes that persists seconds to hours. Consciousness remained intact during the crisis, but the patient was unable to voluntarily move his eyes, except with great effort and only momentarily. The frequency of oculogyric crises varied from patient to patient, and could sometimes be precipitated by emotions.

Chronic encephalitis lethargica was also associated with psychiatric manifestations, which included changes in mood, feelings of euphoria, increased sexual drive, hallucinations, and excessive puns, joviality, and silliness. Psychosis was present in 30% of patients, but milder psychiatric disorders were very common. Mental changes appeared to be more pronounced in children than in adults, with reports of self-mutilation, including one extreme case involving an 8-year-old girl who extracted all of her teeth and self-enucleated both of her eyes.

One of the authors (J.A.V.) has questioned the direct relationship between the acute and chronic phases of encephalitis lethargica owing partly to the long delay—decades, in some cases—between the acute infection and the development of postencephalitic parkinsonism. There are also reports of regional epidemics that were not followed by postencephalitic parkinsonism. Furthermore, many postencephalitic patients could not recall having had an acute case of encephalitis lethargica in the past. In fact, more patients recalled having had influenza than encephalitis lethargica. Therefore perhaps acute encephalitis lethargica is not a necessary prerequisite to developing postencephalitic parkinsonism, but merely a contributing factor.

## Pathology

Gross examination of brains from patients who died of acute encephalitis lethargica showed hyperaemic meninges, a soft, oedematous brain, and reddish discolouration of the brainstem. Von Economo noted that the upper midbrain and substantia nigra showed the most evident changes, followed by the basal ganglia, pons, medulla, and thalamus, which he believed conformed well with the clinical features of the illness. He also noted lymphocytic infiltration of the adventitia of the blood vessels (especially small and medium-sized veins), and widespread, diffuse haemorrhagic and inflammatory lesions, suggestive of an acute infectious process.

At the time of the encephalitis lethargica epidemic, narcolepsy was a recognized illness, and von Economo described a narcolepsy-like disorder associated with encephalitis lethargica. In the brains of patients who succumbed to the somnolent-ophthalmoplegic type of encephalitis lethargica, von Economo observed pathological involvement of the posterior hypothalamus. Given the similarities in symptoms, recent research on narcolepsy could shed light on the hypersomnolence observed in many encephalitis lethargica patients. The most common form of narcolepsy involves a deficiency in hypocretin (orexin), a neuropeptide that promotes wakefulness. The deficiency has been found to result from autoimmune destruction of hypocretin-secreting cells in the hypothalamus.

In the chronic phase of encephalitis lethargica, the brain showed modest degrees of focused or generalized atrophy. Microscopic examination showed evidence of both old and new inflammation, suggestive of persistent infection. Neuropathology of postencephalitic parkinsonism shows marked neuronal loss and gliosis throughout the brainstem, but particularly in the substantia nigra and, to a lesser extent, locus coeruleus. It is not known whether there are pathological differences in the brains of postencephalitic patients with and without a preceding history of acute encephalitis lethargica.

Neurofibrillary tangles (NFTs), which were first identified in 1907 by Alois Alzheimer in the brain of a demented patient, were discovered in 1932 in the brainstem of a

postencephalitic patient who showed no signs of dementia. Subsequent studies of postencephalitic parkinsonism found NFTs in various other regions of the brain including the substantia nigra, locus coeruleus, pons, hypothalamus, subthalamic nucleus, red nucleus, globus pallidus, corpus striatum, and hippocampus. Neurofibrillary tangles are found in a variety of neurodegenerative disorders, and the use of NFTs as a means to distinguish between various degenerative neurological diseases has been a recurrent topic of interest. For example, postencephalitic parkinsonism and progressive supranuclear palsy are nearly identical histopathologically; however, the NFTs present in postencephalitic parkinsonism are composed of both 3R and 4R tau isoforms, similar to those seen in Alzheimer's disease, whereas the NFTs present in progressive supranuclear palsy are almost exclusively 4R tau isoforms. The significance of the NFTs and the differences in their compositions remain to be determined.

## Epidemiology

The number of people worldwide who contracted encephalitis lethargica during the epidemic period is unknown, although the highest estimate puts the figure at more than one million (Ravenholt and Foege, 1982). Early in the epidemic, encephalitis lethargica was not a notifiable illness in all countries, therefore many cases went unreported. The most ambitious survey of encephalitis lethargica was conducted by the Matheson Commission for the Study of Epidemic Encephalitis (in New York). William Matheson was a wealthy businessman who was diagnosed with encephalitis lethargica during the epidemic period, and in 1927 established the Matheson Commission to study the disease. He believed the commission would find a cure for encephalitis lethargica within 2 years. Instead, the commission was defunded in 1940 with no cure in sight. The Matheson Commission's first survey, published in 1929, reported 52 781 cases of encephalitis lethargica between 1919 and 1928. However, the survey only included data from 14 countries where encephalitis lethargica was a reportable illness. And even then, it only included cases that had been formally diagnosed. It has been estimated that 50–75% of cases went unreported, putting the true figure far above that suggested in the Matheson report.

Whereas many cases of encephalitis lethargica likely went unreported, it is equally probable that encephalitis lethargica was over-diagnosed during the epidemic period based on the wide array of non-specific signs and lack of established diagnostic criteria. Because there was no pathognomonic sign or symptom, or diagnostic test, encephalitis lethargica was diagnosed based on the exclusion of other conditions. It seems reasonable that encephalitis lethargica was a heterogeneous group of conditions, rather than a unitary entity, that presented with unexplained neurological symptoms. Post-mortem examinations of alleged encephalitis lethargica cases during the epidemic period sometimes

revealed an alternate diagnosis such as tubercular meningitis, cerebral tumours, meningismus, or other neurological pathology. However, due to the variability in neuropathology, even a post-mortem diagnosis of encephalitis lethargica could not be verified.

Although encephalitis lethargica affected all ages, individuals between ages 10 and 45 were most susceptible with 50% of cases occurring between the ages of 10 and 30. There was no overall sex predilection, although specific outbreaks had higher incidences in one sex or the other. Some reports also suggested a higher prevalence of encephalitis lethargica among Jews and among ‘natives’ in South Africa, India, and the Philippines. There were higher incidences of encephalitis lethargica in large cities and industrial centres than in rural areas; however, this may have been due to these areas having larger populations and better diagnostic facilities than the rural areas.

## Aetiology

After 100 years of research, the aetiology of encephalitis lethargica is still unknown. Although a number of theories have been proposed, there are two main categories of plausible aetiologies: environmental (toxicological) and infectious (viral, bacterial, etc.). More recently, however, there is evidence to support a third theory: auto-immunity. It is also possible that encephalitis lethargica has multiple causes, which could explain the wide array of aetiological hypotheses that have been advanced over the years.

When confronted with his first cases of encephalitis lethargica in 1917, von Economo speculated on the cause of the disease. He ruled out any toxic process such as food poisoning because patients exhibited no gastrointestinal disturbances. Furthermore, there was often only a single case within a household, and some victims were exclusively breast-fed infants. He also ruled out poison gas, typhoid, polio, and syphilis as causes of the disease. Noting that all of the patients had presented with an influenza-like prodrome, and considering the contemporaneous Spanish influenza epidemic, von Economo considered the possibility that encephalitis lethargica was an influenza encephalitis. Indeed, there have been prior accounts of sleeping sickness or encephalitis associated with influenza epidemics. Although there were neuropathological differences in the brains of patients who died of encephalitis lethargica compared with those who died of influenza encephalitis, von Economo could not deny that there seemed to be an epidemiological connection between influenza and encephalitis lethargica. Based on experimental studies using brain tissue from deceased patients, von Economo concluded that encephalitis lethargica was caused by an infectious virus. He, and other clinicians at the time, proposed that influenza might predispose a person to infection with encephalitis lethargica, possibly by increasing the permeability of the nasal mucous membranes allowing the encephalitic virus to enter more easily.

In the years since the epidemic, studies have both supported and refuted the influenza aetiology. Modern experimental studies have examined the association between influenza and encephalitis lethargica using serology, which examine antibodies against influenza present in the serum of postencephalitic patients; reverse transcriptase polymerase chain reaction (RT-PCR), which tests for influenza viral RNA in brain tissue samples, and immunohistochemistry, which uses anti-influenza antibodies to search for influenza proteins in brain tissue samples. Although the findings in the majority of studies refute the influenza hypothesis, this aetiology would provide a convenient explanation for the disappearance of encephalitis lethargica because the influenza strains that caused the 1918 influenza epidemic ceased human circulation sometime before 1933.

During the epidemic period, a massive search was undertaken to identify the causative agent of encephalitis lethargica. Brain tissue, CSF, blood, and nasopharyngeal fluids from encephalitis lethargica victims were injected into various animal species in attempts to develop an animal model of the disease. Most experiments were largely inconclusive and no recognized strain of virus could be identified. Writing in 1942, Josephine B. Neal, a neurologist with expertise in bacteriology, dismissed much of the experimental work that had been conducted, proposing instead that encephalitis lethargica was most likely caused by an unidentified virus. Neal had been appointed by the Matheson Commission to direct clinical trials on encephalitis lethargica. Most of the Matheson Commission's research aimed to develop a vaccine for encephalitis lethargica, and was guided by two main theories: that encephalitis lethargica was a form of herpes; or that it was a focal infection resulting from a neurotropic form of *Streptococcus viridans*. In what could be considered the final report of the Matheson Commission, Neal (1942) described some promising results from the commission's studies using herpes vaccines, although the weight of scientific evidence at the time was against this hypothesis.

An early 21st century hypothesis proposed by Dale *et al.* (2004) is that encephalitis lethargica could be a post-infectious autoimmune disorder, with an aetiology similar to that of Sydenham's chorea. The authors suggested that encephalitis lethargica may be secondary to autoimmunity against basal ganglia and may be a paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) disease. The PANDAS hypothesis is problematic and controversial for several reasons. Over a third of Dale's patients showed no evidence of previous streptococcal infection, and two of his patients were over age 35 at symptom onset, which contradicts the paediatric criterion. Furthermore, PANDAS is not a recognized diagnosis in the International Statistical Classification of Diseases and Related Health Problems (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM), and encephalitis lethargica was never considered to be a paediatric disease.

Dale and colleagues, in a later paper (Dale *et al.*, 2009), seemed to rescind the PANDAS hypothesis, and instead proposed that encephalitis lethargica, specifically the hyperkinetic form, was an autoimmune disorder caused by antibodies against NMDA receptors. Anti-NMDA receptor encephalitis is an autoimmune encephalitis that is commonly associated with ovarian teratomas in young females. It has a striking resemblance to encephalitis lethargica in its symptomatology and often begins with an influenza-like prodrome. Similarly, narcolepsy has been found to result from antibodies against aquaporin-4 in hypothalamic neurons. Furthermore, several European countries reported an increase in cases of narcolepsy following influenza vaccination or infection with influenza during the 2009 H1N1 influenza pandemic, which could explain the apparent connection between Spanish influenza and encephalitis lethargica following World War I. All of these observations point to an auto-immunological trigger as a potential cause of CNS disorders, and lend additional credibility to the autoimmune hypothesis.

In the most recent study on the aetiology of encephalitis lethargica, Dourmashkin *et al.* (2012) pointed to an enterovirus, possibly related to poliovirus, as the cause of encephalitis lethargica, based on immunohistochemical findings and RT-PCR from four cases of epidemic encephalitis lethargica, two modern encephalitis lethargica cases, and one case of postencephalitic parkinsonism. This was a carefully conducted study but, unfortunately, has not been replicated, presumably because of the severe limitations on encephalitis lethargica material.

Current research on the aetiology of encephalitis lethargica is limited by the scarcity and poor quality of existing specimens from the epidemic period and the rarity of new cases. Without another encephalitis lethargica epidemic, we, unfortunately, may never learn the cause of this disease. However, current research on similar CNS disorders such as narcolepsy and anti-NMDA receptor encephalitis could help to shed additional light on this mystery.

## Transmission

Without a true understanding of what causes encephalitis lethargica, it is also difficult to determine how it is transmitted. There are numerous, often conflicting, theories regarding how the disease was spread. Some documented cases from the epidemic period provide substantial evidence that encephalitis lethargica was contagious, but these cases seem to be the exception rather than the rule. One of the most convincing examples was the outbreak of encephalitis lethargica at the Derby and Derbyshire Rescue and Training Home (for girls) in August 1919. Within a period of 2 weeks, 12 of 21 girls and women in the house were affected and six died within 10 days of onset. A thorough investigation of the outbreak was conducted by Dr A. Salusbury MacNalty, a specialist in epidemiology,

who concluded that the disease had been transmitted from person to person.

While the cases at the Derby school and many others suggest that encephalitis lethargica is contagious, there are just as many anecdotal reports to refute such a claim, as in the case of a family with five children living in a small apartment. One child was sick with encephalitis lethargica for weeks while the remainder of the family remained unaffected. Further, among 1156 cases in Vienna, 520 cases in Germany, and 464 cases in France, there was little to no evidence of direct transmission of encephalitis lethargica from person to person. Possibly, there may have been multiple strains of encephalitis lethargica, with some strains being highly contagious, and others not. It is also possible that encephalitis lethargica was spread by healthy carriers who had some type of innate immunity that others lacked.

## Treatment and prognosis

The 1929 Matheson Report lists about 80 treatments for encephalitis lethargica that were used during the epidemic period; however, none of these treatments were particularly effective for treating acute encephalitis lethargica. Approximately one-third of patients died during the acute phase of the illness, one-third survived without sequelae, and one-third showed neurological sequelae.

Likewise, there were few treatments for parkinsonism during the epidemic period or in the decades following. Prior to the introduction of L-DOPA in the 1960s, the most effective treatments for parkinsonism were anticholinergic agents. In the Foreword to the 1990 edition of his book *Awakenings*, Oliver Sacks described the reaction of his postencephalitic patients to the new miracle drug L-DOPA as ‘extinct volcanoes’ that ‘erupted into life’ after they had ‘long been regarded, and regarded themselves, as effectively dead’ (p. xxv). Unfortunately, the period of benefit from L-DOPA was limited, and within several months most of the patients began to experience adverse effects such as tics, chorea, and emotional instability. More recently, however, a postencephalitic patient who had become tolerant to L-DOPA was successfully treated with deep brain stimulation of the subthalamic nucleus (Hu and Hebb, 2012).

## Current state of encephalitis lethargica

Since 1940 there have been ~80 published reports of encephalitis lethargica worldwide; however, the reliability of these diagnoses is limited by the variability in diagnostic criteria. Following the epidemic period, most encephalitis lethargica diagnoses were based on von Economo’s 1929 criteria. In 1987, Howard and Lees proposed new diagnostic criteria that have been used to diagnose more recent cases. Howard and Lees’ description included oculogyric

crises, which were not known to be associated with acute encephalitis lethargica during the epidemic; rather, it was more commonly associated with postencephalitic parkinsonism than with acute encephalitis lethargica. Howard and Lees also described obsessive-compulsive behaviour and akinetic mutism as occurring in acute encephalitis lethargica, but there is no evidence that obsessive compulsive behaviour was characteristic of encephalitis lethargica during the epidemic, and akinetic mutism was only associated with the amyostatic-akinetic form described by von Economo. One of the authors (J.A.V.) proposed that any diagnosis of encephalitis lethargica should be limited to patients whose signs and symptoms cannot be attributed to any known neurological disease, and who show the following signs: (i) influenza-like prodromal signs; (ii) hypersomnolence; (iii) wakeability; (iv) ophthalmoplegia; and (v) psychiatric changes (Vilensky *et al.*, 2011). Among 59 reports of over 200 cases of encephalitis lethargica that were published between 1941 and 2009, Vilensky concluded that only 14 reports seemed to fit these criteria, although it is impossible to be absolutely certain that any patient diagnosed with encephalitis lethargica today actually has the same syndrome that existed during the epidemic.

## Conclusion

The Hollywood film version of Dr Oliver Sacks' marvellous 1973 book, *Awakenings*, was released in 1990. The movie beautifully depicted the 'extinct volcanos' that were post-encephalitic patients in a nursing home in New York coming alive with L-DOPA treatment. This film starred Robin Williams and Robert Di Nero and provided us all with some cinematographic semblance of the effects of encephalitis lethargica following the epidemic period. Without knowing exactly what caused the disease, it is

impossible to know how to prevent it or if it will return. Encephalitis lethargica was characterized in a 2004 BBC documentary as the biggest medical mystery of the 20th century, and remains that to this day.

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