AN INVESTIGATION INTO THE FORGOTTEN MYSTERY OF ENCEPHALITIS LETHARGICA

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Insight

Imagine being so tired that all you want to do is sleep. That must not be hard; you probably experience this every Monday morning, when your alarm clock yanks you out from your dreams to the real world. However, where you would normally be able to drag yourself out of bed with the promise of a good cup of coffee, now nothing on earth can motivate you to wake up. Imagine losing control over the muscles of your face and limbs, not being able to express your emotions or to move your rigid limbs into any other position. Imagine recovering, but developing Parkinson's disease, psychiatric disorders and a range of other neurological symptoms soon after. This is what happened to a large number of people shortly after World War I. Where did this disease come from, what caused it and where did it go? We still do not know.

Introduction

The beginning of the 20th century was shaped by World War I and the subsequent outbreak of one of the deadliest pandemics in human history. In 1918 'the Spanish flu' caused by an influenza virus swept over the world, killing an estimated 50 million people [1-3]. Little-known is that simultaneously, another pandemic arose, moving silently in the tracks of the infamous 1918 influenza pandemic. This disease was named encephalitis lethargica (EL), a condition manifesting in a bizarre and never seen before array of neurological symptoms [4]. Intriguingly, it disappeared as suddenly as it emerged, and to the present day, we still do not know what caused it. As research endeavours are currently focussed elsewhere, I would like to ask you, readers of RAMS, to be my fellow medical detectives. This editorial article will present you with facts and fiction surrounding one of the greatest medical mysteries in history.

The first clue: the discovery

Encephalitis lethargica (EL) was first reported around 1917 by the Viennese neuropsychiatrist Baron Constantin von Economo [5]. Whilst working in a psychiatric clinic in Vienna, Austria, von Economo encountered patients admitted under a variety of diagnoses, such as meningitis and delirium, with a common set of peculiar symptoms [4, 5]. Most striking was that many patients experienced severe lethargy; some would fall asleep and never wake up, which earned this disease the fitting name of 'sleeping sickness' [4, 6]. Von Economo suspected these patients suffered from the same, unknown condition due to encephalitis.

Encephalitis is an inflammation of the brain, often caused by a viral infection such as herpes simplex, though it can also be a result of autoimmune causes, bacterial meningitis, tuberculosis, vasculitis, hypoglycaemia, and brain tumours [7]. Which of these is responsible for Von Economo's encephalitis is unknown, but maybe its clinical presentation will unmask its causative agent. Let us take a look.

Acute encephalitis lethargica

EL can be distinguished into an acute and a chronic phase. Patients could have virtually any neurological symptom in the acute stage, so to bring some order into this chaotic constellation of symptoms, Von Economo differentiated three forms of EL: the somnolent-ophthalmoplegic form, the hyperkinetic form, and the amyostatic-akinetic form [4, 8].

The somnolent-ophthalmoplegic form of EL was often preceded by an influenza-like prodrome. Neurological symptoms soon followed and patients became somnolent [4, 8]. One description by Haynes (1921) captures EL's typical somnolence as '*…lethargic, lying with her eyes closed, but easily roused, answering questions briskly and intelligently, and then relapsing into slumber*' [9]. Another very characteristic symptom was paralysis of the eye muscles [4, 8]. Patients also often experienced weakness of the limbs and presented with a 'mask-like' face. The mortality of this type of EL is high, with 50% of those affected dying [4, 8].

The hyperkinetic form presented itself with quite contrasting symptoms. In this type of EL, the most dominant symptom was restlessness, which presented in motor disturbances such as twitching of the muscles and an anxious mental state [4, 8]. These were patients who were insomniac or whose day-night rhythm completely reversed [4, 8]. They also experienced general weakness, fatigue, disturbances in the muscles of the eyes, nerve pain, and hallucinations [4, 8]. Mortality is estimated somewhat lower than in the somnolent form at 40% [4, 8].

The final and least common type of EL was the amyostatic-akinetic form, of which the most characteristic symptom was rigidity. Patients would often be immobile and rigid for a length of time, but in truth, could easily move when external force was applied. These patients also suffered from reversed day-night rhythm and disturbances of the eye muscles [5, 6].

Chronic encephalitis lethargica

Those who survived the acute form of EL often had lasting chronic neurological consequences that would generally develop one to five years later. It was originally thought that one-third of the patients suffered from severe neurological consequences, but it is now estimated that 80% of patients eventually developed Parkinsonism [10, 11]. Other symptoms included sleep disruptions, abnormalities of the eye muscles, speech and respiratory system, and involuntary movements [5, 6]. Furthermore, chronic EL also resulted in psychiatric

disorders and mental changes, including mood changes, euphoria, increased sexual drive, hallucinations, and excessive joviality [11].

One of the most infamous people speculated to have fallen victim to EL is Adolf Hitler [12, 13]. Hitler was first reported to have symptoms of Parkinson's disease somewhere around 1941, which some surmise to be the result of EL. Hitler appeared to have had oculogyric crises, palilalia (repetition of words and phrases) and a slight form of day-night reversal [12, 13]. However, this cannot be confirmed, as most evidence of any illness was probably carefully hidden by those not wanting to provide ammunition to people questioning Hitler's leadership abilities [12, 13].

Encephalitis lethargica in children

Horribly, EL seemed to have a much more pronounced effect on children than adults. Children underwent bizarre negative personality changes; theft, vandalism, impulsiveness, self-mutilation, sexual precocity and cruelty were all commonly seen behaviours [6]. As a result, many children would be arrested or placed in institutions [6]. One particularly horrifying example is that of an eight-year-old girl who had pulled out all her teeth and clawed out her own eyes [8]. Captured on scans of yellowed pages, Dorothy Kern Hallowell describes another case in 1925:
'*…the parents, after Victor had attempted to stab several members of his family with a carving knife, were terrified as to what mood would next be given vent to. The little boy would run up to strange girls on the street, throw his arms around them and try to kiss them. On one occasion he attempted intercourse. Another abnormal display of this precocity was sexual misuse of a cat which resulted in the animal's death*'. One of the mothers of an EL victim summarises this aptly as: '*just deviltry*' [14].

Treatment

Throughout the epidemic period, there was no effective treatment for either the acute or chronic form of EL, and many sufferers disappeared behind the doors of institutions and mental wards [11]. A glimmer of hope appeared on the horizon in the late 60s when Oliver Sacks, a medical doctor working at a hospital in New York, started treating his frozen patients with levodopa, currently used to treat Parkinson's disease [11, 15]. When administering this drug to his patients, they seemed to come alive again. Unfortunately, this glimmer was extinguished when it became clear the effects were not permanent [11, 15].

In the footsteps of encephalitis lethargica

As the clinical presentation alone makes us none the wiser, we should also look into EL's epidemiology and transmission. The picture of the epidemiology of EL can only be painted in broad strokes, as specific detailed information is missing. After its discovery in Vienna, the disease swept through most of Europe and crossed the ocean to North America, after which it spread to Canada, Central America, and India [11]. It became an epidemic in concurrence with the influenza pandemic [16]. It is generally believed approximately one million people were affected worldwide, and half a million people died before the acute form disappeared again around 1927 [5, 16, 17]. An estimated 50% of cases occurred in people aged 10-30, and it presented equally in men and women [8].

Transmission of EL also remains unclear. Some reports from the time argue that the causative agent was contagious, the most striking example being that of a girls' school where 12 of 21 girls were affected, and six of them died within two weeks [18]. In another school in Warwickshire in 1922, a teacher noticed children were constantly falling asleep during classes. This turned out not to result from sleep-inducing lessons, but instead, they were diagnosed with EL [19]. However, these outbreaks seemed to be rare and in many other cases, only one member of the family was affected despite living in close proximity, which led to the general assumption that EL was not contagious [8].

Interestingly, it appears EL was not an entirely unknown entity when Von Economo discovered it in 1917. Medical historians managed to dig up examples of outbreaks similar to that of EL: 'schlafkrankheit' in the whole of Europe in 1580; 'febris comatosa' in London, between 1673-1675; 'sleeping sickness' in Tübingen, Germany in 1712; 'nona' in Italy between 1889-1890 [4, 20]. Some of these outbreaks were even associated with concurrent influenza epidemics [11]. Whether these outbreaks were actually EL or something similar is undetermined [21].

The answer to EL's aetiology

Many researchers have speculated on the causative agent of this disease. One of the most popular and simultaneously most widely disputed theories is that the 1918 influenza virus had something to do with EL. The appearance of both diseases and disappearance around the same time led many to believe this could not be coincidental. Furthermore, some influenza strains can be neurotropic [4]. Neural damage could be caused by influenza hiding in neurons whilst evading the immune system. This would also explain the delay between acute influenza and the onset of EL, as there would be no symptoms until extensive damage was done [22].

However, there are a number of arguments against this hypothesis. Symptoms resulting from encephalitis caused by influenza clearly differ from the symptoms associated with EL, and until now no influenza virus has been recovered from the brain of an EL victim [4, 22]. In addition, cases of EL already occurred before the influenza pandemic and peaks of influenza did not seem to precede peaks of EL [4, 20]. For example, one large influenza outbreak with 6000 cases in a military camp in New Jersey did not lead to any EL cases [18]. Percentages vary, but according to one review, only 8% of cases were associated with influenza [23].

On the other hand, as it is exceedingly difficult to diagnose influenza, it is also possible that many of the EL patients simply did not know they had had influenza [22]. But then again, the 1918 influenza strain had to have caused quite severe, and therefore hard to miss, disease to be able to cause the type of damage seen in EL [22]. As you can see, both sides have their strong and weak points. This connection between influenza and EL could possibly also be explained by influenza being a predisposing factor for EL [8].

More modern research has proposed that EL could be caused by a post-infection autoimmune disorder, implying that antibodies produced by the body to fight infection suddenly turn against the brain and cause damage [24]. Following this theory, infection with influenza could have caused an autoimmune response leading to antibodies causing EL, but this is difficult to prove [22].
In 2004, one study suggested streptococcal infection might lead to the production of anti-basal ganglia antibodies, causing symptoms similar to EL, but others questioned this. For instance, a substantial number of patients in that study did not experience a previous streptococcal infection [25, 26]. Despite this, the autoimmune theory does have its merits. For example, the same researchers later noted the similarities between EL and encephalitis caused by antibodies against NMDA receptors. So while we might not know the exact mechanism behind autoimmunity and EL, it is

not unlikely. Furthermore, this hypothesis might also explain the increased incidence of narcolepsy that was seen after the 2009/2010 H1N1 influenza pandemic. According to an article published in *The Lancet* in 2014, infection with H1N1 or vaccination could trigger a type of autoimmune narcolepsy [27].

A plethora of other viruses, bacteria, protozoa, toxins and chemical agents have been researched to determine their plausibility as the causative agent of EL. For example, a study from 2012 found evidence for an enterovirus – such as poliovirus – to be the cause of EL. Yet, enteroviruses are not known to cause EL-like symptoms, and most of them tend to cause childhood diseases [4, 28]. Arboviruses, viruses carried by insects, are also known to cause epidemics of encephalitis, such as Japanese encephalitis. Nevertheless, these mostly occur in summer and autumn, whereas EL seems to peak in winter [4]. A comprehensive review from 1998 concludes there are no known viruses that cause encephalitis fitting all EL symptoms [29]. Attempts to culture bacteria from EL cases left researchers empty-handed, nor are any environmental causes or medical treatments likely candidates [4]. As known agents can mostly be ruled out as the cause of EL, some researchers argue that it must have been caused by an unknown agent, circulating through the population and dying out when most people built up immunity [4].

A final, yet anticlimactic theory is that EL was not an actual disease entity, but just a diagnosis given to anyone with symptoms remotely similar to those ascribed to EL, although it seems quite farfetched to attribute all chronic sequelae of EL to some form of mass hysteria [21].

Conclusion

All potential causes treated and my mental stash of synonyms for 'unknown' exhausted, we have arrived at our final conclusion. Over a hundred years after its first appearance, EL's causative agent remains frustratingly elusive, and it is unfortunately likely that this mystery will not be solved anytime soon. Modern cases still sporadically occur, but this is rare, and existing specimens from the beginning of the 20th century are scarce, limiting the potential for research [8, 25, 30]. Thus, we are left in the dark as to whether EL is gone forever, or will reappear somewhere in the future. An uncertainty that could, similar to EL, cause many a sleepless night…

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