Encephalities Lethargica: - Historical Case

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***Abstract*—"Sleeping sickness," or, more formally, encephalitis lethargica, is a rare and complex clinical syndrome, gaining worldwide attention for its outbreak. Occurring primarily between 1916 and 1927, the illness is a sequela, neurologic manifestations, such as "protracted sleep, motion disturbances, personality change, oculomotor dysfunction, and dementia." Acutely, it initially manifests by nonspecific systemic complaints such as "fever, headache, malaise, and sore throat, followed by neurologic symptoms such as lethargy, hyperkinetic movements, and cranial nerve dysfunction." The pathogenesis of EL continues to be not so clear, with various theories having been put forward. Viral infections such as influenza and other neurotropic viruses, as well as autoimmune theories resulting from inflammation of the midbrain, basal ganglia, and brainstem, have all been suggested as the pathogenesis of EL. The pathogenesis of EL lies in the extensive inflammation of the brain, neuronal cell death, perivascular infiltration, and the disruption of the dopaminergic tracts, which underlies the manifestations of the condition. The diagnosis of encephalitis lethargica is highly dependent on clinical assessment and is aided by cerebrospinal fluid analysis and other investigations excluding other forms of encephalitis, including viral, autoimmune, or post-infectious encephalitis. In view of its rarity, it is presently not possible to carry out laboratory confirmation of its diagnostic criteria. EL can be managed supportively and symptomatically. In acute phases, drugs such as corticosteroids and immunosuppressants can be used, whereas in chronic phases, drugs such as levodopa can be used because of parkinsonism. Rehabilitation programs such as physiotherapy and occupational therapy are effective in improving functional results. Though historically significant, instances of encephalitis lethargica are extremely rare in this modern age. However, the significance of EL cannot be underestimated from a clinical or medical perspective. It is because EL provides lessons on post-viral neurological syndromes and autoimmune neuroinflammation, as well as basal ganglia involvement and its subsequent sequelae. It is also possible to derive lessons on managing similar neurological disorders through an understanding of EL.**

***Index Terms*—Encephalitis Lethargica', 'Von Economo Encephalitis', 'Post-encephalitic Parkinsonism', and 'Spanish Flu'.**

I. INTRODUCTION

Encephalitis lethargica is characterized by high fever, sore throat, headache, lethargy, double vision, delayed physical and mental response, sleep inversion, and catatonia. Severe cases may lead the patients to enter a coma-like state (akinetic mutism). [1] Parkinson's Disease (PD) is a progressive brain disorder that primarily affects movement, causing symptoms like tremors, stiffness, slow movement, upper body weakness, muscular pains, tremors, neck rigidity, and behavioral changes, including psychosis. [1]

1.1. General Effects in Children

The affected children experienced a change of behavior, with many of them becoming "delinquents." Boys between the ages of 5 and 18 years were the most affected. Symptoms include change of personality, restlessness, irregular sleeping habits, emotional instability manifesting as irritability, crying spells, and temper tantrums, and unpredictability, what Economo described as "moral insanity." More extreme cases include aggression and "shameless sexual activity." 25-90% of adults also suffered from psychological problems, including hysteria and abnormal behavior and movement. A large minority of patients described having bradyphrenia. [1]

1.2. History

The historical review of encephalitis lethargica begins with its mysterious impact on global health in the early 20th century; indeed, between 1915 and 1928, though lingering cases continued after this. The epidemic has been attributed to the movement of troops in World War I; initial cases reported around 1915 were from Romania, and then an outbreak occurred in Europe and North America shortly thereafter. [2]

1. Early recognitions: Two physicians, Constantin von Economo and René Cruchet, independently described the disease in 1917. They recognized the neurological features of this disease, based on which Von Economo named it encephalitis lethargica, characterized by symptoms such as somnolence, lethargy, headache, fever, eye muscle paralysis, and delayed responses.
2. Spread and Impact: The disease spread rapidly, reaching epidemic proportions during and after World War I, peaking between 1919 and 1924. There were large numbers of cases throughout Europe, the United States, and parts of Asia, with estimates suggesting over a million affected worldwide. It is estimated that as many as half a million deaths were attributed to EL, and many patients developed severe neurological and psychiatric sequelae such as postencephalitic Parkinsonism, dystonia, and various movement disorders.
3. Scientific and Cultural Impact: Researchers such as Constantin von Economo and Oliver Sacks sought to comprehend EL and provide it treatment. Oliver Sacks presented the story of patients coming out of comas after decades in his famous book Awakenings (1973), which was dramatized as a movie later. The development of treatments, notably the use of levodopa in the late 1960s, led to partial recoveries, especially in patients with Parkinsonian symptoms, but many remained with chronic disabilities.
4. Decline and Legacy: The epidemic quite suddenly began to subside about the year 19271928 without any apparent reason being discovered, though conjecture has related this to viral factors and even to the influenza pandemic of 1918. Though the epidemic had passed, postencephalitic syndromes persisted, and sporadic cases have continued to be reported to this day. It remains the source of considerable historical and scientific interest because of the mystery surrounding its origin, the variability in its clinical manifestations, and its after-effects—most notably post-encephalitic Parkinsonism and neuropsychiatric disorders.
5. Modern Perspective: Today, encephalitis lethargica is considered a historical disease, but ongoing research into the cause, which likely involves complex interactions between infectious agents, autoimmune responses, and environmental factors, continues. Its legacy has been significant, greatly improving knowledge of legacy neuroinfectious diseases and autoimmune neurological conditions. [22, 28]

II. LITERATURE REVIEW METHODOLOGY

"A comprehensive search of Literature searches to identify studies for this review was performed using the following databases: PubMed, Google Scholar, and other archives. The key terms included in searches were 'encephalitis lethargica,' 'von Economo encephalitis,' 'post-encephalitic parkinsonism,' and 'Spanish flu.' The review combines historical accounts of patients in the period of 1917 to 1930 with current scientific work done between the years 2000 and 2024." [2, 6]

III. ETIOLOGY AND PATHOGENESIS

The causes of encephalitis lethargica are not certain. Although it was once believed to be linked with the Spanish Flu epidemic, there is evidence from modern research against it. Some research does look into its roots in an autoimmune reaction and, separately or with an immune response, links to pathologies of infectious diseases—viral and bacterial, such as in the case of influenza, where a link with encephalitis is clear. Post-encephalitic Parkinsonism was clearly recorded to have followed an outbreak of encephalitis lethargica following 1918. [2, 4]

Influenza pandemic evidence for viral causation of the Parkinson's symptoms is circumstantial, while evidence arguing against this cause is of the negative sort—for example, lack of viral RNA in post-encephalitic Parkinsonian brain material. The German neurologist Felix Stern, who examined hundreds of encephalitis lethargica patients during the 1920s, noted that their encephalitis lethargica typically evolved over time :

- Symptoms in the early stage would include excessive somnolence or insomnia.
- The second symptom would be an oculogyric crisis.
- The third symptom would be recovery and a Parkinson-like syndrome.

Encephalitis lethargica has not yet been discovered to have one specific cause, though research went into high gear in the early part of the 20th century. Conjectures have been made about this disease from historical evidence to clinical and immunological evidence.

1. Infectious Hypothesis: Encephalitis lethargica initially was considered a viral infection, especially given its apparent temporal relationship to the 1918 influenza pandemic. Nevertheless, no specific virus, including influenza virus, has been consistently isolated from the brain tissue of affected patients. This suggests that EL is not directly caused by influenza but may be triggered by an infectious agent.
2. Post-Infectious Autoimmune Mechanism: Current evidence strongly supports an autoimmune etiology. It is proposed that EL develops as a post-infectious, immune-mediated disorder in which infection may trigger an abnormal immune response against neuronal tissue, especially the basal ganglia and midbrain.
3. Molecular Mimicry: There may be a part played by molecular mimicry in that microbial antigens may have some resemblance to neuronal proteins. This may, in turn, induce the production of cross-reactive antibodies that target dopaminergic neurons in movement disorders and parkinsonian features seen in EL.
4. Genetic Predisposition: While infection can precipitate autoimmune responses, individual genetic predisposition may also play a role in susceptibility, although no specific genetic markers have been conclusively identified. [11, 12]

3.1. Pathogenesis of Encephalitis Lethargica

The pathogenesis of encephalitis lethargica proceeds through a series of steps, including immune mediation and neuroinflammatory events.

3.1.1. Infection Trigger: The initial infection of either a virus or bacteria triggers off the immune system.

3.1.2. Immune Dysregulation: The result is an abnormal immune response, with the activation of autoreactive T-cells and the production of autoantibodies.

3.1.3. Neuroinflammation: Inflammatory cells permeate the central nervous system, specifically the midbrain, basal ganglia, thalamus, and brainstem.

3.1.4. Neuronal Damage: Inflammation drives neurodegeneration, including that of dopaminergic neurons, leading to disturbed dopamine signaling.

3.1.5. Neurotransmitter Imbalance: Motor dysfunction, rigidity, bradykinesia, and postencephalitic parkinsonism due to destruction of dopaminergic pathways.

3.1.6. Chronic Sequelae: The long-term consequences have included movement disorder, behavioral change, sleep disturbance, and cognitive impairment. [15, 21, 25, 27]

IV. TRANSMISSION

The mode of transmission remains debated. While historical clusters, such as the Derby outbreak, suggested person-to-person transmission, most cases were sporadic. Modern consensus suggests that EL is likely not directly contagious in the same manner as influenza but rather a post-infectious autoimmune reaction triggered in susceptible individuals. [1, 12]

4.1. L.A. Hoffman and J.A. Vilensky"

They 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. It is also possible that encephalitis lethargica was spread by healthy carriers who had some type of innate immunity that others lacked. [12, 22]

V. DIAGNOSIS

No specific test for the diagnosis of EL is available, and diagnosis is primarily based on clinical observation and exclusion of other causes of encephalitis. The diagnosis is considered when a patient presents with an acute or subacute encephalitic

illness with symptoms including lethargy or hypersomnolence, ophthalmoplegia, oculogyric crises, psychiatric changes, and signs of basal ganglia involvement such as movement disorders. Recent diagnostic criteria often require three of these major signs, including sleep disturbances, somnolence, akinetic mutism, or central respiratory irregularities. Extensive laboratory and imaging studies are used to exclude the known causes of infection, autoimmune encephalitis, and toxins. CSF can be normal in many cases, although some may present with mild pleocytosis or elevated proteins. Brain imaging, including MRI and FDG-PET scans, may show abnormalities in basal ganglia or other deep structures that help in supporting the diagnosis. EEG findings are generally nonspecific and may only reflect slow activity. In practice, diagnosis will depend on the presence of a constellation of clinical features along with the exclusion of other diseases, supported when possible by specific findings such as antibody presence or characteristic imaging changes. Various diagnostic criteria have been proposed to aid diagnosis, such as the Howard and Lees criteria, among others; however, their sensitivity remains poor, underlining the need for careful clinical examination. [14, 17]

5.1. Historical diagnostic criteria

EL was historically diagnosed clinically (severe sleep disturbance, movement disorder, ophthalmoplegia, psychiatric symptoms), usually in combination with temporal association with the 1915-1926 epidemic and exclusion of other etiologies. Early criteria, such as those of von Economo and later of Howard and Lees, heavily emphasized clinical phenotype and course, with minimal objective testing. These The criteria had high specificity but variable sensitivity, reliant on retrospective case descriptions and expert judgment. Sensitivity in classic criteria was often modest, leading to under-recognition in some cohorts but reasonable specificity in others. [historical context and diagnostic performance references]. Contemporary definitions: Modern definitions emphasize autoimmune and inflammatory etiologies. Incorporating autoantibody testing, findings on CSF, imaging, and response to immunotherapy. EL-like syndromes are considered in the context of a spectrum of autoimmune encephalitis rather than as a discrete, pathogen-specific entity. Contemporary criteria seek to encompass classic EL presentations and atypical phenotypes in a single autoimmune encephalitis construct while recognizing that epidemic-specific criteria may not apply uniformly to sporadic cases or EL-like syndromes. [17]

5.2. Practical Considerations

The use of broad, validated panels increases the yield but needs to be interpreted judiciously in concert with clinical features, imaging, and CSF data. Negative antibody results do not rule out autoimmunity; skilled clinical judgment remains essential, particularly in historical-era or atypical cases. [23]

5.3. Imaging findings

5.3.1. MRI and functional imaging: MRI may reveal bilateral or asymmetric T2/FLAIR hyperintensities in limbic or basal ganglia regions, which are consistent with autoimmune/inflammatory processes, though findings can be nonspecific. Functional imaging and Doppler studies can be helpful in determining the involvement of subcortical structures, networks involved in sleep regulation, or movement-related circuits.

5.3.2. Utility: Imaging assists in diagnosis, excludes alternative etiologies (tumors, infectious etiologies, vascular events), and provides a way to track disease evolution or response to Therapy.[23]

5.4. CSF and laboratory findings

5.4.1. CSF profile: CSF in autoimmune encephalitis can show mild lymphocytic pleocytosis, an increase in protein, or positive oligoclonal bands, though the ranges are broad and can be normal in some cases. The presence of inflammatory markers or autoantibodies in the CSF supports the hypothesis of autoimmunity but is not universally present.

5.4.2. Other tests: Routine infectious panels such as PCR for herpesviruses, enteroviruses, and other pathogens are performed to rule out infectious etiologies. Serum and CSF inflammatory markers such as cytokine profiles may provide additional clues but are not yet standard diagnostic criteria. [23]

VI. TREATMENT

Modern approaches to the treatment of encephalitis lethargica include immunomodulation therapies and treatments of symptom remediation. There is little evidence of a consistent effective treatment for the initial stages, though some patients given steroids have seen improvement. The disease becomes progressive, with evidence of brain damage similar to that of Parkinson's disease. Treatment is then symptomatic. L-DOPA (levodopa) and other anti-Parkinson drugs often produce dramatic responses; however, most people given LDOPA experience improvements that are short-lived. Encephalitis lethargica (EL) has no proven cure, and current management focuses on symptom control, supportive care, and rehabilitation. Treatments historically tried in past epidemics varied widely and often lacked rigorous evidence, though some approaches are still considered in select patients. Below is a concise, plain-language overview of contemporary clinical insights into EL treatment. [9]

6.1. Treatment aims

- Relieve central symptoms: minimize sleep disturbance, control dyskinesia, and manage psychiatric features.
- Maintain physical health: provide optimal nutritional intake, offer respiratory assistance if necessary, and avoid complications associated with acute illness.
- Enhance recovery and long-term functioning: emphasize rehabilitation in efforts to optimize mobility, speech, and activities of daily living. [10]

6.2. Symptom-targeted therapies

- Sleep and hypersomnolence: Supportive sleep management is key; specific pharmacologic options are not consistently effective across cases. Some reports note variable responses to sleep-regulating strategies, but there is no standardized regimen with proven superiority.
- Movement disorders: Levodopa and other dopaminergic agents may transiently improve parkinsonian features in some patients, though benefits are not durable for all, and side effects can limit use. Many cases require reassessment over time as the disease course evolves.
- Psychiatric and behavioral symptoms: mood stabilization and psychosis-like manifestations may respond to standard psychiatric treatments, including antipsychotics or antidepressants, on a case-by-case basis. There is limited evidence regarding electroconvulsive therapy in severe refractory cases.
- Autonomic and respiratory support: Critical care for airway protection, ventilation, and nutrition may be required in acute phases. These, however, are general critical-care measures rather than disease-specific therapies. [10]

6.3. Immunomodulatory and disease-modifying considerations

- Immunotherapies: Interest in autoimmune mechanisms has led to the occasional use of immunomodulatory treatments (e.g., steroids, intravenous immunoglobulin) in selected patients, with variable and often anecdotal responses. No robust, controlled evidence demonstrates consistent efficacy in EL as a whole.
- Antibiotics and antivirals: These are not standard treatments for EL unless a concomitant infectious trigger is established, in which case standard guidelines apply for those infections.
- Anti-gait and vaccine history: Historical vaccine-era interventions did not provide clear benefits; modern practice does not include a routine preventive measure specific to EL. [26]

6.4. Rehabilitation and long-term care

Multidisciplinary rehabilitation: Physiotherapy, occupational therapy, and speech-language therapy are the mainstay of recovery, focusing on improved mobility, communication, swallowing, and activities of daily living. Cognitive and psychiatric rehabilitation may be necessary for remaining deficits. Long-term effects include the fact that many survivors have chronic neurological sequelae, including movement disorders and cognitive or behavioral changes; ongoing therapy is often required for many years.

6.5. Clinical decision-making notes

Individualization is essential: due to the historical rarity and heterogeneity of EL presentations, treatment plans are tailored to each patient's symptom profile,

disease stage, and comorbidities. Diagnostic uncertainty: EL is still mainly a clinical diagnosis with support from the exclusion of other causes. This can, in turn, influence treatment choices and the application of immunomodulatory therapies. [26]

VII. GAPS IN EVIDENCE AND TREATMENT GUIDANCE

- Diagnostic heterogeneity: EL encompasses a spectrum of autoimmune- and post-infectiouslike syndromes, making standardized treatment algorithms difficult. The number of highquality, EL-specific trials is limited; most evidence derives from case reports, small cohorts, and extrapolation from other autoimmune encephalitides. The need exists for controlled studies and international registries.
- Antibody-targeting therapies: Although some reports support rituximab or other targeted agents, the best selection criteria—which antibody profile warrants which agent—and duration of therapy are not well established. [31]
- Long-term outcomes: Data on relapse rates, sustained functional recovery, and late-onset Complications after different immunotherapies are sparse.
- Role of infectious triggers: Clarifying how infection history should influence treatment intensity and duration is an ongoing area of inquiry.
- Practical takeaways: In case of suspected autoimmune mechanism, an early structured immunotherapy should be initiated, and the response frequently reassessed, with adjustment of intensity according to the response and tolerability. Combine symptom-targeted care with immunomodulation and comprehensive rehabilitation to maximize functional targeted recovery. Engage in multidisciplinary care; consider enrolling patients in registries or research cohorts to help advance the evidence base for EL-specific treatment guidance.[1]

VIII. CONCLUSION

Encephalitis lethargica remains one of neurology's most puzzling disorders: a disease of dramatic sleep disturbances coupled with a broad range of neurological and psychiatric symptoms. While its epidemic in the early 20th century left an indelible mark on medical history, the cause of the condition remains unknown, and sporadic cases are still being reported today. The illness can result in severe, long-term disability or death, with many survivors developing lasting movement disorders resembling Parkinson's disease. Despite advances in medicine, encephalitis lethargica has resisted all efforts to identify a clear cause, forcing clinicians to rely on supportive care rather than treatment targeted at the cause. The enduring mystery of encephalitis lethargica serves as a reminder of the need for ongoing research while underscoring ongoing complexities that can arise in the interface of infection, immunity, and brain.

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