Sleeping Princes and Princesses:
The Encephalitis Lethargica Epidemic of the 1920s and a Contemporary Evaluation of the Disease

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Encephalitis Lethargica (EL)

- Epidemic disease 1917-1930
  - Described by Constantin von Economo in 1917
- More than 1 million cases, approx 500,000 deaths, worldwide
- Extremely polymorphic symptoms and signs
Constantin von Economo

- Vienna Psychiatric and Neurological Clinic, Austria
- Observed an Epidemic outbreak of a “sleeping sickness” in winter of 1916-1917

Constantin von Economo (1876-1931)
Constantin von Economo’s Written Account of Encephalitis Lethargica

- Series of cases that did not fit any usual diagnoses
  - Similarity in onset and symptoms
  - Grouped them into one clinical disease picture
- Described as “a kind of sleeping sickness” and gave name Encephalitis lethargica

Progression of EL Epidemic

- 1916-17 Vienna (v. Economo)
- 1918 Influenza Epidemic spreads
- 1918-1919 Germany
- 1918 London
- 1918-1919 North America
• High incidence reached in 1920
• Reached low levels 1922-23
• A second high peak occurred in 1924
Encephalitis Lethargica: Its Sequelae and Treatment

By Constantin von Economo

(1929)

Oxford University Press (1931)
Character of Infection

• Transmission
  – Direct (person to person) rare
  – Possibly airborne
  – Possible non-affected carriers
  – Potential for contagion reduces once localized in CNS
Character of Infection

• Incubation
  – Almost impossible to predict
  – Reported as a minimum of one day, average of ten days, and a maximum of 2 months
Predisposition

• Concentrated populations
• General hardship
• Afflicted with another pathogen
**Etiology**

- **No known cause**
- Different pathogens possibly associated with EL
- Pathogens not found consistently throughout EL brain tissue samples
- Unable to replicate experimental results
Etiology

- von Economo “due to the nature of the disease a virus specific for the mid-brain and lower brain must be the causing agent though it can not be found”
(a) Heavy perivascular infiltration but little loss of nerve cells. (b) Severe destruction of pigmented cells leaving granules of melanin pigment in a subacute case. (Nissl)
Pathology

Mesencephalon

Caudate nucleus

Putamen

Globus pallidus

Basal ganglia

Substantia nigra
von Economo’s Types of EL

• Common Prodromal Stage
• Three described types
  – Somnolent-Ophthalmoplegic
  – Hyperkinetic
  – Amyostatic-Akinetic
Common Prodromal Stage

- Almost always of short length
- General discomfort
- Lassitude, Seediness (Weariness, Lethargy)
- Shivering
- Headache
- Vertigo and Vomiting
- Slight fever
- Mild Pharyngitis
Somnolent-Ophthalmoplegic

• Somnolence
  – falls asleep, even during activity
  – if aroused wakes up quickly and completely
  – Can be present with no rise in temperature or CSF pressure
Somnolent-Ophthalmoplegic

- **Ocular Palsies**
  - Lateral rectus muscle paralysis (outward movement of the eye)
  - Ptosis (Drooping eyelids)
  - Impairment of accommodation (focusing the lens for near vision)
  - Conjugate deviation palsy (Both eyes moving together)
  - Vertical palsy (paralysis of movement up or down)
  - Nystagmus (rapid involuntary movements of the eyes)
  - Strabismus (cross eyed)
Intraocular muscle paralysis
- Anisocoria (pupils are different sizes)
- Myosis (constriction of the pupil)
- Mydriasis (dilation of the pupils)
- Argyll Robertson’s sign (The pupils are small and irregular, they do not react to light but react for accommodation)
Somnolent-Ophthalmoplegic

Other Signs and Symptoms

• Dream like deliria
• Sight Disturbances
  – Diplopia (double vision), Dazzling (Impaired vision in bright light), Indistinct vision
• Facial Paralysis, Soft palate paralysis
• Disturbances in swallowing and chewing
• Hypotonus (decreased muscle tone)
• Ataxia (incoordination of muscle movements)
• Hyperhidrosis (Excessive Sweating)
Hyperkinetic

• Motor unrest
  – **Myoclonic twitches** (involuntary twitching of a muscle or a group of muscles)
  – **Frequently accompanied by stabbing pains**
    – **Clonus** (involuntary muscular contractions causes large motions)
    – **Chorea** (involuntary quick movements of the feet or hands)
    – **Athetosis** (continuous stream of slow, sinuous, twisting movements that distort posture, typically the hands and feet)
    – **Derailments of movement** (Stopping an action in the middle of completion)
Hyperkinetic

- Psychomotor unrest
  - Anxiety
  - Frenzy
  - Apprehension
  - Hallucinations
  - Panic
  - Hypomania
Hyperkinetic Sleep Disturbances

- Sleep Disturbances
  - Insomnia
    - Not responsive to drugs
  - Sleep Inversion
    - Night time motor unrest
    - Daytime Somnolence
Hyperkinetic
Other Signs and Symptoms

- Speech disturbances
- Severe headache
- Pain
  - Facial, Arms and legs, Abdominal (often mistaken for appendicitis)
- Vomiting
- Facial swelling
- Delirium and confusion
- Pupillary disturbances
- Respiratory disturbances
- Seizures
Amyostatic-Akinetic

- **Rigidity** (inflexibility)
  - Common in chronic cases
- **Asthenia** (weakness without actual loss of strength)
- **Bradykinesia** (slowness in the execution of movement)
- **Flexibilitas cerea** (characteristic rigidity that holds the limb in position)
- **Masked facial expression** (face lacks expression and animation)
Amyostatic-Akinetic

- Sleep disturbance
  - somnolence
  - inversion
  - insomnia
  - disassociated body sleep and brain sleep
Amyostatic-Akinetic: Other Signs and Symptoms

- Festinating (progressively more rapid) and slouching gait (pattern of walking)
- Propulsion and/or retro propulsion (compulsory movement forward or backward)
- Hypersialisis (excessive salivation)
- Hyperhidrosis (excessive sweating)
- Hypertonus (increased muscle tone)
- Speech disturbances
- Swallowing disturbances
- Eye muscle paresis
Types of EL

- Any number and combination of symptoms may be seen in a single case
- Clinicians began dividing the disease into additional types
Prognosis

• Varied course
  – Symptoms may appear suddenly
  – Sometimes show a dramatic turn (for better or worse) without warning
Prognosis

• Death
  - In acute cases 40% die
  - In all cases (acute and subacute) 15% die
  - Frequently nonspecific modes of death occur
    • e.g. pneumonia

• Recovery and Sequelae
  - Of all surviving cases
    • 22% complete recovery
    • 44% recovery with slight defect
    • 34% chronic invalids
Sequelae

• Residual Symptoms and Signs
  – Ocular paralysis
  – Spastic muscle paralysis
  – Sensory disturbances
  – Vegetative disturbances

• Protracted States
  – Relapsing cases
  – Intermittent progression
Sequelae

• Post Encephalitic Diseases
  – Psychosis
  – Parkinsonism
Psychosis

- Mostly in Children
- Juvenile pseudo-psychopathia
  - Erethic imbecility (abnormal irritable foolishness)
  - Hypomania
  - Insomnia
  - Lack of inhibitions
  - Sexually inappropriate
  - Able to know they are doing wrong but unable to stop themselves
Post-encephalitic Parkinsonism
Post-encephalitic Parkinsonism
EL’s relevance to the Present

• Sporadic Cases
  – 230 cases of EL cited in the literature throughout the world since 1940 (unpublished observation)
  – 29 of those occurred in the last 10 years

• Possible relationship to Influenza
  - Many reports of EL like diseases occurred with influenza pandemics in world history
  - Some evidence suggest a relationship
  - Researchers have yet to conclusively say that EL is not caused by or associated with EL
Sporadic Case of EL

• In 1999 diagnosed with EL
• Unconscious for three months.
• Passed away on 30th May 2006

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Historical Accounts of Sleepy Sicknesses and Influenza

- 1580 Europe
- 1673-75 London
- 1763 France
Historical Accounts of Sleepy Sicknesses and Influenza

- 1780-82 Paris
- 1830-33 Paris
- 1890-91 Italy
EL and Influenza

- Among Contemporary Observers of EL...
  - Few believed EL and influenza were from the same organism
  - Many believed influenza predispose for encephalitis lethargica

Self-portrait after the Spanish Influenza
Edvard Munch (1919)
Circumstantial Support for a Relationship Between EL and Influenza

- EL Cases in children largely preceded by Influenza (Neal 1920)
- 37% of EL cases from Belarus preceded by Influenza (1918-1928)
- EL either led or followed the flu for the years 1918-19, 20, and 23 (Chasanow 1930)
Circumstantial Support for a Relationship Between EL and Influenza

Hardest hit U.S. city with both influenza & EL: Philadelphia.

Least affected population by both influenza & EL: Blacks.
Circumstantial Support for a Relationship Between EL and Influenza

- 1918 Influenza epidemic on Western Samoa
  - followed by EL for several subsequent years
- Strict quarantine in American Samoa
  - No 1918 influenza epidemic
  - No EL deaths
Evidence Against an EL and Influenza Relationship

• v. Economo’s first case of EL preceded the earliest influenza cases

• Opposing geographical proliferations of Influenza and EL

Possible explanations...
• Variant influenza virus
• Spanish influenza began earlier in Europe
• EL in North America prior to its recognition
Evidence Against an EL and Influenza Relationship

- EL and influenza had notable medical differences:
  - Prevalence, Clinical features, Infectivity

- Other diseases have different stages with very different signs and symptoms (Maurizi 1989)

  - Primary Syphilis: effects genitals, 10-90 day incubation period
  - NeuroSyphilis: effects CNS, occurs some time after original infection
  - Measles: effects general body, 4-12 day incubation
  - Subacute Sclerosing Panencephalitis (SSPE): effects CNS, 6-15 years after initial infection
Evidence Against an EL and Influenza Relationship

- Modern Studies of Preserved EL/PEP Brain Tissue

  - McCall et al., 2001
    - Influenza RNA not detected

  - Lo et al., 2003
    - Influenza RNA not detected
Limitations Of EL-Influenza Studies

• Failed to test non-CNS tissues
• RNA sequence mismatch

1918 Influenza, Bronchopneumonia. Inter-lobar pleurisy.
Credit: National Museum Of Health And Medicine.
Limitations Of EL-Influenza Studies

• EL material rare

• Tissue Prep and Handling not reliable
Is EL caused by an Autoimmune Response?

• 20 putative modern cases of EL (Dale et al. 2003)
  – Significant increase in recent streptococcus infections in EL vs. control patients
  – 95% had basal ganglia autoantibodies

• Group A Streptococcal infections may cause latent neurological effects
  – Sydenham’s chorea
  – Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (P.A.N.D.A.S)

- 60% normal MRI findings
- 35% no anti-streptolysin-O elevation
- No data for disease duration vs. control
- No data for the cross reactivity of antibody
Why EL-Influenza Studies may have false negatives

- **Hypothesis by Hayase and Tobita (1997): How influenza can cause encephalitis by:**
  - Molecular mimicry
  - Cerebrovascular endothelial cell infections
  - Alteration of normal blood-brain barrier
The EL and Influenza Relationship

• Case of 2 Vietnamese siblings, 4 & 9 year old (deJong et. al. 2005)
  – Probable encephalitis associated with H5N1 bird influenza virus
  – No respiratory symptoms presented

 Raises the possibility that the avian H1N1 influenza virus of 1918 may also have had unusual manifestations (i.e. EL)
If EL is Related to Influenza

- Waking to a New Flu Threat
  (Sacks and Vilensky 2005)
Conclusions

• Encephalitis lethargica produces variable symptoms and signs
• Encephalitis lethargica effects patients long after initial sickness is over in the form of sequelae
• Understanding how encephalitis lethargica is diagnosed is critical because a new epidemic is possible and sporadic cases still occur
• Research into encephalitis lethargica causative agent is still needed to better understand this disease
• Economo wrote in 1929
  – “One thing is certain: whoever has observed without bias the many forms of encephalitis lethargica… must of necessity have quite considerably altered his outlook on neurological and psychological phenomena…. Encephalitis lethargica can scarcely again be forgotten.”