What caused the 1918–30 epidemic of encephalitis lethargica?

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Encephalitis lethargica, often called epidemic encephalitis at the time of the epidemic, was prevalent worldwide during the years 1918–1930. The acute phase, characterized by somnolence and a mask-like facial appearance, was associated with a 20–40% mortality.

Later in the epidemic, almost all those who had had an acute episode of encephalitis lethargica developed sequelae to a greater or lesser degree. In some cases, the symptoms persisted without respite to the chronic state; in others they developed weeks, months or years after the patient was thought to have recovered. The outstanding motor manifestation was the parkinsonian syndrome, present in almost every case. This resembled the picture of Parkinson's disease (paralysis agitans), except that the 'pill-rolling' movement typical of Parkinson's disease was often absent; the tremor in postencephalitic parkinsonism was usually coarse. The common general features of the latter were rigidity of all the muscles, loss of automatic or synergistic movements, loss of equilibrium, and a running or shuffling gait. Oculogyric crises were an important feature. There were mental changes, especially in children, and respiratory tics were often noted[2]. Sometimes signs of pyramidal tract damage were found[3].

EPIDEMIOLOGY

In the USA, few cases were reported before 1920, the peak period being between 1920 and 1929. The epidemic of influenza burst upon the USA a year before the epidemic of encephalitis lethargica in 1919. There were 3100 cases during 1920–1924 and 1222 cases during 1925–1929. Subsequently, the incidence decreased rapidly. At the outset of the encephalitis epidemic in the USA, 46% of patients with encephalitis gave a history of influenza compared with 30% for the rest of the population[3]. Many patients reported a flu-like illness at the onset with stupor, unconsciousness or fever[4,5]. These observations led the US Surgeon General's medical officer to state in 1920 that the aetiology of encephalitis lethargica was the same as that for influenza[6].

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The opinion in Britain as to the aetiology of encephalitis lethargica was varied[1,7]. The frequent observation within living memory of isolated cases before the great epidemic suggested that this was not a new disease. During the epidemic, the years in which encephalitis lethargica occurred more frequently coincided with a drop in the number of cases of influenza. Other theories as to the cause of the epidemic included botulism[8] and poliomyelitis[9,10]. Some cases of encephalitis following influenza in young children and infants would be regarded today as post-influenzal encephalitis or Reye's syndrome[11]. In others the description of encephalitis with a preceding history of influenza was well documented[12]. Of von Economo's 13 cases of encephalitis lethargica in 1916–1917[13], none showed signs attributable to influenza. He differentiated the characteristic clinical and pathological signs of encephalitis lethargica from post-influenzal encephalitis. He found that the earliest cases of encephalitis lethargica in Central Europe preceded the influenza epidemic by three years. The first cases were reported in Romania in 1915[13]. In France, 40 cases of encephalitis lethargica occurring in the winter of 1916–1917 were reported by Cruchet at a military neuropsychiatric centre[14]. These represented 3% of the patients admitted. The French cases closely resembled those that occurred later in England in their presentation and evolution. Hall[15] found reports of cases of encephalitis in Europe in the years 1903, 1907, 1908, 1910, 1912 and 1913. In northern Italy there was a serious outbreak of what probably was encephalitis lethargica in 1889–1890, called *la nona*[16]. It followed an epidemic of influenza the year before[13]. Crookshank and von Economo reported other epidemics of encephalitis in the past that might have been encephalitis lethargica[13,17] dating back to the sixteenth century.

By 1918, the number of sporadic cases of encephalitis lethargica reported in Europe and elsewhere increased rapidly and the condition became epidemic at the same time as the influenza pandemic of 1918. The disease prevalence was greatest in the colder months of the year, as with influenza. Stallybrass[1], however, found that of over 1000 cases reported in 1923, only 4 had a history of influenza within six months, of which 2 were doubtful. Similar observations were made by others. Conversely, in a very large influenza epidemic at Camp Dix, New Jersey, in

1918, there were 6000 cases of influenza with 800 deaths but no concurrent cases of encephalitis lethargica[18]. While the encephalitis lethargica epidemic was distinct from the epidemic of influenza, there is no doubt that historically the two diseases repeatedly occurred in close proximity of time.

Any study of encephalitis lethargica must take into account the recent characterization of the 1918 influenza virus by Taubenberger *et al.*[19]. This work established that the virus was a H1N1 influenza A virus of probable swine-human origin. With parts of the genome sequenced, it is possible to identify, by polymerase chain reaction (PCR), residual influenza virus that may be in archival material of encephalitis lethargica.

Stallybrass[1] noted that the most common age of incidence of encephalitis lethargica was 10–20 years of age. He remarked that this was at variance with the age of incidence of most communicable diseases at the time and it was also the age group in which such diseases were least fatal. The rarity of person-to-person spread was noted in every country and in every outbreak. Exceptionally, local spread of the disease in isolated communities was recorded, with a variable incubation period[15]. In a severe wave of encephalitis lethargica that engulfed certain villages in Lapland in 1921, the morbidity rate varied from 7.1% to 45%; whole families were involved, and side by side with acute typical cases were others in which the disease was mild[20]. In a girls' home in Derby, 12 cases of encephalitis lethargica occurred in a total community of 22 persons within two weeks, resulting in 5 deaths[21]. In a rural school in Warwickshire in 1922 a child developed encephalitis after a visit to town. Four to five weeks after her return to school 3 other girls in her dormitory fell ill. This suggested an incubation period for the disease of up to four weeks[22]. Infants born to mothers ill with the disease were reported to develop encephalitis[15]. Parsons[23] estimated that the incubation period ranged from one day to two weeks or more. In 1926, the Scottish Board of Health[24] stated that carriers of the infective agent in the nasopharynx were common, but only a minute fraction of those exposed to the disease acquired it; the factor of lowered resistance was far more potent than the presence of the agent. The outbreaks of encephalitis in Britain were generally local and ran their course over several weeks. High morbidity in the local epidemics suggested a low level of immunity in the population[1,8,10,24]. The manner of spread of encephalitis lethargica suggests an intermediate vector of infection. With this epidemiological background von Economo[13], Duvoisin and Yahr[3] and others[24] rejected an aetiological relationship to influenza.

More recently, Ravenholt and Foege[25] reviewed the incidence of influenza and encephalitis lethargica in Seattle and Samoa. They found that both these diseases appeared in Western Samoa—influenza in 1918 and encephalitis lethargica in 1919. Outbreaks of these two diseases continued and their peak incidence was always separated by a year.

Contemporary observers in Europe calculated that the incubation period for encephalitis lethargica varied from one day to several weeks (see below). The incidence of encephalitis lethargica in England up to 1924 was as follows: 1919, 541 cases; 1920, 890 cases; 1921, 1470 cases; 1922, 454 cases; 1923, 1025 cases; 1924, 5039 cases; 1925, 2635 cases. A total of 12 054 cases were reported in England and Wales from 1918 to 1925. Yearly totals did not appear in the leading British medical journals thereafter. In addition, there were many mild and abortive cases, including epidemic hiccup, that were widely described but not reported. These patients frequently went on to develop serious post-encephalitic sequelae[26,27]. By 1927, the acute cases occurring in England were often so mild that the acute phase would pass without much notice; however, the post-encephalitic sequelae continued to be devastating[2]. In France there were at least 10 000 cases up to 1920 and 3900 cases in Italy[15]. Subsequently, sporadic cases continued to be reported; recently, Rail *et al.*[28] described 8 patients whose disease was initiated between 1945 and 1968, one of whom was screened for virus antigen by Elizan[29] (see below).

OTHER CHRONIC ENCEPHALITIDES

Because of the lack of virological techniques for virus isolation and characterization, the establishment of encephalitis lethargica as a clinical entity rests on the abundant contemporary epidemiological, clinical and pathological descriptions. Nevertheless, several other viral encephalitides occurred during the twentieth century. In Japan, recurrent outbreaks of 'summer encephalitis' were described[30]. The virus was isolated in mice and called Japanese B encephalitis virus to show its association with 'B' or summer type of encephalitis virus, differentiating it from encephalitis lethargica, known as 'A' type. It is now classified as a member of the mosquito-borne complex of the family Flavoviridae. The outbreaks during summer months were caused by the transmission of the virus by culicine mosquitoes, which spread the disease over a large part of East Asia. It was also found in Japan that birds and domestic animals served as hosts for the mosquitoes that transmitted the disease. There was evidence of persistent virus infection in some patients. After recovery from the acute episode some patients developed progressive neurological signs. Virological and immunological evidence of virus persistence could be demonstrated and signs of continuing inflammation were found in the brain at

necropsy. A mouse model of chronic virus infection was established.

In the USA there were outbreaks of summer encephalitis in St Louis in 1933 and 1937, caused by a virus that was immunologically distinct from Japanese B.

In Britain, the syndrome called myalgic encephalomyelitis (ME) or more commonly chronic fatigue syndrome (CFS) has been studied in the laboratory. CFS may be a blanket description covering several conditions; however, some of the cases follow a pattern in which patients develop sore throat and a flu-like illness, followed by weeks and months of debilitating fatigue. Physical mobilization often worsens the condition. Unlike the encephalitides, CFS has no neurological signs. PCR studies by Clements *et al.*[31] have identified enterovirus genome in the serum of significantly more patients with CFS than controls. Bowles *et al.*[32] demonstrated enterovirus RNA by molecular hybridization in the muscle of a substantial numbers of patients with CFS. It is possible, therefore that CFS is caused by a persistent enterovirus infection.

In Bulgaria, Bojinov[33] described an outbreak of encephalitis in 1965–1970 in which the disease ran an acute course and the patients developed parkinsonian symptoms. Necropsy of the fatal cases revealed inflammatory necrosis of the substantia nigra. This syndrome had a more rapid course than encephalitis lethargica and may or may not have had the same aetiology.

CLINICAL DESCRIPTION

The signs and symptoms of the acute phase of encephalitis lethargica were described in excellent detail by the early observers[4,8–10,13,14]. The afflicted individuals became ill suddenly with only slight prodromal upper respiratory signs and low-grade fever. In the acute 'oculo-lethargic' stage, most common early in the epidemic, the presenting features were: somnolence, at times deep, but from which the patient could be roused; mask-like facies accompanied by mental apathy; tired, expressionless, toneless speech, often thick and slurred; eye signs (e.g. oculogyric crises, diplopia, ptosis, squint, nystagmus, pupil irregularity); convulsive seizures, and stroke[1]. These features differentiated the disorder from other types of encephalitis recognized at that time.

From early in the epidemic, encephalitis lethargica was separated from other clinical entities such as purulent meningitis (cerebrospinal fever as it was then known), postinfectious and postvaccinal encephalomyelitis, poliomyelitis, herpes encephalitis, rabies and Japanese encephalitis. The parkinsonian sequelae of encephalitis lethargica were almost unique. Exceptionally, however, post-encephalitic parkinsonism was reported after measles, herpes, Coxsackie virus encephalitis[3] and Japanese encephalitis[30]. Bassoe[34] subdivided encephalitis lethargica into several types according to the patients' affective behaviour.

In 1923 Stallybrass[1] noted a change in the clinical picture of the disease. He observed that only 45% of cases could be classified as oculo-lethargic. Other forms were found, including myoclonic (14%), choreiform (25%), or psychomotor (16%). These had been described earlier[13] but became more common by 1923. Instead of lethargy Stallybrass observed delirium, excitement, sleeplessness, myoclonus and tachypnoea. A striking observation made in the early work was the frequent appearance of a generalized rash early in the acute illness. The rash was papular, macular, morbilliform or even petechial[4,7,1]. One observer reported a 'glove' desquamation of the hands and feet akin to that of scarlet fever but clearly different[35]. Such exanthems may have been caused by the same vasculitis that was found in the brain in acute cases coming to necropsy. Curiously, exanthems were not mentioned in the copious reports after 1923. Conceivably mutation of the causal virus changed in the clinical picture over time.

Related, perhaps, to the dermatological signs were reports of a haemorrhagic syndrome, most often in fulminating cases of encephalitis. These presented as purpura, epistaxis, gastrointestinal haemorrhage and meningeal haemorrhage[15]. Gastrointestinal symptoms were often found; at the onset the patients suffered from persistent vomiting, sometimes accompanied by diarrhoea but more often by constipation. In contrast to most observers, Parsons quoting Gardner[23] stated that the illness was heralded by a severe sore throat in which the pharynx was deeply inflamed and the tonsils were covered with a patchy white exudate. The tongue and the throat were very dry and there was difficulty in swallowing. This pointed to an upper respiratory infection as the primary portal of entry. Yates and Barnes[36] suggested that the nasal sinuses were a route of infection.

PATHOLOGY

An early description of the morbid anatomy of acute cases of encephalitis lethargica by Buzzard and Greenfield[4] in 1919 is illuminating. Examination of necropsy specimens and of the brain *in vivo* (in ill-conceived surgical intervention for increased intracranial pressure) showed vascular congestion leading to thrombosis, infarction and haemorrhage. Involving all parts of the brain and all vessels down to small capillaries, this was due predominantly to lymphocytic vasculitis and proliferation of the endothelial cells. Vascular calcification was also noted, not explainable by arteriosclerosis. There was nerve cell death, neuronophagy, and astrocytosis. In acute cases the grey matter was chiefly affected—largely in the pons, basal ganglia, midbrain and, most of all, cranial nerve nuclei[24].

In 1923 McAlpine[5] examined the brains of patients dying with post-encephalitic parkinsonism. In these patients, most of whom had been ill for months or years, most of the changes were in the basal ganglia. There was disagreement at the time as to whether the disease affected the substantia nigra or the globus pallidus. An important finding was calcification and hyaline degeneration of the blood vessels, most remarkably in the corpus striatum. McAlpine decided that post-encephalitic parkinsonism resulted in damage to the substantia nigra, with loss of neuronal cells and depigmentation. Subacute vascular inflammation was also present, varying in its site but found predominantly in the basal ganglia. Beattie[37] found irregular rounded or oval bodies, sometimes with an apparent central spot in the nerve cells suggesting virus inclusion bodies. Geddes *et al.*[59] described the neuropathological findings in 8 patients who had an initial bout of encephalitis and subsequently suffered a long period of post-encephalitic parkinsonism. There were no signs of active inflammation in the brain. The most severely affected area was the substantia nigra, which showed severe cell loss and gliosis. The locus coeruleus was less affected. There was no demyelination.

Neurofibrillary tangles were seen in the substantia nigra, coeruleus, hippocampus, parahippocampus and amygdala. In addition, neurofibrillary tangles were found elsewhere in the basal ganglia and the cortex and, occasionally, in the anterior horns of the spinal cord. Anti-tau immunohistochemistry showed small neurofibrillary tangle-bearing neurons and granular cytopositivity in nerve cells. Occasionally, this was also seen in the cytoplasm of microglia, macrophages and astrocytes.

EXPERIMENTAL RESEARCH

At the time of the acute epidemic of encephalitis lethargica there was no lack of post mortem material for experimental research. Pathologists attempted to infect rabbits, monkeys and guineapigs with preparations from diseased brain tissue. Most of the experiments would be criticized today for their lack of controls, the presence of an endogenous meningoencephalitis in uninoculated rabbits (possibly caused by a microsporidium[38,39]), the frequent presence of herpesvirus in the material for inoculation, and failure to observe the correct filtration procedure for bacteriological sterilization of the inoculum.

Strauss and Loewe[40,41] successfully passaged filtrates of encephalitic human brain and nasopharyngeal mucosa to monkeys and rabbits by cerebral inoculation, maintaining the virus through four passages in rabbits. Non-encephalitic tissue filtrates were negative. About 50% of rabbits showed natural immunity to inoculation. Levaditi *et al.*[39,40] noted the presence of inflammation of the upper respiratory tract in encephalitis lethargica patients. After scarifying or applying croton oil to the nasal passages of rabbits they were able to passage the disease by nasal inoculation. Without damaging the nasal mucosa they were unable to reproduce the disease by that route. In a later paper, the same group described complex experiments in which they seem to have chosen data out of context. They reported a virus from normal human saliva that could be passed by rabbit corneal scarification, an encephalitic virus from healthy carriers, and a virus from herpes lesions transmissible to rabbits, all of which were thought to be variants of the same virus. The incubation period for transmission of the encephalitis virus was 5–9 days. Protection from serum of inoculated rabbits or from sheep inoculated with encephalitis brain was either doubtful or negative. These early experiments in animal transmission of encephalitis were the antecedent of modern virology. By today's standards some of these experiments were poorly controlled and misinterpreted. Modern technology might reveal interesting information from fixed tissues taken from the animal passages in the more successful experiments.

MacCartney[43] examined 400 untreated rabbits at the Rockefeller Institute and found that half had perivascular inflammatory lesions similar to those seen in experimental encephalitis. Pathological evidence for animal transmission therefore could not depend on perivascular inflammation alone, as in many experiments mentioned above, but required the demonstration of neuronal damage and gliosis.

In the interwar years, virological research could not progress until Smith *et al.*[45] isolated a human influenza virus. Subsequently, the neurotropic strains WNS and WSN of influenza virus were developed by passage in mice[46,47]. The course and pathological features in mice, however, were dissimilar to those of the human disease, encephalitis lethargica. The sites of viral replication in the mouse brain were in the parenchymal cells surrounding the lateral and third ventricles, the corpus callosum and the ependyma. Common strains of inbred mice all died within 5 days; however, the resistant mouse strain A2G survived the infection as the result of interferon production. Virus could still be detected in A2G mice immunosuppressed with cyclosporin for 19 days[48,49]. Mirchink *et al.*[50] developed a substrain of influenza AA/WSN/33 (H1N1) by inoculation of pregnant C57B16 mice and the recovery of virus from their progeny. This substrain differed from the original virus antigenically and produced a persistent infection. Cerebral isolates from progeny mice continued to show neurotropism for several passages. The infected mice were immunodeficient.

Gamboa *et al.*[51] demonstrated intranuclear influenza virus antigen in frozen sections of hypothalamus and midbrain in six cases of postencephalitic parkinsonism using directly fluorescent-conjugated anti-WNS and anti-WSN

rabbit globulin with appropriate controls. The polyclonal antisera were provided by Choppin and Compans at Rockefeller University. The antisera directed against WNS and WSN reacted with all 6 cases whereas other influenza virus antibodies reacted poorly or not at all. Blocking experiments confirmed the specificity of the reactivity. Parkinson's disease and other control brain tissues were negatives. Measles and herpes antisera did not react. Elizan *et al.*[26], however, also used neurotropic virus antiserum in addition to various other conventional anti-influenza sera in 2 cases of encephalitis lethargica but were unable to confirm Gamboa's findings. Elizan used an indirect immunoperoxidase staining method on paraffin embedded sections; it is possible that differences in technique could account for the contradictory results of these two groups. Elizan was unable to find antibodies to influenza A and B in the sera of 2 patients with encephalitis lethargica.

There have been few electron microscopic (EM) studies of encephalitis lethargica. An EM study by Waggener *et al.*[52] revealed filaments in the brain of a case of juvenile Parkinson's disease. Ishii and Nakamura[53] showed Alzheimer's neurofibrillary tangles in the brain of postencephalitic parkinsonism. A review of papers relating to postencephalitic parkinsonism reported no EM studies for virus particles[54]. Schwartz and Elizan[55] examined the brains of 9 patients with idiopathic Parkinson's disease and 3 matched controls using EM, tissue culture explants of brain, and immunofluorescence, with negative results. Elizan *et al.*[56] found an association of 'postencephalitic Parkinson's disease' with HLA B14 antigen in an American-Jewish ethnic group.

CONCLUSIONS

The contemporary observers of the encephalitis epidemic of 1916–1930 carefully recorded the clinical and pathological details of the disease. Some observers noted that its onset resembled influenza with severe upper respiratory inflammation. Others found that prodromal signs were very mild. It appeared to follow waves of epidemic influenza. The epidemiology, transmission and progress of the disease, however, were unique and differed greatly from those of influenza. There were outbreaks of what may have been encephalitis lethargica previous to the great epidemic and also after it had receded. Chronic progressive inflammation of the brain resulted in destruction of the basal ganglia over months and years and caused the disastrous syndrome that was aptly named post-encephalitic parkinsonism. The more recent care and treatment of these patients has been described by Sacks[57], who elicited transient remissions with levodopa.

The early observers studied the epidemiological characteristics of its spread—a baffling mixture of phenomena, in which tens of thousands in Europe, America and worldwide fell ill. The spread of the disease nevertheless was sporadic, without obvious relation to economic class, geography or age group. There were documented outbreaks of person-to-person spread of encephalitis lethargica but these were notable for their rarity. The disasters of the First World War and the starvation and population displacement that followed may have contributed to the epidemics of the period. These conditions are being re-enacted in some parts of Eastern Europe today.

The early virologists developed acceptable evidence for a viral aetiology but the methods available were limited to animal transmission. The technique for long-term preservation of infective virus had not been developed and so little material remains for modern study. In the 1970s attempts were made to relate the aetiology of post-encephalitic parkinsonism to an influenza virus. Conflicting results were obtained by different workers using immunofluorescence of tissue with anti-influenza antibodies. Today, it is possible to examine fixed tissue by electron microscopy and also to rescue virus nucleic acid by PCR, if there are clues to suggest which virus probe to use. The characterization of parts of the genome of the 1918 influenza virus is a great step forward and will be instrumental in this endeavour. Monoclonal antibodies may turn out to be more specific in localizing influenza antigen in preserved tissues than the polyclonal sera previously used. Luck *et al.*[60] showed that influenza virus antigen could be demonstrated in fixed paraffin-embedded tissue only after trypsin treatment of the sections.

An autoimmune mechanism for the pathogenesis of postencephalitic parkinsonism should be investigated[58]; however, the lack of patient sera for autoantibody examination makes such study difficult. There is only one surviving patient in Britain.

It would be well to understand this disease better, as it has not disappeared entirely. The knowledge retrieved by this historical study will be useful in the molecular and EM investigation of encephalitis lethargica that is in preparation in this laboratory.

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