

# ENCEPHALITIS LETHARGICA

## A LITERATURE REVIEW

Encephalitis lethargica (EL) was named and described by Von Economo in 1916, and further detailed in a monograph in 1931 [1] following the pandemic of 1919 to 1926, but for many years was regarded as a phenomenon of the past. In recent years there has been a recurrence of interest in the disease, concerning aetiology and links with post-encephalitic parkinsonism. Oliver Sacks described awakening of past cases, but recent papers have described contemporary cases and defined the disease in modern terms. In 2003 we undertook a literature survey to assess the published information on this disease in the last 20 years.

We first searched medical and general databases using a variety of search engines, and perused references in available papers. This identified over 30 sources in English language journals. These can be divided into three sections.

First are review articles, often concentrating on a historical perspective of EL, and the influence it has had on neurology and psychiatry. These do not provide new information about the disease.

Second, some articles have addressed possible aetiology, several arguing that it stemmed from the 1919 influenza epidemic as either an acute viral, or a post-viral syndrome. Some epidemiological and neurohistological data are available from these sources, but thus far no consensus on aetiology has emerged. Recent work linking EL to streptococcal infection is being further developed, and may prove more compelling than the influenza theory.

The main focus of this review is the third section, published data on recent cases. No controlled, retrospective or prospective trials were identified in EL, probably because it has been reported so rarely. We identified 13 papers containing 19 case reports since 1982, all but one since Howard and Lees [3] proposed diagnostic criteria for EL which have been widely accepted. These are set out in Box 1. We analysed these cases for age, gender, symptoms, investigations and outcomes. Case reports are often brief and incomplete but a clear pattern has emerged.

Most cases are women (14/19) and young, average age 23 with a range of 5-63. Precipitating events are rarely described, although foreign travel is identified in 3. Most cases presented after an acute illness characterised by headache, malaise, fever (although in many cases this occurred as a later hypothalamic syndrome), vomiting and vertigo. A minority of cases (5) presented as a psychiatric syndrome without clear acute onset or physical illness. There is little mention of infective aetiology, and baseline investigations including blood white cell count, renal and liver function were usually normal, although two cases describe disturbed LFTs at presentation. Most cases had lumbar puncture performed, but this was often normal, with CSF protein varying from 0.3 to 2.1, minor lymphocytosis in some cases, and oligoclonal bands. In most cases a wide range of antibodies to infectious diseases was checked and found negative, except for one slight

rise in measles titre, and one case of mycoplasma pneumonia [6]. EEG showed slow wave activity in most cases, with some theta waves; most were abnormal. CT/MRI scans in more recent cases were normal even during severe neurological disturbances, except for one case in Singapore which showed marked substantia nigra change.

At presentation, most cases already had neuropsychiatric symptoms. Bizarre behaviour, delusions, and obsessive compulsive traits, often led to a psychiatric label initially. Mutism, catatonia, agitation and more extreme behaviour change such as coprolalia ensued. This was accompanied by hypokinesia, rigidity, oculogyric crises and fits in most cases. Tremor and chorea are rarely described. Dystonia and blepharospasm often developed. Sleep disturbance and hypersomnolence are almost universal, with sleep inversion and insomnia common. Eye signs include ophthalmoplegia and gaze palsies, ptosis in some, but rarely brain stem signs, although respiratory patterns were often variable, leading to ventilation. Most cases required intensive support, and the duration of illness varied from one to 40 weeks.

Since 1999, a London group has gathered 30 new sporadic cases in adults and children [15]. These were also mainly young, equal male and female, with variations on the symptoms described above. All met Howard and Lees' criteria for the diagnosis of EL. The group is researching aetiology, and postulates an autoimmune pathogenesis, following a streptococcal illness.

No clearly effective treatment emerges. Success has been claimed for steroids, antiparkinson drugs, ECT [10] and supportive intensive care [7]. Outcome was surprisingly good, with 8 cases which required intensive support returning to normal or near normal lives; only 4 of the 19 recorded cases ended in death, and the remainder had some disability requiring support in the community. Prolonged psychiatric variants had a worse prognosis than acute severe illness with predominantly neurological signs.

Combining the literature and current work in London, we have therefore identified 50 cases of this disease in recent years. There are likely to be many more, either unidentified, or not known to current researchers, or simply never reported. It is hoped that national surveillance of this disease will shortly be commenced. The youth of subjects, the severity and complexity of the disease, yet with potentially good outcomes, lead us to conclude that the disease merits significant future research. Although incidence is sporadic at present, the potential for further epidemics is significant. We need to be prepared with knowledge of presentation, course, cause and outcome.

Richard Wharton December 2003

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## BOX 1

### Diagnostic Criteria

An acute or subacute encephalitic illness including at least three of the major criteria, where all other known causes of encephalitis have been excluded.

1. Signs of basal ganglia involvement
2. Oculogyric crises
3. Ophthalmoplegia
4. Obsessive-compulsive behaviour
5. Akinetic mutism
6. Respiratory irregularity
7. Sleep disturbance