Post-infectious encephalomyelitis: some aetiological mechanisms

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Summary

The possibility that acute disseminated encephalomyelitis (ADEM) and epidemic myalgic encephalomyelitis ('epidemic neuromyasthenia') may share a common pathogenesis is examined and many factors common to the two diseases are described. It is suggested that further study of ADEM may help our understanding of epidemic myalgic encephalomyelitis.

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM), post-infectious or para-infectious encephalomyelitis, is a disease which receives little attention in text books of neurology, gets brief mention in large books of medicine and is rarely considered in text books of psychiatry. Yet it is relatively common, constituting one third of all cases diagnosed as encephalitis (Scott, 1967) and is often clinically indistinguishable from acute multiple sclerosis. Despite the neglect of ADEM, however, a considerable amount of information is available and may help in our understanding of epidemic myalgic encephalomyelitis (EME).

ADEM usually occurs after a banal virus infection (Miller, Stanton and Gibbons, 1956). It may also develop after vaccination (Spillane and Wells, 1964), as an adverse reaction to drugs (Russell, 1937; Cavanagh, 1953), or rarely, as a complication of serum therapy (Csermely, 1950). The disease usually presents within one week of the preceding event but may occur at any time up to one month later. In this regard it is important to note that second attacks may occur after subsequent infections or vaccinations (Holt *et al.*, 1976; Behan, 1977; Callaghan, Feely and Walsh, 1977).

It is not well recognized that ADEM has a wide spectrum of clinical presentation. It may present as a fulminating encephalitis ending fatally after a few days but at the other end of the spectrum it can be an illness which is clinically indistinguishable from EME or the disease described here today as 'epidemic neuromyasthenia' (Table 1). Those cases which

present with definite neurological deficits, a clear-cut history of an antecedent infection, and abnormalities of the CSF are readily diagnosed as ADEM. When, however, psychiatric symptoms predominate and neurological features are inconspicuous or absent the disease is rarely if ever diagnosed as ADEM. In this paper, the author wishes to stress that far from being rare, psychiatric symptoms, indistinguishable from those described in the syndrome of EME, are relatively common in ADEM. It is his contention that EME and ADEM share a common pathogenesis.

In other publications, the clinical, pathological and immunological features of ADEM are listed in detail (Behan and Currie, 1978) so that only a brief description of these features will be given here. In the typical case, some days to one week after a viral infection, the patient complains of headache, loss of appetite, tiredness, muscle aches, joint pains and often a curious type of 'lumbago'. There is generally a low grade fever rising to 38°C or more with the onset of neurological signs. In the severe form, the commonest mental change is a depression in the level of consciousness progressing to stupor and sometimes coma. Irritability, hallucinations, difficulty in concentration, memory disturbances, Korsakoff's syndrome and acute paranoia have also been noted. When the disease involves the brain rather than the spinal cord, seizures of any type, hemiplegias, visual disturbances, choreoathetosis and bilateral optic neuritis have been found. When the spinal cord bears the brunt of the disorder, paraplegia may result. In some cases with spinal cord involvement, decreased reflexes which may be asymmetrical, mild disturbances of bladder or rectal sphincters, and muscle fasciculations have been observed. The patients may complain of a wide variety of different forms of paraesthesia: often there are unusual chest pains, difficulty with respiration, painful muscles and pain over the vertebral column.

Patients with a similar antecedent viral infection to that causing ADEM may present with purely

TABLE 1. Features of acute disseminated encephalomyelitis (ADEM) and epidemic myalgic encephalomyelitis (EME) contrasted

Clinical data	ADEM	EME
Ages affected	Not before 2 years All other ages affected	Predominantly in young adults
Sex	Both sexes affected equally	Preponderance of females
Incubation period	1-3 weeks	1-3 weeks
Bacterial studies	Negative	Negative
Virus isolation	None	None
Toxin isolation	None	None
Headache, muscle pains, anorexia, malaise, fever, somnolence	+	+
Stupor, coma, hemiplegia, hemiparesis, seizures, paraplegia	+	+
Choreoathetosis, cranial nerve palsies, optic neuropathy, areflexia, muscle paresis, fasciculations, sensory disturbances, nystagmus, ataxia, diplopia	+	+
Irritability, memory disturbances, hypochondria, severe neurosis	+	+
Personality changes, emotional instability	+	+
CSF		
Protein	May be increased	May be increased
Gammaglobulin	May be increased	May be increased
Cells	May be present	May be present
Sugar	Normal	Normal
Culture	Sterile	Sterile
Blood	Leucocytosis may occur	Leucocytosis may occur
EEG	Abnormal	May be abnormal
EMG	Not reported	May be abnormal

psychiatric manifestations. These may be non-specific; they include inability to concentrate, poor memory and poor 'psychic energy' so that any prolonged task involving intense concentration is virtually impossible; paranoia and severe hypochondriasis have also been noted. Indeed, several of these patients bear an obvious resemblance to those described with encephalitis following rabies immunization; the latter are described thus: 'personality changes were conspicuous and consisted of deterioration of highly integrated emotional and intellectual functions and of constructive conduct' (Shiraki and Otani, 1959). In other patients, the psychiatric manifestations are of a purely neurotic nature with mild personality changes, the predominant symptoms being those of hypochondriasis and poor concentration. Detailed neurological examination of such cases often reveals mild cerebellar signs or evidence of long tract damage in addition.

When a patient does develop the purely psychiatric symptoms following a virus infection or an

immunization, the case rarely presents to a neurologist and the inciting event is often overlooked. Because of the author's interest in this condition he has seen individuals who, following an upper respiratory tract infection, had a plethora of neurotic symptoms. The ADEM would have been overlooked were it not for a little asymmetry of reflexes, the occasional extensor plantar response and the finding of a mild leucocytosis in the CSF.

In ADEM the CSF pressure may be elevated but is usually normal; leucocytosis can occur, with neutrophils in the early stages, but a lymphocytosis is more usual, the cell count varying from a few to several hundred cells. The protein may or may not be elevated but it is usually below 100 mg %. The gammaglobulin has been reported to be increased in ADEM following anti-rabies vaccination. The EEG is abnormal in most cases, the abnormalities being those of diffuse slowing in the theta and delta frequencies. Changes in the EEG are helpful in diagnosis but are most useful in following the patient's progress. Indeed the patient's condition is

reflected graphically in the EEG and 'electrical deterioration' is often the first warning of a relapse (Ziegler, 1966; Durston and Milnes, 1970).

Externally the brain appears normal although it may show some congestion and swelling in severe cases. On section it may also appear normal but in severe cases small petechial haemorrhages may be observed in the white matter. In the early stages of the disease lymphocytes, plasma cells and occasional neutrophil leucocytes are found in the Virchow-Robin spaces. At a later stage there is proliferation of histiocytic and microglial elements around the veins, and new reticulin fibres are formed. In a sleeve-like zone of from 1 to 2 mm wide, around these small vessels, there is tissue destruction with the predominant feature being fragmentation of myelin. There is a relative sparing of axis cylinders. For a variable region beyond this peri-vascular cuff there is proliferation of microglial cells and swelling of astrocytes. Fat stains reveal that the microglial cells are phagocytic and laden with fat (myelin). In patients who die months to years after the acute attack, perivenous demyelination and gliosis can be found. Some of these perivenous demyelinated areas may coalesce to form larger lesions which, however, are quite distinct from those present in multiple sclerosis.

It is difficult to know whether steroids are effective or not in this disease since no controlled studies have been done. The author's own experience with a large number of cases strongly suggests that high dose steroids are beneficial in the early stages. In one study reported, more than 60% of the patients treated with corticotrophin showed improvement (Selling and Meilman, 1955) and in other series steroids have also been found to be of value (Miller and Gibbons, 1953; Ziegler, 1966; Spillane and Wells, 1964). Reduction of steroids may be followed by reactivation of the disease (Ziegler, 1966).

Genetic factors are probably involved in ADEM (André-Balisaux, 1953; Keuter, 1960; Ehrengut, 1961). Families have been described in which the disease has occurred in more than one member and has recurred in siblings following repeated infections. (Miller and Gibbons, 1953; Callaghan *et al.*, 1977). There is some circumstantial evidence implicating viruses in the pathogenesis of the disease. Histological studies have shown the presence of glial nodules (Babès' nodes) in four cases, two following rubeola and two following mumps (Hart and Earle, 1975). Rubeola virus has been cultured from the CSF of one patient (Shaffer, Rake and Hodes, 1942) and rubeola antigen has been demonstrated in the brain of a patient dying of ADEM (ter Meulen *et al.*, 1972). A virus has also been isolated from a case of post-vaccinal encephalomyelitis (Angulo, Pimenta-de-Campos and Desables-Gomes, 1964).

Whilst these rare reports suggest that ADEM is the result of direct viral invasion of the central nervous system, demonstration of a virus is the exception rather than the rule and in the majority of cases studied no virus has been isolated.

A variety of theories have been brought forward to explain the pathogenesis of ADEM and, of these, that of autoimmunity seems to have the most support. Van Bogaert (1950), in favour of this hypothesis, cited the frequency of recurring focal infections, skin allergies and joint disease in patients and their families. The disorder may follow immunization and can occur as an adverse reaction to certain drugs (Russell, 1937; Cavanagh, 1953). The latter reaction is regarded as due to sensitization since drugs such as sulphonamides and para-aminosalicylic acid can act as haptens. Such haptens may combine with blood vessel walls and render them highly antigenic.

There is good evidence that the primary lesion in ADEM is a vasculopathy (Poser, 1969): the blood vessels are the predominant site of disease with diapedesis of red cells, oedema and fibrinoid necrosis being found. The fact that the disorder may occur as a complication of serum therapy, i.e. in serum sickness (Csermely, 1950; Miller and Stanton, 1954), supports this hypothesis. Cases of ADEM following serum therapy have identical histological changes to those found in ADEM following virus infections, immunizations or drugs. Experimentally, similar brain lesions have been produced in dogs by repeated injections of tetanus antiserum (Putnam, McKenna and Morrison, 1931). All the events which incite ADEM may be associated with a vasculopathy: it is postulated that in the case of a virus infection, antigen-antibody complexes are formed and deposited in blood vessels causing damage; in the case of drugs or foreign serum, similar immune complexes may be involved. Rare cases of thrombocytopenia purpura with vessel lesions resembling those found in ADEM, have also been reported (Symmers, 1956) again supporting vascular lesions as the basis of the disease.

It has recently been noted that patients dying of endotoxic shock may have cerebral lesions like those of ADEM (Graham, Behan and More, 1978). These patients are considered as showing the generalized Schwartzman reaction and their widespread vessel lesions are due to massive activation of the complement system (Mergenhagen *et al.*, 1968). Similar perivascular lesions are produced when local complement activation is achieved by injecting Forssman antisera into the carotid artery of guinea-pigs (Jervis, 1943). A noteworthy feature is that perivenous demyelination is also found, related to these lesions. Thus, the vasculopathy found in ADEM may be secondary to endothelial

damage produced by localization of immune complexes with or without activation of complement, or by activation of complement alone.

Experimental allergic encephalomyelitis (EAE) is regarded as the animal model of ADEM. The histological features, especially in the monkey, are strikingly similar to those of ADEM (Behan *et al.*, 1973). There is compelling evidence that EAE is mediated immunologically through cellular immune mechanisms. The demyelination that occurs, has been demonstrated as being due to sensitized lymphocytes, and sensitization of lymphocytes to myelin can be shown *in vivo* and *in vitro* (Behan *et al.*, 1973). The sleeve-like demyelination which is found in EAE, however, may be the result of inflammatory vessel lesions and the role of the lymphocyte specifically sensitized to myelin is likely to be that of directing the inflammatory reaction to the brain. Thus, a similar type of demyelination is found when specific antigen is injected intracerebrally into sensitized animals (Wisniewski and Bloom, 1975).

ADEM occurring after rabies vaccination, where the vaccine contains neural tissue, is similar in all respects to EAE; ADEM following a virus infection is also similar to EAE in every respect except that in place of the vaccination a virus infection has been the inciting event. The evidence cited elsewhere in this paper suggests that ADEM is primarily a vasculopathy. In the past, the main reason for considering that it was a primary demyelinating disease was because of its histological similarity to EAE. Sensitization to myelin in EAE is undisputed but this sensitization may serve only to direct the inflammatory reaction to the brain: it has been shown by Wisniewski and Bloom (1975) that any inflammatory response in the brain will cause demyelination similar to that found in EAE. In some cases of ADEM, cell-mediated immunity has been demonstrated (Behan *et al.*, 1968; Lisak *et al.*, 1974) but, apart from ADEM associated with rabies vaccination, this most likely represents an epiphenomenon.

Since it is postulated that ADEM and EME may share a common pathogenesis, further study of ADEM may help in our understanding of EME.

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Discussion

A SPEAKER: How can a large reaction of this sort explain an epidemic disease?

DR P. O. BEHAN: We can explain it very nicely. What I was showing you was that this is the reaction of a man's head, a man's brain, to a virus, or rather it is an immunological reaction set off by the presence of a virus. It is all

a matter of gradations of this reaction.

We have found clustering of this disease, particularly in Glasgow children. We had two young children who came in with blindness who were school mates. Then we found another child from the same street blind with exactly the same disease.