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Acute disseminated encephalomyelitis: postinfectious, postimmunization and variant forms

Expert Rev. Neurother. 9(9), 1321–1329 (2009)

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Acute disseminated encephalomyelitis is not an uncommon disorder and affects both children and adults, being more frequent in the younger group. It is said to constitute one third of all encephalidities and usually follows in the wake of a banal viral infection, but may occur after immunizations and as a complication of diseases affecting the cerebral endothelial cells. There is no specific diagnostic test but a good clinical history, attention to clinical findings along with MRI scan often help to make the diagnosis. Treatment with high dose steroids clearly helps as do immunosuppressives and plasma exchange. Whilst the prognosis is generally good, some series have shown 20% mortality, often with high morbidity.

KEYWORDS: endothelial cell damage • endotoxin • immune vasculopathy • plasma exchange • postimmunization • postinfectious

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is classified as one of the primary demyelinating diseases. It involves predominantly the white matter of the brain and spinal cord and has long been recognized as distinct from true viral encephalitis. It has been known clinically for more than 200 years since its description by Clifton in 1724 [1]. The terms used by various authors to describe the disease have included postinfectious, parainfectious, postvaccinal, perivenous, microglial or postrabies encephalomyelitis. It is remarkable how little study has been made of the exact pathogenesis when one considers that this form constitutes one third of all cases clinically diagnosed as encephalitis in the USA. ADEM is related to acute hemorrhagic leucoencephalitis (AHLE) since the histological features of both diseases are often found in the same brain; indeed, AHLE is considered the hyperacute form of ADEM. These forms have been reproduced clinically, histologically and immunologically in nonhuman primates.

Clinical features

There are no accurate statistics of the true incidence of the disease and those officially recorded strongly suggest an underestimate – one study gives an estimate of the incidence at 0.4 per 100,000 per year [2]. The reasons for this include the difficulty of precise diagnosis, the fact that ADEM is often considered to be an encephalitis caused by the primary infection, and the clinical resemblance of ADEM to acute multiple sclerosis. The disease has been reported following a variety of infections: measles, rubella, mumps, smallpox, infectious mononucleosis, herpes zoster, varicella, *Mycoplasma* and legionella.

Acute disseminated encephalomyelitis may also follow immunizations and vaccinations, classically following anti-rabies vaccination (using the Pasteur, Semple and duck embryo-type vaccines) and also following vaccinia, pertussis and influenza immunizations. ADEM has occurred as a complication of antitetanus serum administration and as an adverse reaction to drugs, particularly arsphenamines. Some forms

occur in relationship to certain HLA haplotypes [3]. Disease involving the cerebral endothelial cells may present clinically as ADEM, as can cases of Hashimoto's encephalopathy [3]. Here again the role of genetics may be evident.

Acute disseminated encephalomyelitis is not rare, constituting a third of all the encephalitides. It is not easy to give the incidence of the disease for each of the predisposing factors since wide variations occur. Examples of this variation are seen in the figures recorded for postvaccinal encephalomyelitis. The incidence of ADEM following smallpox vaccination varied markedly from country to country and, indeed, even within countries. It also varied in the same place from year to year. In the state of New York, USA, following anti-smallpox vaccination in 1947, the incidence was less than three in 100,000. In Holland, however, the incidence was recorded as one in 63 out of those vaccinated. In 1942 the incidence in Glasgow was one in 70,000 whereas in Edinburgh in the same year it was one in 20,000. With regards to postrabies encephalomyelitis, there was again wide variation in the number of cases reported, with a range between one in 7000 and one in 50,000 out of those immunized. The true mortality is unknown, but most authors have found the death rate in adults to range between 20 and 25%, with neurological psychiatric sequelae occurring in approximately 30% of sufferers. The pediatric rate in untreated patients is notable, "In untreated patients the mortality rate may be as high as 20%" [4]. In recent studies of children presenting with ADEM undergoing treatment (steroidal) whilst under study, the mortality rate is significantly lower, ranging from 0 to 8% [5-7]. Detailed epidemiological studies have yet to be performed.

The clinical presentation, no matter what the predisposing cause, is essentially similar. Clinical signs usually begin from 4 to 21 days after the inciting event, whether it is an exanthema or immunization. ADEM may also begin within days when it occurs as a complication of serum sickness or as a drug reaction. It usually commences with nonspecific signs, such as fever, headache, meningism, vomiting and anorexia. These are rapidly followed by delirium, confusion, stupor and sometimes coma. Disturbance of consciousness is probably the most common sign together with a rise in temperature. Focal neurological signs are often found, referable to the cerebral hemispheres, brainstem, cerebellum, spinal cord and, in some cases, the spinal roots. Bilateral optic neuritis may also occur, with or without ataxia, these two signs being more common in children. Amnesia may be a prominent feature: it was found in some cases after smallpox vaccination. True Korsakoff's psychosis has also been recorded, in particular in a large number of the cases following anti-rabies treatment. Involuntary movements, usually choreoathetoid, may occur; in some instances there may be a purely cerebellar-type syndrome. This is particularly seen with varicella and is generally benign. Seizures can occur at any stage in the disease, so that grand mal seizures and petit mal status have been described. When the spinal roots are involved, severe chest pain, mimicking angina pectoris, may present early in the course of the disease.

Most authors have not paid much attention to the psychiatric complications, but whereas true psychiatric disorders may not be evident in the acute phase, they have been documented as common on follow-up [8]. In the cases following postrabies vaccination, Shiraki and Otani noted: "The majority of the patients showed behavioural disturbances. Personality changes were conspicuous and consisted of deterioration of highly integrated emotional and intellectual functions and of constructive conduct" [9]. Depression and paranoid psychosis resembling paranoid schizophrenia have been observed.

The duration of symptoms and signs is variable. Some non-fatal cases have a mild attack lasting from a few days to a month, and some fatal cases have a course lasting from a few days to nearly a year. The clinical sign that correlates most closely with the prognosis is the level of consciousness. The disease has been stated not to occur before the age of 2 years and several patients have been described with multiple recurrences. In children, usually below the age of 2 years, an encephalopathy rather than an encephalomyelitis occurs. The clinical features of this are as follows: the initiating event is usually a mild upper respiratory tract infection. Soon afterwards the child becomes irritable, vomits, develops seizures, and then lapses through drowsiness into stupor and coma. There is often a rise in temperature to 40°C or more. All laboratory tests on cerebrospinal fluid (CSF) are essentially normal except for increased pressure. In ADEM in older children, as opposed to this childhood encephalopathy, the CSF can contain a few to 100 cells or more, often with an admixture of leucocytes. Neutrophils in the CSF occur in acute transverse myelitis and in AHLE.

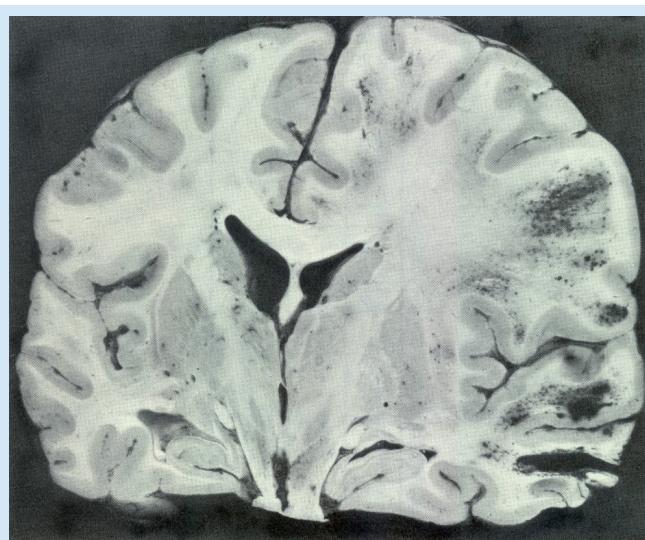


Figure 1. Acute hemorrhagic leucoencephalitis (AHLE).

A 30-year-old male developed AHLE 5 days after a nonspecific upper respiratory tract infection. Coronal section of fixed brain showing swelling and multiple hemorrhages maximal in the white matter of the right hemisphere. The defect in the middle temporal gyrus corresponds to a burr hole biopsy. Note enlargement of the hemisphere with asymmetry of the ventricular system, a shift of the midline structures and an ill-defined supracallosal hernia to the left.

No inflammatory cells are found in children with acute post-viral encephalopathy, which occurs below the age of 2 years. These children have a swollen brain, increased CSF pressure but without CSF cellular reaction. Most of these cases are Reyes syndrome. Macroscopically there is gross brain edema; histologically there are changes in the nerve cells, which are probably secondary to anoxia. No inflammatory changes are found. Some children have bronchopneumonia, while others have a swollen fatty liver, which, on occasion, contains inflammatory cell infiltrates and areas of focal necrosis. All attempts at a virus isolation in this condition have failed: its exact cause and its relationship to ADEM remain in dispute.

One variant of ADEM is a condition in which the cerebellum is specifically involved. This presents typically as an ataxia with or without long tract signs. It has been described with a variety of childhood infections including mycoplasma, legionella, cytomegalovirus, infectious mononucleosis and occasionally varicella. Interestingly, it has been our experience of this condition that the MRI is normal as opposed to being abnormal in ADEM. Furthermore, on research studies DNA fragments of varicella zoster and mycoplasma genomes have been found in the spinal fluid of such cases.

Another variant is transverse myelitis, where there may be complete or incomplete paraplegia. This syndrome resembles anterior spinal artery occlusion in which a spinal spastic paraplegia and loss of pain sensation below the level of the lesion on the trunk may be found. Confusion may arise because of the CSF cellular reaction, this being also found in cases of AHLE, which is the hyperacute variant of ADEM.

An important form of ADEM is the recurrent type. Recurrent ADEM certainly occurs and is the form that is likely to be confused with multiple sclerosis. In a unique study where a case of acute ADEM was biopsied and the brain examined later after further attacks showed that the recurrent form is identical histologically to the acute condition. Here, perivascular demyelination of 1–2 mm was the primary finding but larger lesions could be found and consisted of coalescence of multiple, smaller acute lesions rather than the demyelination that is found in MS, which is the large plaque [10].

Laboratory findings

No consistent abnormalities have been found in the blood or urine, although some cases occurring after anti-rabies vaccination have shown an initial leucopenia followed by a lymphocytosis. In severe cases, particularly those with an admixture of acute AHLE lesions, one may find protein in the urine. The CSF is usually normal in the early stages although the pressure may be elevated. Depending on the type of ADEM, cases of AHLE may show a leukocytosis of the CSF and particularly with transverse myelitis showing predominantly neutrophils. Lymphocytosis of the CSF is the most common finding. The protein may be elevated, but it is usually below 100 mg/l. Intrathecal oligoclonal bands are rare in ADEM (0–10%) in children and if they do appear are evanescent, appearing just for a few weeks, but they are common in MS [8,11,12]. The γ -globulin has been reported to be increased

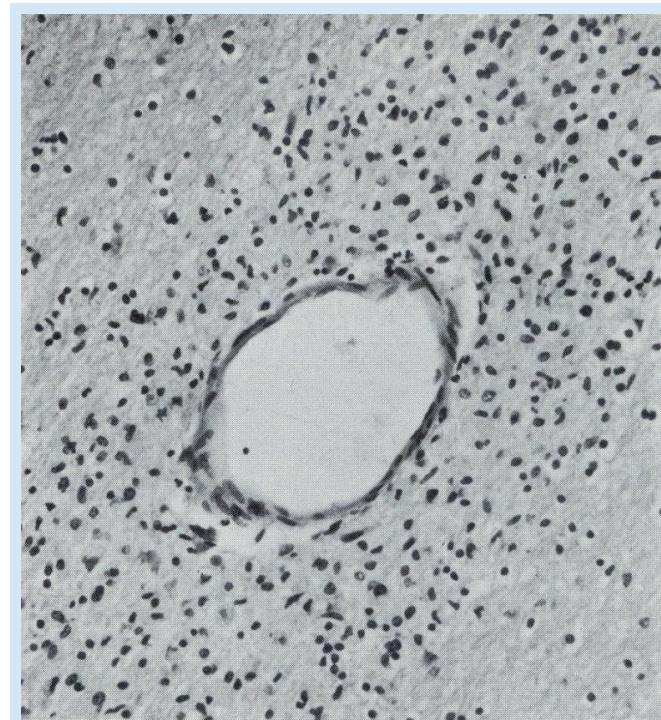


Figure 2. Frontal white matter, stained with H & E. A dilated venule at the center of a 'sleeve' of myelin breakdown is surrounded by a wide zone of mixed inflammatory cells, including polymorphs and macrophages, migrating outwards. This is a very different appearance from the customary 'encephalitic' pattern of lymphocytic 'cuffing'. Magnification $\times 200$. Reprinted from [29,30] copyright 1978.

in ADEM following anti-rabies vaccination and after postviral and postimmunization ADEM. The EEG is abnormal in most cases, the abnormalities being those of diffuse slowing in the θ and δ frequencies. Changes in the EEG are helpful in diagnosis but are most useful for following the patient's clinical progress. Indeed, the patient's condition is reflected graphically in the EEG and 'electrical deterioration' is often the first warning of a relapse. Fragments of the genome of different viruses have been found by advanced research techniques in the CSF in rare instances.

Diagnostic criteria

Differential diagnosis in children

The differential diagnosis of ADEM in children consists of true encephalitis, meningoencephalidities, acute transverse myelitis and acute MS. Children with acute transverse myelitis often have a distinct sensory level on the trunk with absent reflexes in their legs. Myelitis may be longitudinally extensive. Children with acute transverse myelitis often have a more severe outcome than children with ADEM in whom the prognosis is generally good [13].

A note should be made of ADEM occurring in children below the age of 2 years. Whether it is owing to the immaturity of the nervous system or the immune system, it is clear that the brain reacts differently at this immature age than in older children. The illness following a viral infection in children below age 2 years



Figure 3. Coronal section of the corpus callosum and right superior frontal area, stained for myelin. There are small and large sleeves of perivascular myelin destruction, becoming confluent in the centrum ovale and elsewhere. The grey matter of the cortex is hardly affected. Magnification $\times 2$.

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has been termed acute encephalopathy of childhood. This may follow a banal viral infection, but it differs in several respects from ADEM. In childhood encephalopathy there are usually seizures and headache progressing to coma, but the CSF is normal apart from raised pressure. At post-mortem the brain can be seen to be swollen. There is neuronal necrosis but no inflammatory lesions. Some of these children are examples of Reyes' syndrome whilst others consider acute encephalopathy of childhood to be a variant of ADEM, but having a different clinical and pathological expression owing to the immaturity of the brain and/or immune system.

As stated, acute cerebellar ataxia of childhood presents less difficulty in diagnosis and the prognosis is essentially good. The condition is often confused with, but is entirely different from, acute fulminating MS. The elevated temperature, meningism, confusion and disturbance of consciousness associated with ADEM is extremely rare if it ever occurs in acute MS, whilst diplopia and unilateral retrobulbar neuritis, which are usually associated with acute fulminating MS, are rare in ADEM. Loss of the deep tendon reflexes in the presence of extensor plantar responses and abdominal reflexes are common in ADEM but rare in acute fulminating MS. Recurrent ADEM usually demonstrates clinical reactivation of the previous anatomical lesion, whereas new symptoms are more indicative of further lesions, which is the rule in MS.

In an epidemiological study of acquired demyelination of the CNS in Canadian children, the incidence of pediatric acquired demyelinating syndromes (ADS) was found to be 0.9 per 100,000 Canadian children. The clinical presentations in this group of children were influenced by age. A total of 219 children with ADS whose mean age was 10.5 years were studied. The most common presentations were optic neuritis (23%), ADEM (22%) and transverse myelitis (22%). Children with ADEM were younger than 10 years and family history of MS was reported in 8% [14].

To help with this problem, detailed study of MRI in ADEM of children was carried out. Quantitative analysis of MRIs in children with monophasic ADEM has yet to be compared with those from children with MS and, indeed, MRI criteria capable of distinguishing ADEM from MS at onset has yet to be derived. The authors carried out a retrospective analysis of MRI scans obtained at the first attack from 28 children subsequently diagnosed with MS and 20 children with ADEM [15].

MRI measuring T2/fluid-attenuated inversion recovery showed hyperintense lesions. These can be quantified and characterized according to location and lesion size. In a further study by the same authors, T1 images before and after gadolinium were evaluated for the presence of black holes and for gadolinium enhancement. Results showed that the total lesion number did not differentiate to the two conditions but that periventricular lesions were more frequent with MS. They arrived at criteria that helps to distinguish MS from ADEM in childhood, namely the absence of diffuse bilateral lesions, the presence of black holes and the finding of two or more periventricular lesions, since by using these data acute MS could be distinguished from monophasic ADEM with an 81% sensitivity and 95% specificity. Hence, MRI diagnostic criteria may be helpful in differentiating these two conditions [15].

In a study of 12 children, who were reviewed retrospectively, it was found that patients presented most often with motor deficits (75%), secondly loss of consciousness (33%) and seizures (33%). CFS abnormalities were found in 41.6% of patients whilst cranial and spinal MRI showed hyperintense signal changes mainly in the basal ganglia and thalamus (58%) and cortical subcortical areas (33%). Transverse myelitis was found in two cases. Whereas 50% of the patients were treated with steroids, three patients were treated with intravenous immunoglobulin. In total ten patients recovered completely. Interestingly, relapses were found in one case and recurrence in two cases. Their conclusion was that the clinical recovery was generally good and treatment with prednisolone has an important factor [16].

Clearly, the evaluation of childhood MS is difficult since there are many conditions to be considered in the differential diagnosis, and childhood MS often presents as an encephalopathy with seizures with or without brain stem and cerebellum symptoms during the first event. Initial brain MRI scans of these children may show more frequent involvement of the posterior foci and the higher number of ovoid, ill-defined T2 bright foci. Again, as opposed to adult MS the CSF may fail to show oligoclonal bands or abnormalities of the IgG index [17].

Value of MRI as a diagnostic marker

Attempts to use MRI studies in the differential diagnosis and treatment of ADEM are becoming more frequent and it is clear that MRI studies can be extremely helpful [18]. Dormez *et al.* investigated radiologically fulminant ADEM on diffusion-weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) images and correlated these findings with clinical outcome. Scans of eight patients were retrospectively evaluated for distribution of lesions on FLAIR images and presence of haemorrhage or contrast enhancement. The DWI of the patients was evaluated as to cytotoxic versus vasogenic edema. Of these patients four died, three had full recovery and one had residual cortical blindness. The distribution of the hyperintense lesions on FLAIR sequence showed involvement of the frontal (37.5%), parietal (50%), temporal (37.5%) and occipital lobes (62.5%), basal ganglia (50%), pons (37.5%), mesencephalon (37.5%) and cerebellum (50%). The three patients who died had brainstem involvement, two had cytotoxic edema, one of whom died and the other developed cortical blindness. A total of six patients had vasogenic edema: three of these rapidly progressed to coma and death, whilst three recovered. The authors stated that DWI is not always helpful for evaluating the evolution or for predicting the outcome of ADEM.

In a study of six cases of children with ADEM, MRI showed variable areas of hyperintensities on T2-weighed images [19].

In comparing the clinical and laboratory data of children with transverse myelitis with those of ADEM, 22 children had acute transverse myelitis and 12 had ADEM with spinal cord involvement. Children with acute transverse myelitis were more probable to have a definitive sensory level (55%) with areflexia. A total of 68% of children with acute transverse myelitis and 92% of children with ADEM had longitudinally extensive transverse myelitis. Greater inflammation was found in ADEM. The outcome was good to normal in 82% of children with acute transverse myelitis, but 100% with ADEM. Poor prognostic factors in acute transverse myelitis were flaccid paraparesis, respiratory failure and very young age (less than 6 months) [13].

Further studies of children with ADEM looking at the effect of severe ADEM on DWI found that DWI is not always helpful for evaluating the evolution or predicting the outcome of ADEM. The finding of extension of the lesions in the brainstem will have a definite influence on the prognosis [18].

In a further study, 12 children with ADEM were reviewed retrospectively. These patients presented most often with motor deficits (75%), loss of consciousness (33%) and seizures (33%). Serious abnormalities were found in 41% whilst MRI scanning revealed hyperintense signal changes mainly in the basal ganglia and thalamus (58%), and cortical and subcortical areas (33%). Of the patients, two had myelitis, six were treated with steroids, ten recovered completely, there was relapse in one case and recurrence in two cases. General impressions were that high-dose intravenous prednisolone was of help and they recommended early treatment with prednisolone. There are lesions in the white matter detected as diffuse or multifocal and assymetrical lesions seen classically on T2- and FLAIR-weighed sequences [16].

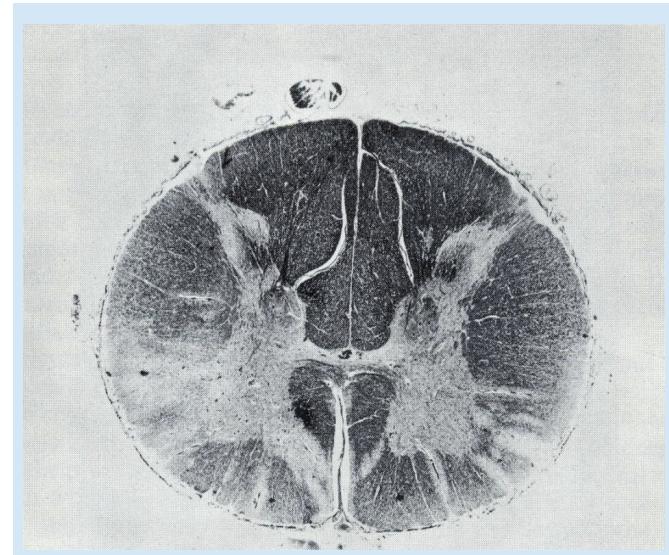


Figure 4. The spinal cord, upper lumbar segment, stained for myelin. Perivascular myelin destruction is seen in the anterior and anterolateral white columns. Magnification $\times 8$.

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To date there are no biological markers, but it is clear that cerebral MRI is helpful in diagnosis. Tenembaum *et al.* discuss a proposal for four classifications each describing different patterns of cerebral involvement found using MRI on ADEM patients. These classifications have not proven to correlate with any specific outcome or disability but they may prove helpful in improving rapidity of differential diagnosis. In particular, they can be used to help distinguish early stages of MS from ADEM in those children who exhibit an initial ADEM phenotype [8]. In one pediatric study [20], resolution of MRI abnormalities within 6 months was positively associated with a final diagnosis of ADEM [8]. Despite the problems associated with assessing MRI results, it is certain that they aid diagnosis.

Pathology

Macroscopic findings

The brain and the spinal cord usually appear normal but may show congestion and swelling. In severe cases, hemorrhage may be evident (FIGURE 1).

Microscopic findings

Histological examination in the early stages shows the Virchow-Robin spaces to contain lymphocytes, plasma cells and occasional neutrophil leucocytes. At a later stage there is proliferation of histiocytic and microglial elements around the veins and new reticulin fibres are formed. In a zone around these small vessels (1–2 mm wide) there is tissue destruction, the predominant feature of which is fragmentation of myelin. Also, relative sparing of axis cylinders is found. There is an associated perivascular cellular cuff and, for a variable region beyond this, a proliferation of microglial cells occurs and the astrocytes show some cytoplasmic swelling. The microglial cells become phagocytic and

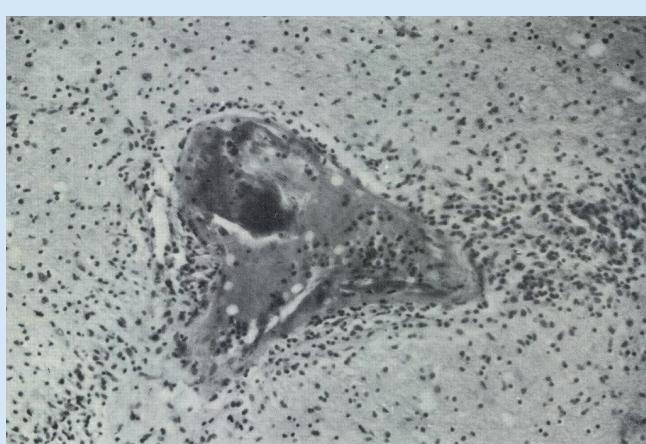


Figure 5. A small arteriole with conspicuous fibrinoid necrosis. Hematoxylin and eosin staining. Magnification $\times 400$. Reprinted from [29,30] copyright 1978.

Sudan stains reveal that these cells are laden with fat (myelin). If the brain is examined at a later stage, there is perivenous fibrous gliosis. Although some of these perivenous demyelinated areas may coalesce to form larger lesions (FIGURES 2–4), these are different from those found in MS. In the perivenous lesions of MS, the highest density of cells is at the edge, while in ADEM it is at the center of the lesion.

The histological findings found in ADEM are essentially a vasculopathy with perivascular cellular cuff as described. Usually this is all that is found at post-mortem but in severe cases the vasculopathy can be more severe and exhibit frank fibrinoid necrosis. (FIGURE 5). Experiments show that by blocking the expression of Ia antigens on endothelial cells experimental allergic encephalomyelitis (EAE) is prevented [21]. These hyperacute cases also contain not only cerebral edema but frank ball and ring hemorrhages. (FIGURE 6). Usually, the brain in these hyperacute cases is an admixture of severe and mild perivascular changes (FIGURE 7).

Pathogenesis

Whilst the histology is essentially a perivenous cellular infiltrate it must be realized that this histological finding, whilst common to all cases of ADEM, belies a different pathogenesis in each case. Thus, the cellular infiltrate is that the accepted vasculopathy is responsible for the essentially uniform histological expression across the different forms of ADEM. This may explain why treatment results may vary and research should be directed at the specific and different pathogenic mechanisms rather than as at present to an assumed single common etiology. To illustrate this, the condition postrabies vaccination encephalomyelitis is identical in every way to EAE because both are caused by sensitization to brain antigens. EAE is different from postviral encephalomyelitis in that the vasculopathy resulting from the viral infection is due to a different mechanism involving the interaction between viruses and the resultant immune attack on the blood vessel. Again, the vasculopathy complicating severe burns that, as a result of endotoxic shock, causes a vessel lesion

that itself bears similarities, if not being identical to, the vessel lesion in EAE, yet it has an entirely different pathogenesis. All in all, for the common endothelial cell damage that is found in all variants of ADEM, it should be stressed that these all have a different pathogenesis. This underscores the importance of direction of research and may explain the different responses to treatment.

Treatment

There are no controlled studies using either steroids or immunosuppressive drugs in ADEM. Our own experience suggests strongly that corticotrophin and large dose steroids may be of help, certainly in the early stages. Two thirds of the patients treated by corticotrophin are reported to improve. Steroids have been found helpful in several series. Indeed, in previous reports there was recurrence of ADEM in cases in which the dose was reduced. These uncontrolled studies cannot be viewed as definitive because the prognosis of the disease is too variable. Indeed, it must be appreciated that not only are there genetic variations in ADEM, but there is a wide spectrum of clinical severity, for example, some patients may have nothing more than mild perivenous cellular infiltrates whereas others may have frank hemorrhagic lesions secondary to fibrinoid necrosis of vessels. It is difficult in these cases to compare the results of treatment protocols. However, steroids has been shown to be effective. We have found that azathioprine combined with steroids has been



Figure 6. Same case as Figure 5. Digitate white matter showing perivascular loss of myelin and petechial hemorrhages. Woelke myelin. Magnification $\times 170$. Reprinted from [29,30] copyright 1978.

highly efficacious, whereas others have found plasma exchange to be of benefit, occasionally under circumstances where initial steroids and immunoglobulin treatments have failed. Tosun *et al.* in their study of 12 children found that ten patients had recovered completely. They had treated six patients with steroids, and three with intravenous immunoglobulin. Relapse was observed in one case and recurrence in two; they found that "these cases responded well to high-dose intravenous prednisolone followed by oral prednisolone for 6 months" and "early treatment of prednisolone is one of the most important factors to determine the prognosis in this disease" [16]. In a further study, Hagiwara *et al.* found that symptoms did not improve in a 26-year old man with ADEM treated with steroids or with immunoglobulin, but plasmapheresis was effective [22]. It is clear from virtually all reports on treatment that steroids are the mainstay and are effective in a high proportion of cases. There are no controlled studies of steroids but the general experience is that they are effective. Other forms of treatment, such as plasma exchange, can be combined with steroids, and whilst plasma exchange might not be as effective there are several studies to show it is efficacious and we would therefore recommend a combination of steroids and plasma exchange.

As stated, there are no controlled studies and we and others have found that intravenous methylprednisolone 10–30 mg/kg/day would be the drug of choice with plasma exchange, particularly if there was not a good clinical response to the steroid dosage [8]. We are strongly against the use of β -IFN or glatiramer for the reasons detailed in our paper [23].

A special note is required for fulminant cases of ADEM. By definition, fulminating ADEM is termed AHLE [24] or, more correctly, acute necrotizing hemorrhagic encephalopathy [25]. Clinically, as a condition with rapidly expanding edema often of a focal nature, following a nonspecific infection or immunization and vaccination, this condition is the number one differential diagnosis. In fact, to quote from one of the leading authorities in the *New England Journal of Medicine* "Only two diseases of white matter result in a monophasic illness characterized by rapidly progressive, widespread demyelination, ADEM and acute hemorrhagic leukoencephalopathy. The two disorders share many features and may be part of a spectrum of diseases rather than distinct entities" [26,27]. Brain biopsy is contraindicated for several reasons. The changes are nonspecific and are found in many conditions; a large block biopsy, whilst telling us more regarding the diagnosis on theoretical grounds, is likely to aggravate and worsen the condition. With a good history and a MRI scan there should be no need for a brain biopsy; unless it was a block biopsy the findings would not be specific and a diagnosis could not be made. Furthermore, with steroid treatment to reduce the swelling, surgical intervention, that is decompressive craniectomy, can be relegated to the historical literature.

Etiology

There is evidence that genetic factors may play some role in ADEM. This is seen classically where ADEM occurs in several members of the same family at different times. Again, the

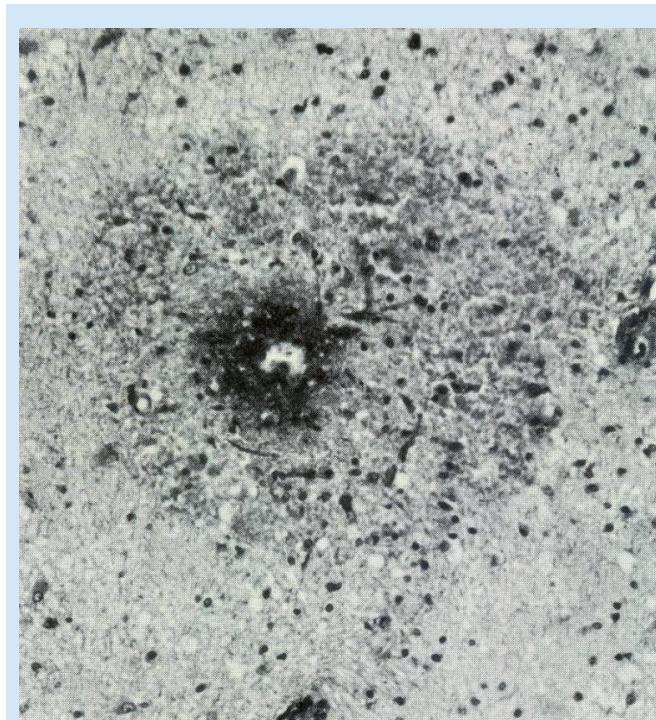


Figure 7. Acute disseminated encephalomyelitis (AHLE).

A 56-year-old female who developed AHLE 8 days after a respiratory infection. Note the ring hemorrhage centered on the necrotic (fibrinous) vessel, and the slight perivascular infiltration by lipid phagocytes, the occasional lymphocyte and enlarged astrocytes. Masson trichome. Magnification $\times 420$. Reprinted from [29,30] copyright 1978.

ADEM that occurs as a complication of Hashimoto's thyroiditis is clearly genetically mediated since 88% of patients with recurrent ADEM and Hashimoto's encephalopathy were positive for HLA-B8DRW3 haplotypes [28]. These HLA findings are certainly common in patients with acquired myasthenia gravis, another system-specific autoimmune disease, and gives support to an immunopathological mechanism in ADEM. Several children of a family may develop ADEM at different times. The precise mechanism of how viruses institute a pathological reaction is unknown, although there are several reports of having found glial nodules in the brains of fatal cases. Rarely, a virus has been cultured from the CSF of a patient with ADEM. In this regard, rubeola virus has been cultured and rubeola antigen has been demonstrated in patients dying of the disease. In the past, the theory was put forward that diverse groups of viruses associated with ADEM share the common property of fusing cells. Demyelination was said to result from fusion of myelin membranes without damage to the oligodendroglia. It should be noted, however, that the demyelination is strictly limited to a 1 or 2 mm sleeve of perivenous demyelination and the demyelination appears to be classically bystander. Taken together, these results strongly suggest at times a possible genetic influence, as well as viral involvement and an immunopathological reaction in the pathogenesis of ADEM.

Expert commentary

The statement that ADEM is often classed as one of the primary demyelinating disease cannot be allowed to go unchallenged. Since ADEM has many causes including postviral, postimmunization, postrabies and encephalomyelitis occurring as a complication of endotoxic shock in burns in patients with aplastic anemia, thrombotic thrombocytopenic purpura, as a reaction to drug sensitizations and as a disorder complicating Hashimoto's encephalopathy, clearly a single etiology is unlikely. The disease can be mimicked in nonhuman primates immunized with encephalitogenic proteins to develop EAE but the syndrome can also be reproduced in animals as a complication of intravenous detergents or as a manifestation of the experimentally induced Forssman reaction.

Certainly, myelin is damaged in ADEM but the long sleeve of perivenous demyelination is a bystander reaction and hence the disease can no longer be considered a primary demyelinating disorder. ADEM has been erroneously considered to be a form of acute MS but this tenet can no longer stand. There are few electron microscopic studies of ADEM, but routine histological findings have shown the endothelial cells to bear the brunt of the disease. Therefore, what we have in ADEM is damage to cerebral endothelial cells from a variety of different causes producing clinically and histologically identical pictures but having different etiologies.

Five-year view

The main emphasis in ADEM over the next 5 years will focus on pathogenesis and treatment. We know that high-dose steroids can be highly effective but there are cases in which steroids, although bringing some relief, are not as effective as certain immunosuppressive drugs or plasma exchange. Again, plasma exchange may work in some cases where steroids and immunosuppressives have been ineffective. A better understanding of what constitutes the vasculopathy, that is, how endothelial cells are damaged and repaired together with a study of how endothelial and glial factors are disrupted, will constitute future research. It is no longer tenable to assume that EAE is a true model for all forms of ADEM and more sophisticated MRI and electron microscopic studies, together with a study of the molecular biological mechanisms involved in endothelial cell damage, will constitute the main focus of research.

Financial & competing interests disclosure

This work was supported by the Sir David and Sir Frederick Barclay Trust. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- An overview of acute disseminated encephalomyelitis (ADEM) shows that it is a relatively common disorder and one needs to emphasise that it predominantly affects children.
- A very much neglected aspect is the realization that there are many different disorders that give rise to ADEM, which clinically and histologically look similar yet have an entirely different pathogenesis.
- An early MRI scan helps to make the diagnosis.
- One aspect of research that has not been well covered is electron microscopic changes.
- Since the basic pathology is a disruption of endothelial cell function, future research should be aimed at this aspect and at how the BBB can be healed.
- The disease is clearly different from multiple sclerosis and it is wrong to regard ADEM as a primary demyelinating disease rather than the unique expression of acute cerebral endothelial cell function.

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