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REVIEW

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Infection-associated encephalopathies – *their investigation, diagnosis, and treatment*

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Abstract Reduced level of consciousness is a common clinical finding in acutely sick patients. In the majority of cases a cause for the encephalopathy is readily identifiable, whilst in a minority the aetiology is more difficult to ascertain.

Frequently the onset of encephalopathy is associated with, or follows, infection. The mechanisms through which infection leads to encephalopathy are diverse. They range from direct microbial invasion of the brain or its supporting structures, to remote, infection-triggered mechanisms such as acute disseminated encephalomyelitis. Most common however, is the encephalopathy caused through a remote effect of systemic sepsis – septic encephalopathy.

This article discusses the clinical presentation and underlying pathogeneses of the acute encephalopathies associated with infection, aiming to aid both their recognition and treatment.

Key words encephalopathy · encephalitis · CNS infection · neuroimmunology

Abbreviations

ADEM	acute disseminated encephalomyelitis
AHLE	acute haemorrhagic leukoencephalopathy
AIE	acute infectious encephalitis
ATE	acute toxic encephalopathy
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
EBV	Epstein Barr virus
EEG	electroencephalogram
HSE	herpes simplex encephalitis
HSV	herpes simplex virus
JEV	Japanese encephalitis virus
PCR	polymerase chain reaction
PNS	peripheral nervous system
PLEDS	periodic lateralised epileptiform discharges
SE	septic encephalopathy
UK	United Kingdom
USA	United States of America
WNV	West Nile Virus

Introduction

Altered level of consciousness is an emergency commonly encountered in medical practice. Whether this state occurs in the presence or absence of focal neurological signs, it may be termed an acute encephalopathy and represents a rapid deterioration in cortical function [72]. The cause of the majority of acute onset en-

cephalopathies often becomes apparent after baseline clinical assessment and investigations. Common aetiologies include: metabolic derangement, cerebral hypoxia or ischaemia, ingested poisons, and intracranial lesions (Table 1). However, at presentation some encephalopathic patients show evidence of recent or current infection. After the exclusion of other aetiologies for their encephalopathy, such patients are considered as suffering *infection-associated encephalopathies*.

The association of encephalopathy with acute infection or inflammation is ancient. Both Hippocrates and Galen noted that delirium or "phrenitis" may accompany inflammation [12, 64], and in the 17th century Sydenham described a syndrome of coma accompanying fever (*febris comatosa*) that in more contemporary times would be recognised as an encephalitis [90]. It is now apparent that the pathogenic mechanisms linking infection and encephalopathy are diverse, and that these may be through *direct* or *indirect* mechanisms (Table 2).

Direct causes of infection-associated encephalopathy require microbial invasion of either the parenchyma of the brain, or its supporting structures. For example, herpes simplex virus (HSV) type-1 encephalitis is an example of the former, in which the virus invades the frontotemporal, cingulate and insular cortex resulting in parenchymal infection. Another example of a direct mechanism is varicella zoster virus (VZV) reactivation complicated by infection of one or more major cerebral arteries, causing a giant cell angiitis. In such cases the damage to the brain occurs principally through infarction rather than through inflammation or infection.

Indirect causes of infection-associated encephalopathy do not involve microbial invasion of the brain or its supporting structures. Instead, extracranial infection triggers other mechanisms that result in encephalopathy. Such "parainfectious" syndromes may by immune-mediated, (e. g. acute disseminated encephalomyelitis

Table 1 Groupings of common causes of encephalopathy in adult patients

Group	Example
Hypoxia	Post cardiac arrest
Metabolic	Endocrine, hepatic or renal dysfunction
Toxic	Drug overdose
Vascular	Subarachnoid haemorrhage
Neoplastic	Astroglioma
Nutritional deficiency	Wernicke's encephalopathy
Traumatic	Head injury
Genetic disorders	Mitochondrial cytopathies, Acute intermittent porphyria
Non-convulsive status epilepticus	Complex partial seizures
Hypertensive	Accelerated hypertension
Systemic autoimmune diseases	Systemic lupus erythematosis
Infection	See Table 2
Others	Paraneoplastic syndromes Neuroleptic malignant syndrome

Table 2 Classification of infection-associated encephalopathy

Direct
Acute infectious encephalitis e. g. HSV-1 encephalitis
Infectious vasculitis e. g. VZV giant cell angiitis
Cerebral abscess or subdural empyema
Indirect
Parainfectious inflammatory encephalopathies e. g. ADEM or AHLE
Acute toxic encephalopathy e. g. Reye's syndrome
Septic encephalopathy

ADEM acute disseminated encephalomyelitis; *AHLE* acute haemorrhagic leucoencephalopathy

Table 3 Key points – Acute infectious encephalitis

Characterised by CNS inflammation with parenchymal microbial invasion
Aetiology dependent upon patient's immunocompetence and exposure risk
Fever, seizures, and focal neurological signs are common
HSV-1 is the commonest sporadic cause of severe acute infectious encephalitis
Epidemic vector-borne flaviviruses (e. g. Japanese encephalitis) are a major cause of morbidity and mortality worldwide
Treatment is specific to the causal microbe

Table 4 Key points – Acute parainfectious inflammatory encephalopathies

Characterised by CNS inflammation that lacks evidence of parenchymal microbial invasion
Viral exanthem, vaccination, or non-specific upper respiratory tract infection are common precipitants
Pathogenesis is thought to be autoimmune
Treated by immunomodulation

Table 5 Key points – Acute toxic encephalopathies

Rare group of diseases most frequent in early childhood
Characterised histologically by diffuse cerebral oedema that lacks an inflammatory infiltrate
Pathogenesis thought to be infection-triggered metabolic dysfunction
Treatment is supportive

Table 6 Key points – Septic encephalopathy

Common complication of systemic infection
No pathognomic histopathology
Characterised clinically by reduced level of consciousness with symmetrical neurological findings
Features of metabolic encephalopathy are not common
Treatment is directed at the underlying infectious illness
Outcome is related to the underlying cause

[ADEM]), or multifactorial (e. g. septic encephalopathy [SE]). The least well understood group of indirect causes of infection-associated encephalopathy are those termed acute toxic encephalopathies (ATE). In ATE infection is thought to trigger a metabolic catastrophe resulting in acute cerebral dysfunction.

In the following sections we outline the pathophysiology and clinical features of AIE, the parainfectious inflammatory encephalopathies, ATE, and SE. The key differences are summarised in Table 7.

Acute infectious encephalitis

Pathology and aetiology

Encephalitis is defined as inflammation of the brain's parenchyma. Although both infectious and non-infectious aetiologies may result in such inflammation, infectious encephalitis has histologically distinctive features. It is predominantly a disease of the grey matter, marked by perivascular inflammation, neuronal destruction, neuronophagia and tissue necrosis [42]. Furthermore, the causal microbial organism may be detected in, or cultured from, the diseased tissue. The clinical signs observed in AIE result either from the selective vulnerability to infection of neurones or their supporting tissue, or due to the effects of cerebral oedema.

Although viruses are the most frequent aetiological agents of infectious encephalitis, bacterial, rickettsial, fungal and protozoal infections may also be causal. The microbial agents able to cause AIE are defined by a patient's age, immunocompetence and geography of residence. Organisms that cause encephalitis require the ability to infect brain tissue (neurotropism) but not necessarily the ability to infect neurones (neuronotropism).

Within the United Kingdom and North America, after the neonatal period, the commonest severe form of infectious encephalitis is that caused by HSV-1 [24, 97]. Other aetiologies include VZV, Epstein Barr virus (EBV), cytomegalovirus (CMV), human herpesviruses 6 and 7, enteroviruses, adenovirus, influenza virus A and B, and *Mycoplasma pneumoniae*. In many countries arthropod-borne viruses account for large numbers of

Table 7 Summary of clinical findings in syndromes of infection-related encephalopathy

	Acute infectious encephalitis	Acute disseminated encephalomyelitis	Acute haemorrhagic leucoencephalopathy	Acute toxic encephalopathy	Septic encephalopathy
Ages	All	> 2 years	All	< 2 years	All
Antecendent infection	No	Yes	Yes	Yes	Yes
Clinical features:					
Fever	Common	Variable Uncommon in adults	Common	Common	Yes
Systemic Involvement	Sometimes	No	Yes	Sometimes	Yes
Altered level of Consciousness	Yes	Yes	Yes	Yes	Yes
Seizures common	Yes	No	No	Yes	No
Meningism	Sometimes	Sometimes	Yes	No	No
Focal CNS signs	Yes	Yes	Yes	Yes	No
Involvement of PNS	Flavivirus, CMV & EBV encephalitis	Rarely	No	No	No
CSF examination:					
↑ opening pressure	Yes	Yes	Yes	Yes	No
Pleocytosis	Lymphocyte predominant	Lymphocyte predominant	Neutrophil predominant	No	No
↑ protein	Yes	Yes	Yes	Yes (but less common in Reye's syndrome)	Small increase in severe cases only.
Intrathecal IgG Synthesis	After 10 days	Yes, varying proportions	No	No	No
Detection of microbe by PCR	Yes	No	No	No	No
CNS imaging (CT/MRI)	Focal areas of inflammatory change	Diffuse enhancing white matter lesions	Multiple white matter lesions with haemorrhage	Diffuse cerebral oedema	Unremarkable
EEG	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Brain histopathology	Perivascular inflammation with neuronophagia & neuronal destruction	Perivenous inflammation with demyelination	Small vessel vasculitis with fibrinoid necrosis	Cerebral oedema without inflammatory infiltrate	Unremarkable

CMV cytomegalovirus; *CNS* central nervous system; *CT* computerised tomography; *CSF* cerebrospinal fluid; *EBV* Epstein Barr virus; *EEG* electroencephalogram; *MRI* magnetic resonance imaging; *PCR* polymerase chain reaction; *PNS* peripheral nervous system

AIE cases. For example, throughout rural areas of Asia the transmission by mosquito of Japanese Encephalitis virus (JEV) results in approximately 10,000 deaths per year [87]. However, arthropod-borne encephalitides are not only diseases limited to resource poor countries. Since 1999, West Nile virus (WNV), has swept across the United States of America (USA) leading in 2003 to 2866 cases of neuroinvasive disease (meningitis & encephalitis) and 264 deaths [1]. Other flaviviruses that can cause encephalitis include St Louis encephalitis virus (USA), Murray Valley encephalitis and Kunjin viruses (Australia), and Rocio virus (Brazil). In central and eastern Europe as well as Russia tick-borne flaviviruses are common in woodland areas and transmission to humans can cause encephalitis.

The incidence of AIE has been poorly studied and estimates are based predominantly on retrospectively collected data. The lack of accurate epidemiological data for AIE is even more surprising given that in many countries cases of suspected encephalitis are statutory notifiable diseases. In England analysis of hospital episode statistics suggested an incidence of AIE of 1.5 cases per 100,000 population per year [22] and a similar figure has been reported in Finland amongst adults [76]. However, studies of AIE incidence in the USA suggest a higher figure of 7.3 cases/100,000/year [50, 69].

Rapid identification of suspected cases of infectious encephalitis is of critical importance in order to institute appropriate therapy. However, the "blunderbuss" approach of giving aciclovir to all patients with suspected infectious encephalitis, without final confirmation of diagnosis, risks not only the side effects of the agent, but also missing other diagnoses requiring alternative interventions [13].

Clinical and diagnostic features

AIE may affect all age groups but its incidence is greatest in infants and those aged 65 years or older [50]. Whilst encephalopathy accompanied by a fever is classically considered the hallmark of AIE, occurring in 90 % of adults with proven HSV encephalitis [98], it is noted in fewer cases where the presentation is atypical [27], or where AIE is suspected but an organism not found (41 %) [48]. Furthermore, fever lacks specificity to AIE as it may occur in all of the infection-associated encephalopathies. Similarly a history of a prodromal illness occurs in a proportion of cases of AIE but is also common in both ADEM and ATE. Seizures are common in AIE, and in adults are useful in distinguishing AIE from the parainfectious inflammatory encephalopathies where seizures are less frequent. A detailed clinical history regarding the patient's recent travel (e. g. JEV in South East Asia), season (e. g. enteroviruses in the Summer and Autumn), contact with animals (e. g. rabies, Bartonella and Brucella) and risk of immunosuppression (e. g. CMV in AIDS) is essential in determining the probable causes of AIE.

In HSE findings such as the personality change (85 %) and dysphasia (76 %) are commonly noted [98], and result from infection of the temporal lobe and limbic system. Atypical findings may occur in HSE when the non-dominant hemisphere is primarily infected [27]. In contrast patients with Japanese encephalitis can manifest extrapyramidal signs due to the inflammatory changes found in basal ganglia in this disease. Brainstem signs may occur as a result of tonsillar herniation secondary to cerebral oedema, or alternatively through direct infection. Typically the organisms with a predilection for the brainstem are those that also cause meningitis (e. g. *Listeria monocytogenes,* Brucella, *Mycobacterium tuberculosis* and HSV type-2). A poliomyelitis-like syndrome can accompany the flavivirus encephalitides (e. g. WNV, JEV, Tick-born encephalitis) leading to peripheral neurological signs [46]. Similarly, radiculitis may accompany EBV encephalitis [60]. Rashes are found in some cases of AIE particularly in those caused by rickettsia or enteroviruses. However, the finding of labial herpes has no diagnostic specificity to HSE, being instead merely an indicator of critical illness [98].

Magnetic resonance imaging (MRI) is the cerebral imaging modality of choice in cases of suspected AIE, although where the patient is exceedingly agitated computerised tomography (CT) is an alternative. Both CT and MRI studies performed early into the disease course may be unremarkable (Fig. 1) [35, 93]. MRI is of particular use in distinguishing AIE from ADEM and the characteristic findings in ADEM are discussed below. Recently a small study and two case reports have suggested that diffusion-weighted MRI sequences are more sensitive at revealing early cortical changes in HSE when compared to conventional sequences [34, 53, 62].

Electroencephalography (EEG) is an essential investigation in any patient with suspected AIE. Non-convulsive status epilepticus may mimic or be caused by AIE and needs to be excluded in all cases. Although EEG is very sensitive at detecting encephalopathy, the findings lack specificity to an individual aetiology. For example, periodic lateralised epileptiform discharges show little specificity to HSE [10].

In the absence of contraindications, such as evidence of mass effect, examination of the cerebrospinal fluid (CSF) should be performed in cases of suspected central nervous system (CNS) infection. Where encephalitis is caused either by viruses or mycobacteria, the typical CSF findings are of a moderate lymphocytosis (10–500 cells/μL) with a mild or moderate elevation in total protein (0.4–1.5 g/L). In contrast, the CSF in encephalitis caused by pyogenic organisms usually contains polymorphonuclear cells with or without lymphocytes. Oc-

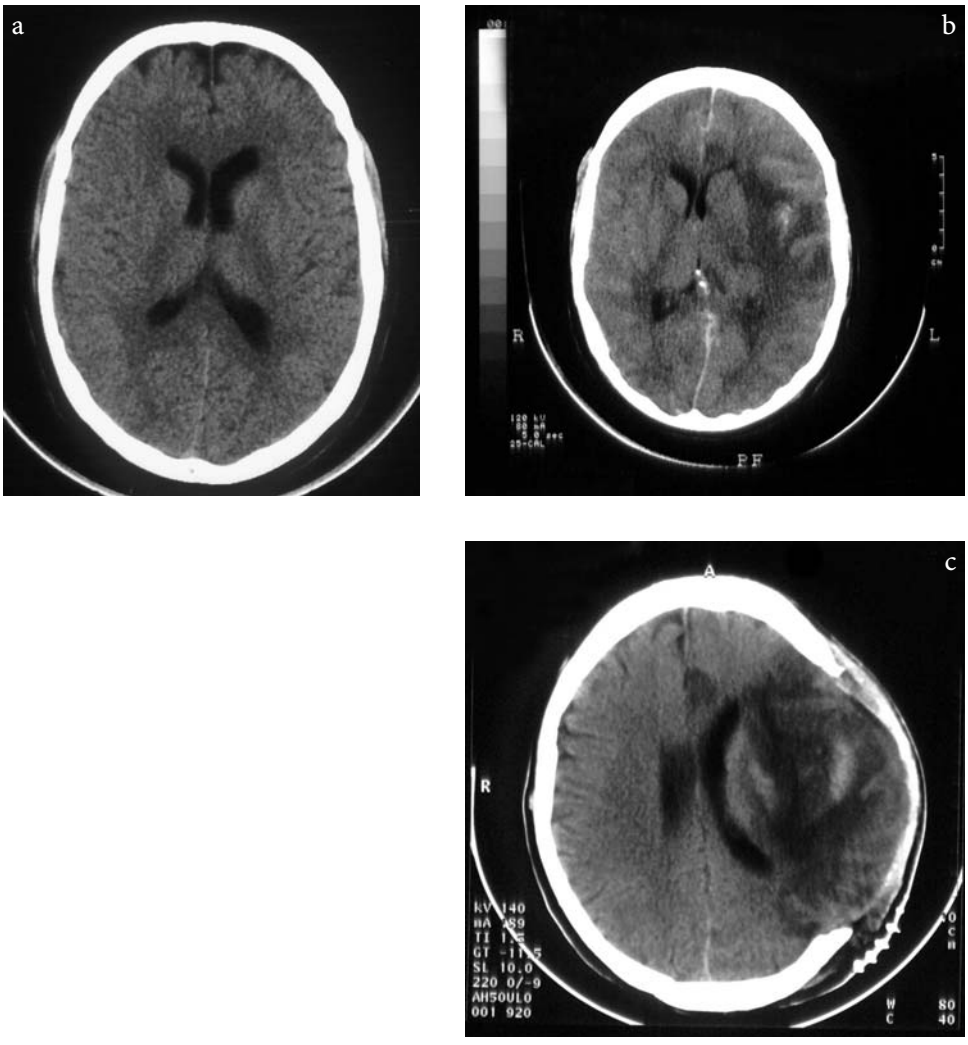

Fig. 1 Series of non-enhanced axial CT scans from a patient with HSV encephalitis. (**a**) At initial symptom onset; (**b**) 72 hours after symptom onset illustrating parietotemporal oedema, haemorrhage and midline shift; (**c**) after decompressive hemicraniectomy

casionally CSF may lack a pleocytosis, even in cases of proven HSE [98]. CSF to plasma ratio of glucose is generally > 50 % in cases of viral encephalitis, but < 50 % is seen in bacterial cases, particularly where *M. tuberculosis* is the cause. Culture of CSF remains the mainstay for isolating bacteria, but has been superceded by the polymerase chain reaction (PCR) based tests for the detection of viruses. Tests to detect bacterial antigen have no greater sensitivity than Gram's stain and may produce false positive results [91]. However, the agglutination test for cryptococcal antigen has both high specificity and sensitivity and remains of diagnostic importance. PCR is rapidly becoming the "gold standard" technique for detection of many CNS viral infections, such as HSV, VZV and the enteroviruses. Many of these assays are "homegrown" and not necessarily standardised against external control material. Hence there may be inconsistencies between laboratories in the reporting of PCR findings [82]. PCR has been best studied in HSE, where detection of HSV DNA has both a high sensitivity and specificity for the disease [4, 55]. However, HSV PCR may be negative early (< 3 days) or late (> 10 days) in the disease process [55, 74]. Thus PCR should be complemented by examination of CSF and serum samples paired in time for intrathecal synthesis of antibody specific for HSV [15]. Again caution should be exercised in interpreting CSF antibody studies as cross-reactivity can occur between antigens (e. g. HSV & VZV) and the intrathecal response may persist for many years after the infection.

Detection in serum alone of microbe specific antibodies may provide evidence of recent infection but the result does not confirm involvement of the CNS. Specific CSF IgM tests are principally used for identification of flavivirus encephalitides. They are less useful in the diagnosis of AIE caused by herpesviruses, as encephalitis caused by these viruses is frequently due to virus reactivation or re-infection, which is accompanied by a poor

IgM response. Particular care should be taken with the interpretation of *M. pneumoniae* complement fixation test results. This assay contains a lipid antigen that cross-reacts with brain lipids. Autoantibodies that bind to brain lipids may be detected, thereby giving erroneous results false positive mycoplasma titres [51]. Blood cultures should be taken prior to commencing antimicrobials. At present they remain the most sensitive investigation for isolating Listeria. Prior to the advent of PCR brain biopsy was the "gold standard" investigation to diagnose HSE. Whilst far fewer biopsies are now performed, it may still play a role where a patient's condition is deteriorating and the aetiology of their encephalopathy remains unclear. In the National Institute of Allergy and Infectious Diseases HSE antiviral studies brain biopsy was used to confirm diagnosis. In 22 % of cases biopsy established an alternative diagnosis, of which 40 % were treatable [96].

Treatment and prognosis

The treatment of HSV encephalitis is high dose intravenous aciclovir (10 mg/kg body weight intravenously three times daily in adults). There is no consensus on duration of therapy, but most centres give at least 14 days therapy in proven cases [49]. We repeat lumbar puncture on or around day 14 of treatment and ensure the CSF is HSV PCR negative before halting aciclovir [15]. The benefit of prolonged oral high dose valaciclovir following 14 to 21 days intravenous aciclovir is currently being studied [2]. Steroids, mannitol, and, in severe cases, decompressive hemicraniectomy may be indicated to control raised intracranial pressure. Intravenous aciclovir (10–15 mg/kg body weight three times daily for 7–10 days) is also appropriate treatment for VZV related CNS disease [29]. Current opinion recommends the addition of steroids to aciclovir in VZV large vessel angiitis (60–80 mg prednisolone daily for 3–5 days) [29]. The new anti-picornavirus agent pleconaril may offer benefit in the treatment of severe enterovirus CNS infections [80]. Ribavirin and interferon alpha-2b have in vitro activity against the WNV and pooled immunoglobulin from populations previously exposed to the virus offers protection in a mouse model of the encephalitis [6]. The role of these agents in treatment of human WNV encephalitis has yet to be established. Bacterial encephalitides should be treated with antibiotics that have adequate CNS penetration as well as appropriate spectrum of antimicrobial cover. Choice of antibiotics is determined by local resistance patterns. Where infection by Listeria is suspected, the recommended antibiotic regimen is ampicillin and gentamicin.

Although high dose intravenous aciclovir has reduced mortality from HSE in adults from 70 % to less than 20 % [86, 95], survivors frequently suffer a range impairments including memory impairment (69 %), personality and behavioural changes (45 %), dysphasia (41 %) and epilepsy (24 %) [63]. Often survivors perform well on screening tests such as the Mini-Mental State examination but more detailed neuropsychological testing reveal more subtle long-term cognitive sequelae [32]. Early aciclovir treatment is essential for optimum outcome in HSE [77].

Mortality from WNV encephalitis ranges between 12–14 % with higher rates found in the elderly [14, 67]. Survivors have a favourable outcome save for recovery of strength in limbs affected by the poliomyelitis syndrome [84]. Mortality rates from JEV encephalitis are much higher (30 %) with up to 50 % of survivors suffering severe neurological sequelae [88]. However, the parkinsonian syndrome common during acute JE is often transient [65].

Amongst patients where a diagnosis of AIE is suspected but despite extensive investigation no infectious aetiology identified, prognosis is better than that in HSE. However, such patients still have a disease-related mortality rate of 6–10 % with only 65–69 % making a full recovery [30, 48, 50].

Acute parainfectious inflammatory encephalopathies

Pathology and aetiology

Acute parainfectious inflammatory encephalopathies are monophasic encephalitides characterised by multifocal inflammatory lesions principally affecting the white matter of the CNS. A variety of terms have been used to describe the clinical syndrome based around aetiology (e. g. postvaccinal encephalomyelitis), pathological features (e. g. perivenular encephalitis) or suggested pathogenic mechanism (e. g. allergic encephalomyelitis) [45]. There are two consistently distinguishable pathological subdivisions: acute disseminated encephalomyelitis and acute haemorrhagic leucoencephalopathy (AHLE), both of which have pathognomic histopathology.

Microscopically the brain in ADEM classically shows multiple perivenous zones of demyelination in the cerebral white matter. The changes found in patients dying early in the disease course are in the small blood vessels of both grey and white matter, and show hyperaemia, endothelial swelling, vessel wall invasion by inflammatory cells, perivascular oedema, and haemorrhage all preceding the demyelination. Patients dying later in the disease process show zones of demyelination and lymphocyte infiltration, often with relative axon sparing [73]. In contrast, the key neuropathological finding in AHLE is the presence of a necrotising small-vessel vasculitis in the CNS. Microscopically the CNS capillary, arteriolar, and

venular walls are necrotic, impregnated with fibrinoid material and infiltrated with polymorphonuclear leucocytes, lymphocytes, and occasionally eosinophils. The necrotic vessels are foci for haemorrhage and tissue necrosis, interspersed with demyelination [33].

Whether ADEM and AHLE represent different ends of a clinical spectrum or nosologically separate entities is not clear. However, distinction between the two syndromes is of clinical relevance as AHLE has a worse prognosis, and warrants a more aggressive treatment strategy.

The incidences of ADEM and AHLE are unknown, but historically parainfectious inflammatory encephalopathies were thought to account for one third of encephalitis cases [43]. ADEM accounts for the majority of cases of parainfectious inflammatory encephalopathies, and since Hurst first described AHLE, fewer than 100 cases have been reported in the medical literature [3, 37, 56].

Recent infection or vaccination is the commonest identified precipitant of ADEM or AHLE. Historically the most frequent precipitants were the childhood exanthemata and smallpox vaccination; around 1 per 1000 cases of measles typically is complicated by ADEM [45]. Primary smallpox vaccination is less frequently complicated by ADEM but still the most recent figures from the USA suggest an incidence in adults of 3.5 cases per 1,000,000 vaccinations [9]. In resource rich countries measles, mumps and rubella are now rare due to vaccination and routine smallpox vaccination has largely been abandoned. However, more contemporary studies of ADEM continue to demonstrate an association with infection or vaccination. Amongst children with ADEM between 71–74 % suffered a prodromal infectious illness or vaccination [19, 41]; whereas a lower figure has been recorded amongst adults (46 %) [83].

Infectious agents or their inert antigens are thought to precipitate ADEM and AHLE indirectly as the presumed aetiological microbes cannot be isolated from the brain lesions [23]. An autoimmune mechanism is hypothesized to underlie ADEM. This is supported by evidence that patients with ADEM have loss of self-tolerance. T cell clones are found both in CSF and blood that are reactive to myelin basic protein, that disappear upon clinical recovery [57, 58]. Furthermore, the neuropathology of ADEM is closely mimicked by that of experimental autoimmune encephalomyelitis, an animal model of acute CNS demyelination.

The precise mechanism(s) through which microbes precipitate ADEM remain unclear. The spectrum of infections reported to precipitate ADEM is wide and therefore it seems unlikely that cross-reactivity between a host and microbial antigen is likely to be the sole mechanism of autoimmunity generation. However, a specific clinical phenotype of ADEM, characterised by a movement disorder, has been linked to preceding Group A beta haemolytic streptococcus pharyngitis [18]. These children possess anti-neuronal antibodies that bind both to basal ganglia tissue as well as extracts of streptococcus. Whilst these antibodies appear key to the pathophysiology of the movement disorder it is not clear what role, if any, they play in the generation of the multifocal white matter lesions characteristic of ADEM.

Less is known regarding the infectious precipitants of AHLE, but as in ADEM an autoimmune mechanism is thought to underlie the pathology. Patients frequently report upper respiratory tract symptoms prior to the onset of neurological symptoms and several case reports have implicated *Mycoplasma pneumoniae* as a precipitant [26, 78]. However, it may well be the case that the "explosive" onset of neurological findings in AHLE masks symptoms due to the precipitant.

Clinical and diagnostic features

Typically the parainfectious encephalopathies follow an otherwise innocuous insult such as an upper respiratory tract infection. The usual latency between the precipitant and the onset of neurological symptoms in ADEM lies between 4–21 days, although this may be shorter in AHLE [23]. The patient may be asymptomatic between the precipitating illness and the onset of ADEM, giving a "bimodal" pattern to the disease process. Systemic symptoms are frequently found in AHLE at presentation, but in ADEM they are less common, with fever being more frequently found amongst children than adults (43–52 % vs 15 %) [19, 41, 83]. As the inflammatory lesions may affect any part of the CNS the spectrum of neurological signs found is wide, and they may result in unilateral focal findings. Monophasic parainfectious demyelinating syndromes may affect solely the optic nerves, when it is usually bilateral, or the spinal cord resulting in myelitis, which typically is complete. Isolated involvement of the cerebellum frequently complicates chickenpox infection in children and is usually benign. Seizures are uncommon being reported in only 4 % of adult ADEM patients but more frequently in children, where they are often associated with fever [19]. Rarely, demyelination may occur in both the CNS and peripheral nervous system simultaneously. This was reported most frequently after the administration of rabies vaccines, such as the Semple vaccine, which contained brain extracts from the manufacturing process [83].

Neuroimaging is the most helpful tool in distinguishing ADEM/AHLE from the other infection-associated encephalopathies. In ADEM, MRI usually reveals acute enhancing white matter lesions throughout the CNS and often, in contrast to multiple sclerosis, lesions in the cortical and deep grey matter (Fig. 2). Frequently the meninges show enhancement; but T1 weighted hypointensities ("black holes") indicative of previous de-

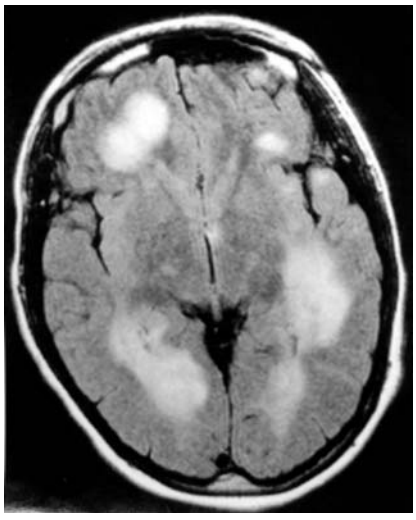

Fig. 2 Axial fluid-attenuated inversion recovery (FLAIR) MRI scan from a patient with ADEM, illustrating multifocal white matter lesions

myelination are absent. In AHLE the diffuse white matter lesions are more often non-enhancing but accompanied by evidence of raised intracranial pressure and haemorrhage [54]. CT imaging of the brain may be unremarkable in the first 4 to 5 days of ADEM. Although most clinical series studying ADEM patients require MRI white matter lesions for inclusion, cases have been reported with unremarkable imaging [36]. In such cases imaging of the spinal cord may reveal typical enhancing white matter lesions not seen elsewhere, or else repeat imaging after 7–10 days can reveal abnormalities. EEG may show evidence of encephalopathy, such as the presence of bilateral slow waves, but no finding is specific to ADEM or AHLE.

The CSF usually shows a lymphocytic pleocytosis in ADEM, whereas a polymorphonuclear leucocytosis accompanied by an elevated red cell count and xanthochromia is found in AHLE. Moderately raised CSF protein levels are found in both conditions. Intrathecal synthesis of oligoclonal IgG is found in varying proportions of ADEM patients (0–58 %) being a rarer finding in the paediatric age-group and unusual in AHLE [19, 41, 83, 92]. Where found, intrathecal oligoclonal IgG production usually ceases upon clinical recovery from the disease process [28].

Routine blood tests are often unremarkable in ADEM although a peripheral neutrophilia and lymphopenia may occur in some cases [19]. In contrast systemic abnormalities are common in AHLE, where the blood film can show peripheral polymorphonuclear leucocytosis, circulating lymphoblasts and atypical lymphocytes In addition the erythrocyte sedimantation rate is often elevated and albuminuria may be present [23].

Treatment and prognosis

Treatment of both ADEM and AHLE is by immunomodulation. There are no randomised controlled clinical trials of treatments in these conditions, but high dose methylprednisolone is routinely given (1 g intravenously daily, for 3 to 5 days). In cases where clinical improvement does not follow treatment with corticosteroids, plasma exchange (7 exchanges over 14 days) or intravenous immunoglobulin (2 g/kg body weight over 5 days) can be of benefit [47, 81]. More aggressive therapy is thought to be beneficial in AHLE, where both surgical management of raised intracranial pressure and immunosuppression with cyclophosphamide may be indicated [61].

The mortality of AHLE is high (~70 %) and few who survive are left without sequelae, in contrast to the lower mortality reported in ADEM [23]. However, in a recent prospective study of ADEM whilst the majority of patients had a substantial improvement in their neurological symptoms; 35 % of adult patients progressed to develop clinically definite multiple sclerosis during the follow up period (mean 38 months) [83]. Early relapses of symptoms are common in children with ADEM, particularly during periods of tapering of oral steroid treatment, and are termed multiphasic disseminated encephalomyelitis (MDEM). However, in this age-group early relapses are not a poor prognostic sign and seldom do these patients develop multiple sclerosis.

Acute toxic encephalopathies

Pathology and aetiology

Acute toxic encephalopathies are not a well-defined single disease entity but a group of syndromes characterised by the pathological finding of cerebral oedema that lacks an inflammatory cellular infiltrate [44]. Such a clinical entity occurring as a complication of infection has been recognised for many years [59]. For the purposes of this review ATE includes: Reye's syndrome [79], acute necrotising encephalopathy of childhood [66], and autosomal dominant acute necrotising encephalopathy [68].

It remains unclear how an infection triggers the cerebral oedema characteristic of ATE. The changes could occur through direct viral injury to the CNS, viral precipitation of a genetically determined metabolic condition, or as a consequence of viral infection with an unspecified cofactor [44]. Although no consistent inborn errors of metabolism have been described amongst ATE patients, the evidence for metabolic dysfunction is most striking in Reye's syndrome where hyperammonaemia, hypoglycaemia and lactic acidaemia are found. Furthermore in Reye's syndrome, histopathological evidence of

the failure of oxidative metabolism include the fatty changes present in the liver and brain, as well as the finding of pleomorphic mitochondria in these organs. In addition, the epidemiological association between the use of aspirin and Reye's syndrome is in keeping with metabolic dysfunction [38, 39]. Similar, but non-specific, changes in mitochondria have also been described in acute necrotising encephalopathy of childhood [66]. Whereas in autosomal dominant acute necrotising encephalopathy histological evidence of mitochondrial dysfunction has been supported by biochemical evidence of loose coupling of oxidative metabolism, although the cause of such dysfunction remains unclear [68].

As in ADEM, various infectious illnesses have been associated with ATE, ranging from viral exanthemata to non-specific upper respiratory tract infections. Influenza A and chickenpox are the classical precipitants of Reye's syndrome [31], and influenza A is the most frequently identified antecedent infection in acute necrotising encephalopathy of childhood [66]. For reasons that have not yet been elucidated acute necrotising encephalopathy of childhood is much commoner in Japan than in Europe or North America; whereas the incidence of Reye's syndrome is related to the frequency in a country of the use of aspirin as an antipyretic in childhood infections [5].

Clinical and diagnostic features

ATE is predominantly a condition of early childhood (under 2 years old) although similar conditions have been reported in older children and adults [94]. Typically the syndromes have a sudden onset often following an innocuous infection; fever, headache, vomiting and seizures are common findings. Focal neurological findings occur as the syndromes progress, typically as a result of increasing intracranial pressure.

The common laboratory findings of Reye's syndrome have between outlined above. In acute necrotising encephalopathies of childhood liver enzymes are abnormal in 82 % and a base deficit (> 2mEq/L) is found in 83 % of cases, but ammonia is less frequently elevated (6 %) and hypoglycaemia uncommon (3 %). Neuroradiological investigations in Reye's syndrome typically show diffuse cerebral oedema. Whereas in the acute necrotic encephalopathies more focal lesions may be seen, particularly affecting the thalami. In all types of ATE lumbar puncture reveals a high opening pressure but rarely does the CSF show a pleocytosis. CSF total protein is commonly raised in the acute necrotic encephalopathies but less frequently in Reye's syndrome.

Treatment and prognosis

There are no specific treatments for ATE. Therapeutic efforts are principally supportive particularly aimed at reducing intracranial pressure and correcting hypoglycaemia. The morbidity and mortality associated with Reye's syndrome and the acute necrotic encephalopathies are high [23].

Septic encephalopathy

Pathology and aetiology

SE is the commonest form of encephalopathy encountered in intensive care medicine and is present in 50–70 % of septic patients [7, 25, 100]. The syndrome encompasses those patients with encephalopathy unexplained by lung, liver, kidney or cardiac dysfunction, or diagnoses discussed above, but who have evidence of extracranial infection or inflammation. It is the least well studied or documented of the infection-associated encephalopathies. At present it is a diagnosis of exclusion. There are no diagnostic tests with high specificity for SE, nor does it have pathognomic histopathology. Clinically, SE represents the severe end of the spectrum of "sickness behaviour". That is the constellation of symptoms such as anorexia, weakness, malaise, and inability to concentrate, commonly found in febrile patients.

The pathogenesis of SE is likely to be multifactorial and the hypotheses proposed to explain the encephalopathy are not mutually exclusive. SE is unlikely to be due to toxin release from a microbe as similar encephalopathies occur in sepsis syndromes that lack an infectious aetiology (e. g. acute pancreatitis). Similarly, SE is not solely a consequence of a high fever as the encephalopathy is not reversed by antipyretic drugs alone. In addition, neither multiple cerebral microabscesses nor characteristic metabolic abnormalities are consistently reported [7, 25]. Instead SE is more likely to be caused by mediators of inflammation (such as interferon alpha, interleukin 1 beta or TNF-alpha) which induce symptoms of sickness behaviour when infused into humans and additionally somnolence when administered to animals [20, 52]. Extracranial infection results in production of pro-inflammatory cytokines both systemically and within the CNS [11]. Such cytokines have a direct effect upon the function of neurones and the blood brain barrier [17, 75].

Cerebral endothelial dysfunction has not been widely studied in sepsis. Characteristic changes in the blood brain barrier have been described in an animal model of septic encephalopathy [71]. Such changes are likely to be due to inflammatory mediators, and *in vitro* studies have shown that interferon gamma causes increased permeability to human brain endothelial mono-

layers [40]. Additional factors associated with sepsis may also contribute to microvascular and blood brain barrier changes, such as stimulation of vascular alpha-1 adrenoceptors [21]. The effects of alteration in BBB and cerebral microvascular function include: impaired delivery of nutrients and removal of metabolic waste products, as well as increased access to the CNS of compounds whose presence is usually tightly controlled. Such compounds include the aromatic amino acids that may act as "false neurotransmitters". Aromatic amino acids have been reported to be in higher concentration in the plasma of patients suffering SE, and have been used to quantify the severity of encephalopathy [89]. At present there is little *in vivo* human data supporting blood brain barrier breakdown in systemic sepsis, although a mildly raised CSF total protein has been reported amongst patients with severe SE, indicating impairment of barrier function [99].

Outcome specifically attributable to SE is difficult to separate from the outcome related to the precipitating condition. In contrast to ADEM, where the infectious trigger is often innocuous, the sepsis syndromes resulting in SE independently have high morbidity and mortality. Ischaemic changes have been described in the cortex of patients dying from septic shock [85]; and an animal model of septic encephalopathy without haemodynamic compromise has shown evidence of degenerating frontal cortex neurones after 8 hours of sepsis [70]. Whether such pathological changes occur in humans with SE but without shock, and what long-term impairment such changes cause is unknown.

Clinical and diagnostic features

Clinically SE is characterised by slowing of mentation, impaired attention, disorientation, delirium or coma. Neurological findings are symmetrical and paratonic rigidity is common; whereas the asterixis, tremor and multifocal myoclonus found in metabolic encephalopathies are rare [8]. Patients with underlying CNS pathology are at greater risk of SE, and this clinical observation has also been reported in an animal model [16]. Usually an extracranial site of infection can be identified and appropriate treatment commenced, but in < 50 % of SE cases is an organism isolated from blood cultures [70]. EEG is the most sensitive diagnostic investigation for septic encephalopathy but the findings lack specificity. EEG recordings ranked in order of severity (normal, excessive theta, predominantly delta, triphasic waves, and suppression or burst suppression) correlate well with the severity of encephalopathy and mortality [99]. Similarly, sensory evoked potentials show impaired function of sub-cortical and cortical pathways in SE [101]. CT or MRI imaging of the brain is usually unremarkable. In severe SE (defined as septic patients suffering stupor, coma or delerium) CSF total protein may be mildly elevated but cell counts remain within normal limits and CSF microbiological cultures are negative [99].

Treatment and prognosis

SE is potentially reversible so the aims of treatment are removal of the underlying source of sepsis and supportive intensive care. There are at present no specific therapies for SE, but in the future selective antagonists of pro-inflammatory cytokine receptors may warrant investigation. In general a patient's level of consciousness rapidly improves with treatment of the underlying sepsis. However, the mortality in SE is high, and a Glasgow Coma Score between 3 to 8 has been reported to be associated with a 63 % mortality rate [25].

Conclusion

Infections may trigger encephalopathy through a variety of direct and indirect mechanisms. Where an infection-associated encephalopathy is suspected, it is important to establish the nature of the pathogenic mechanism linking the infection to the encephalopathy. Careful investigation of these patients will facilitate implementation of appropriate therapy, which can vary from antimicrobials to immunosuppression. Development of specific therapies and vaccines are urgently required to combat emerging neuroinvasive infectious diseases.

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