Acute childhood encephalitis and meningoencephalitis: Diagnosis and management

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EL Ford-Jones, D MacGregor, S Richardson, F Jamieson, S Blaser, H Artsob. Acute childhood encephalitis and meningoencephalitis: Diagnosis and management. Paediatr Child Health 1998;3(1):33-41.

This paper seeks to discuss the differential diagnosis of childhood encephalitis and to review the course of investigation in a child presenting with encephalopathy, encephalitis and meningoencephalitis. The paper also reviews the current understanding of acute demyelinating encephalomyelitis (ADEM) and presents the crucial therapeutic alternatives in the management of childhood encephalitis, including ADEM and infectious diseases.

Key Words: *Continuing medical education, Encephalitis, Encephalopathy, Fever, Meningoencephalitis*

The clinical finding of an altered state of consciousness, ie, encephalopathy, with some or all of headache, neurological signs and fever, presents the physician with a variety of challenges. A number of infectious and noninfectious conditions can present with encephalopathy with or without cerebrospinal fluid (CSF) pleocytosis (Table 1). The purpose of this paper is to outline an approach to discovering the infectious causes of encephalitis and meningoencephalitis including those for which particular therapy may be urgently required, such as herpes simplex virus and acute demyelinating encephalomyelitis (ADEM). New microbiological molecular technology is evolving so that identification of an infectious agent is now possible through methods such as polymerase chain reaction (PCR) and highly sensitive antibody- or antigen-detection systems (1). ADEM can be diagnosed by

Le diagnostic et la prise en charge de l'encéphalite et de la méningoencéphalite infantiles aiguës.

RÉSUMÉ : Le présent article porte sur le diagnostic différentiel de l'encéphalite infantile et sur l'approche de l'investigation d'un enfant atteint d'encéphalopathie, d'encéphalite ou de méningoencéphalite. Il examine également les connaissances actuelles de l'encéphalomyélite démyélinisante aiguë (EDA) et présente les possibilités thérapeutiques cruciales dans la prise en charge de l'encéphalite infantile, incluant l'EDA et les maladies infectieuses.

highly sensitive (but less specific) magnetic resonance imaging (MRI), and responds well to steroid treatment. Etiological information may also be helpful from a prognostic standpoint for the individual patient and from a public health point of view for the community, particularly in the cases of enterovirus and arbovirus infections.

DEFINITIONS OF ENCEPHALOPATHY, ACUTE ENCEPHALITIS AND MENINGOENCEPHALITIS

The following definitions of encephalopathy, acute encephalitis and meningoencephalitis are summarized in Table 2.

Encephalopathy is defined as an altered or fluctuating state of consciousness including profound lethargy.

Acute encephalitis infection of brain parenchyma is manifest by an altered state of consciousness with head-

TABLE 1: Differential diagnosis of encephalopathy**Conditions**

Bacterial sepsis
CNS infections (subdural empyema, brain abscess, meningitis, encephalitis)
Degenerative disease
Epilepsy (nonconvulsive/convulsive, status epilepticus)
Encephalitis (see Tables 2 and 3)
Endocrine and metabolic disorders (electrolyte and glucose abnormalities, organic acid disorders)
Hepatic failure
Intoxication (drugs, lead, alcohol, carbon monoxide)
Leukodystrophy
Malignancy (brain tumour, CNS leukemia or lymphoma)
Mesial temporal sclerosis
Mitochondrial defects and inborn errors of metabolism
Neuropathy
Psychoses
Pulmonary disease (hypoxia)
Renal failure
Reye's syndrome
Trauma including shaken baby syndrome
Vascular disorders (hypertensive encephalopathy, stroke, complicated migraine, vasculitis including St Louis encephalitis or viral-associated varicella zoster virus, Epstein-Barr virus, parvovirus)

Note that some of these conditions may be associated with cerebrospinal fluid pleocytosis. CNS Central nervous system

ache, disorientation and neurological signs evolving within a two-week period (2). At some point in the illness, inflammation will be manifest as CSF pleocytosis, although this may not be present on admission to hospital. These findings of inflammation mark the difference between 'opathy' and 'itis'. Clinically, encephalitis has been defined as encephalopathy plus two or more of fever, seizure, focal neurological findings, compatible electroencephalogram (EEG), abnormal diagnostic imaging or CSF pleocytosis (Encephalitis Registry, The Hospital for Sick Children).

ADEM or postinfectious encephalitis generally follows acute non-neurological infectious illness by one to three weeks. Symptoms begin with fever, headache, nuchal rigidity, nausea and vomiting, and progress to include alterations in mental status and focal neurological signs. The disease is characterized by global depression of the sensorium, ranging from drowsiness to coma. While the neurological findings vary, they may include ataxia, decreased deep tendon reflexes, urinary retention and bilateral optic neuritis (3). While CSF findings are variable, MRI findings in the white matter are highly suggestive in the correct clinical setting (ie, absence of a course compatible with multiple sclerosis) and can lead the clinician to highly effective steroid therapy (3).

Acute hemorrhagic leukoencephalitis (AHLE) is heralded by the briefest of prodromes, before patients spike a fever, and experience malaise and seizures. This fatal

disease is associated with peripheral blood neutrophilic pleocytosis, and CSF abnormalities with predominant neutrophils, an increased protein level and a normal glucose level. There may also be hundreds of red cells. While most cases are diagnosed at autopsy, computed tomography (CT) abnormalities are a consistent finding (4).

Meningitis and meningoencephalitis are two separate diseases. The aforementioned features of encephalitis, ADEM and AHLE distinguish patients with encephalitis from those with meningitis in whom abrupt onset of fever, headache, photophobia, nuchal rigidity and other meningeal signs predominate. In meningoencephalitis, there are features of both encephalitis and meningitis.

A new condition of encephalomyeloradiculopathy has been reported by investigators in Halifax (5). This newly described entity is heralded by fever and headache, followed by neurogenic bladder, transverse myelitis and encephalopathy, in association with mononuclear pleocytosis of the CSF and nerve conduction studies showing polyradiculopathy.

PATHOPHYSIOLOGY

In general, meningoencephalitis and encephalitis represent uncommon responses to common infections. Most infected patients have a mild syndrome of meningoencephalitis rather than severe encephalitis (6). Many cases are of viral origin. As well as acute encephalitis, ADEM and AHLE, viral encephalitis also includes slow viral and chronic degenerative diseases of presumed viral origin (6). This review focuses on acute and ADEM syndromes that represent, respectively, direct invasion of the brain or activation of autoreactive T cells by the primary infection, leading to autoimmune disease.

The involvement of the central nervous system (CNS) usually follows hematogenous dissemination of the pathogen. Direct parenchymal involvement occurs via the choroid plexus or endothelial cells. Herpes simplex and rabies infections follow axonal transmission. Specific viruses prefer particular brain cells, for example, polio virus prefers motor cells, rabies prefers limbic cells and mumps prefers ependymal cells (2).

Acute viral encephalitis is predominantly a disease of the grey matter while ADEM is a disease of the white matter characterized by demyelination (7). Pathologically, in acute encephalitis, acute capillary and endothelial inflammation of cortical vessels ('*eptomeningitis*') is a prominent finding with perivascular lymphocytic infiltrate ('*cuffing*'). With disease progression, either astrocytosis and gliosis or immune-mediated demyelination occurs (7,8).

In ADEM, activated T cell clones recognize small fragments of two myelin proteins that induce inflammatory processes in the CNS, resulting in the destruction of normal brain white matter by the immune system (4). Autoreactive T cells recognizing myelin-specific proteins circulate in normal persons. A viral infection presumably activates these myelin reactive T cells, which migrate into

TABLE 2: Classification of encephalitic syndromes

	Acute encephalitis	Acute disseminated encephalomyelitis (postinfectious, ADEM)	Acute hemorrhagic leukoencephalitis
Associated infection	<ul style="list-style-type: none"> • Direct infection with HSV, enterovirus, mumps, arbovirus 	<ul style="list-style-type: none"> • May follow childhood exanthematous disease, EBV, influenza, HSV, group A streptococcus, probably mycoplasma, unknown infection, immunization* 	<ul style="list-style-type: none"> • Unknown
Presentation	<ul style="list-style-type: none"> • Fluctuating or alternating level of consciousness, disorientation, diffuse neurological signs and, at some point, fever 	<ul style="list-style-type: none"> • Three weeks of acute or subacute illness of fever, headache, nuchal rigidity, nausea, vomiting, altered mental state and focal neurological signs • Ataxia, decreased deep tendon reflexes, urinary retention, bilateral optic neuritis • Hemiplegia, paraplegia, sensory defects, cranial nerve palsies 	<ul style="list-style-type: none"> • Short latent period after illness • High fever, malaise, delirium, coma, death • Signs of expanding mass (progressive focal signs, increased intracranial pressure) • Rapidly progressive paraplegia • Mild nuchal rigidity
Cerebrospinal fluid	<ul style="list-style-type: none"> • Predominantly lymphocytes • Variable intracranial pressure 	<ul style="list-style-type: none"> • May be normal • Or up to several hundred white cells, initially may be polymorphonuclear but predominantly lymphocytes • Normal glucose • Elevated cerebrospinal fluid protein • Absent oligoclonal bands • Variable intracranial pressure 	<ul style="list-style-type: none"> • Neutrophil pleocytosis ($>1000/\text{mm}^3$), many red blood cells, elevated erythrocyte sedimentation rate, high protein • Characteristic initial intracranial pressure >300 mmHg • Normal glucose
Diagnostic imaging	<ul style="list-style-type: none"> • Variable, may be normal • Cerebral angiography may demonstrate vasculitis 	<ul style="list-style-type: none"> • CT often normal • Serial MRI studies may show diagnostic white matter lesions or characteristic localization 	<ul style="list-style-type: none"> • Abnormal with characteristic CT changes
Therapy	<ul style="list-style-type: none"> • Acyclovir for presumptive or confirmed HSV infection, varicella zoster virus only if direct viral invasion was likely cause • Use of empiric corticosteroid therapy in the child who fails to improve after a few days of hospitalization should be discussed with neurology consultants 	<ul style="list-style-type: none"> • Corticosteroids 	<ul style="list-style-type: none"> • None
Comment	<ul style="list-style-type: none"> • Often cannot distinguish direct infection from vasculitis without additional imaging studies or retinal examination 	<ul style="list-style-type: none"> • Often cannot be distinguished from acute encephalitis 	<ul style="list-style-type: none"> • Peripheral leukocytosis

*Extraordinarily uncommon, encephalopathy/encephalitis may follow immunization. Events have been summarized in *Adverse Events Associated with Childhood Vaccines, Evidence Bearing on Causality*. Institute of Medicine, National Academy Press, Washington DC, 1994. ADEM Acute demyelinating encephalomyelitis; CT Computed tomography, EBV Epstein-Barr virus; HSV Herpes simplex virus, MRI Magnetic resonance imaging

the CNS and recruit neutrophils, triggering massive multifocal tissue destruction. Macrophages and lymphocytes predominate. In contrast, in acute hemorrhagic leukoencephalitis, there is a profound neutrophilic response (4).

Isolated angitis of the CNS may also occur. It is most commonly related to varicella zoster virus (VZV) infection but also to *Bartonella henselae* (cat scratch) infection, parvovirus, mycoplasma, Epstein-Barr virus, group A streptococcus, human immunodeficiency virus infection and others (9).

ETIOLOGICAL AGENTS

A list of many of the possible etiological agents, their clinical clues and recommended tests are provided in Tables 2 to 4. Diagnosis depends on timely collection of

blood during the initial and convalescent phases (two to six weeks) of illness, testing of CSF and ideally MRI, to investigate possible ADEM.

In Canada, children with encephalitis who have no clinically obvious cause of infection (eg, exanthem of varicella or measles) and in whom an etiology is determined through laboratory testing are most likely to have an infection associated with an enterovirus, herpes simplex virus (HSV), influenza virus, human herpesvirus 6, Epstein-Barr virus or an arbovirus. *Mycoplasma pneumoniae* and *Bartonella henselae* also appear to be emerging as important causes of encephalitis. Infections that may mimic viral encephalitis include brain abscess, bacterial meningitis or sepsis, parameningeal infections, subacute bacterial endocarditis, tuberculosis, fungal in-

TABLE 3: Clues to etiology of infectious encephalitis

Etiology	Possible exposure	Symptoms and signs	Diagnostic imaging/ electroencephalogram/ other	Comments
Arbovirus In Canada – Powassan, California, St Louis, Eastern and Western Equine encephalitis In United States and else- where – St Louis en- cephalitis, Western equine encephalitis, Japanese B, other	<ul style="list-style-type: none"> • Summer or fall • Known insect bite (mosquitos, ticks) or exposure, eg, camping, outdoors • Warm damp region • Travel 	<ul style="list-style-type: none"> • California – abrupt onset of seizures 		
Eastern equine encephalitis	<ul style="list-style-type: none"> • Southeastern Canada, United States (east of Mississippi), July to October, contact with horses 	<ul style="list-style-type: none"> • Influenza-like prodrome with fever, headache, vomiting, malaise; convulsions progressing to coma 	<ul style="list-style-type: none"> • Diffuse or focal, mimics herpes simplex virus; normal in 50% of cases 	<ul style="list-style-type: none"> • Frequently polymorpho-nuclear response
Cat scratch disease <i>Bartonella henselae</i> formerly <i>Rochalimaea</i> species	<ul style="list-style-type: none"> • Variable history of kitten or cat scratches • Other exposures 	<ul style="list-style-type: none"> • Variable signs of inoculation (scratch, lick, bite) or papule • Variable history of lymphadenopathy • Two to six weeks after regional lymphadenopathy (if present) in 1% to 2% of cat scratch disease • May have pleurisy, hemolytic anemia, glomerulonephritis 	<ul style="list-style-type: none"> • Bartonella antibody titres of 1:512 or higher 	
Enterovirus	<ul style="list-style-type: none"> • Predominantly summer-fall, but year round 	<ul style="list-style-type: none"> • Variable nausea, vomiting • Erythematous rash, may be vesicular 	<ul style="list-style-type: none"> • Focal encephalitis, may mimic herpes simplex virus 	<ul style="list-style-type: none"> • Enteroviruses 70/71 produce severe encephalitis versus other enteroviruses (Coxsackie, ECHO) producing benign viral meningoencephalitis
Epstein-Barr virus		<ul style="list-style-type: none"> • Variable syndrome of infectious mononucleosis 		
Herpes simplex virus		<ul style="list-style-type: none"> • Bizarre behaviour, aphasia/dysphasia • Focal seizure or neurological defects • Complex partial seizure +/- secondary generalization • Hemiparesis with greater involvement of the face and arm • Superior quadrant visual field defects 	<ul style="list-style-type: none"> • 90% focal temporal lobe findings • 50% show low attenuation in frontal, temporal lobes with scattered hemorrhages 	<ul style="list-style-type: none"> • Hemorrhagic, lymphocytic pleocytosis • Treat empirically with acyclovir until disease ruled out through electroencephalogram, diagnostic imaging, cerebrospinal fluid examination and clinical course • Treat before loss of consciousness, within four days of illness • Requires further study
Human herpes virus 6		<ul style="list-style-type: none"> • Primary encephalitis • Recurrent febrile seizures 		
Influenza	<ul style="list-style-type: none"> • Fall, winter 	<ul style="list-style-type: none"> • Variable history of respiratory disease 	<ul style="list-style-type: none"> • May preferentially affect thalamus, pons 	
Lymphocytic choriomeningitis	<ul style="list-style-type: none"> • House mouse, hamster 	<ul style="list-style-type: none"> • Variable presentation; fever, myalgia, headache, pharyngeal inflammation 		

Continued on next page

TABLE 3: Clues to etiology of infectious encephalitis (continued)

Etiology	Possible exposure	Symptoms and signs	Diagnostic imaging/ electroencephalogram/ other	Comments
<i>Mycoplasma pneumoniae</i>		<ul style="list-style-type: none"> • May have antecedent bronchitis, pneumonia, upper respiratory infection 		
Rabies	<ul style="list-style-type: none"> • Often no history of animal exposure or travel to endemic area • Animal (domestic, bat, fox, raccoon, skunk) bite in approximately 50% of cases 	<ul style="list-style-type: none"> • Paresthesia at bite site • Hyperalert • Laryngospasm • Progressive peripheral neuropathy 		<ul style="list-style-type: none"> • Discuss the regional likelihood of rabies with local medical officer of health
Rubella	<ul style="list-style-type: none"> • Unimmunized 			
Rocky Mountain spotted fever	<ul style="list-style-type: none"> • Travel to endemic area 	<ul style="list-style-type: none"> • Petechiae 		
Shigella		<ul style="list-style-type: none"> • Bloody diarrhea, seizure 		
Varicella		<ul style="list-style-type: none"> • May occur with primary viremia preceding exanthem by approximately 10 days • During exanthem or its resolution 		

fection, parasitic infection (*Naegleria* species, cysticercosis, toxoplasmosis), Rocky Mountain spotted fever, syphilis and leptospirosis (2).

HISTORY

Information to be obtained in a history includes duration of illness before admission, temporally associated illness (eg, VZV, diarrhea, skin lesions), recent immunizations, animal exposures including bites or scratches, insect exposure including ticks and mosquitoes, travel, camping, the nature of the symptoms, the poorest level of consciousness (normal, disoriented, stuporous [rousable], unconscious [unrousable] and the occurrence of convulsions [one, focal, generalized]). Information obtained on history may lead the physician to the diagnosis before the microbiological testing is complete (Table 3).

Nonspecific prodromal findings may include malaise, anorexia, vomiting, myalgia and headache with or without symptoms of viral respiratory or enteric disease. In ADEM, the symptoms follow a vague viral syndrome by days or weeks, and findings are characterized by symptoms of demyelination, either focal or diffuse. Direct brain involvement may be heralded by a prodrome of lethargy, drowsiness or stupor and disorientation, hallucinations, behaviour and speech disturbances, and irritability lasting 24 h or longer.

In severe acute encephalitis including AHLE, patients experience an abrupt onset of convulsions, altered consciousness and focal neurological deficit over two to seven days (1). While seizures and focal neurological signs are

variable features, there are ultimately characteristic CSF findings, EEG abnormalities, abnormalities in neuroimaging studies and, at some point in the illness, fever (2,10).

PHYSICAL EXAMINATION

On physical examination, general physical findings should be noted including heart rate, respiratory rate, blood pressure, presence or absence of meningismus, and signs of involvement of other systems, particularly skin rashes and lymph nodes, as well as signs of trauma. Fundoscopic examination including indirect ophthalmoscopy may elucidate the shaken baby syndrome or vasculitis. Neurological findings depend on which part of the brain is primarily involved. Findings may predominate in any part of the brain or non-CNS sites may predominate (2).

Specific neurological findings include mental status, Glasgow Coma Score, state (alert, disoriented/awake, stuporous, coma/decorate or coma/decerebrate), the presence of photophobia, aphasia, abnormalities of cranial nerves (ophthalmoplegia, facial paralysis, ptosis), deep tendon reflexes, motor (hemiparesis) and sensory and cerebellar (ataxia) defects. Findings should be described as to whether they are intact or abnormal, their symmetry and focality.

Alterations in sensorium may range from mild somnolence and lethargy to intense irritability and deep coma (1). In infants, findings are commonly as vague as somnolence, irritability, high-pitched cry, diffuse hyper-reflexia,

TABLE 4: Diagnostic testing and potential therapy for acute childhood encephalitis and meningoencephalitis

Agent	Diagnostic testing	Potential therapy
Arbovirus	Paired serology (also single serum IgM, antibody capture ELISA)	No
Acute demyelinating encephalomyelitis	Magnetic resonance imaging	Corticosteroids
Cat scratch disease (<i>Bartonella henselae</i>)	Paired serology	Nil or rifampin, trimethoprim/sulphamethoxazole, azithromycin
Enterovirus	Throat, stool, CSF culture, CSF PCR. Paired serology for specific pathogen in reference laboratory	No
Epstein-Barr virus	Epstein-Barr virus serology, CSF antibodies, PCR, heterophile antibody (if older than age five years)	No
Herpes simplex virus	CSF PCR, paired serology	Acyclovir
Human herpes virus 6	Paired serology, CSF PCR	No
Influenza	Throat, NP culture, paired serology	No
Lymphocytic choriomeningitis virus	Paired serology, viral culture of CSF, blood	No
Lyme disease (<i>Borrelia burgdorferi</i>)	CSF antibody, PCR, paired serology	Ceftriaxone
Measles	Paired serology, throat, NP culture, IgM-specific antibody	No
Mumps	Paired serology, CSF, throat culture	No
<i>Mycoplasma pneumoniae</i>	Paired serology, mycoplasma-specific IgM antibody, throat swab and culture, CSF PCR	Controversial (chloramphenicol, doxycycline; erythromycin does not penetrate CSF adequately)
Parameningeal (suppurative focus)	Computed tomography scan (cranial, petrous, sinuses), culture	Third generation cephalosporin plus metronidazole plus cloxacillin, vancomycin pending results of sensitivity testing
Parvovirus	Paired serology	No
Rabies	Skin, brain biopsy, serology (after day 15), saliva culture, corneal impression	No
Rubella	Paired serology, rubella-specific IgM, urine, throat culture	No
Shigella	Stool culture	No (unless diarrhea)
Syphilis	Venereal Disease Research Laboratory test, fluorescent treponemal antibody absorption test	Penicillin
Varicella	Paired serology	Possibly acyclovir
Vasculitis	Paired serology, viral detection for varicella zoster virus, Epstein-Barr virus and parvovirus	Corticosteroid therapy

CSF Cerebrospinal fluid; Ig Immunoglobulin; NP Nasopharyngeal; PCR Polymerase chain reaction

or a full or bulging fontanel and symptoms of poor feeding and vomiting (1). Some manifestations are the result of the increase in intracranial pressure. Findings of increased intracranial pressure (1) rather than direct brain infection include papilledema, abnormal respiratory pattern, flexor or extensor posturing, ophthalmoplegia or pupillary abnormalities, and bradycardia.

The etiology can rarely be determined on clinical examination alone unless it is associated with an exanthematous illness such as varicella or measles. The National Institute of Allergy and Infectious Diseases (NAIAD) Collaborative Antiviral Study Group found no statistical differences in the presenting signs and symptoms of patients with biopsy-proven herpes simplex encephalitis that distinguished them from those without that infection (5).

NONMICROBIOLOGICAL DIAGNOSTIC STUDIES

From the therapeutic point of view, the detection of the focal findings of possible HSV infection, the MRI changes in ADEM, the presence of continuous seizures and increased intracranial pressure are most important. All patients require prompt clinical evaluation, usually including neuroimaging studies, examination of the CSF and an EEG (1) (Table 5).

Diagnostic imaging: Neuroimaging studies such as MRI or cranial CT scan with and without contrast should be undertaken in children with clinical encephalitis. If the child has evidence of increased intracranial pressure with a closed fontanel or focal signs, this is usually undertaken before a lumbar puncture in order to rule out other lesions, such as abscess, subarachnoid hemorrhage, tu-

mours and stroke, and to localize lesions (2). The need for diagnostic imaging will likely require prompt transfer of the child to a centre where such study is possible unless the cause is very obvious, eg, varicella or the child is only very transiently encephalopathic and completely normal within a short period of time, eg, 24 h. MRI may provide improved resolution and indeed suggest the etiology of ADEM (3) or a newly recognized multifocal or diffuse HSV encephalitis variant in preschoolers, requiring acyclovir therapy (4,11). CT scan may be preferable for sinuses and parameningeal foci. Brain scan may show early signs of HSV encephalitis that are not identifiable on CT scan.

CSF examination: The usual CSF findings are elevated protein, normal glucose levels and a pleocytosis (7 cells/ μ L or more) with a predominance of mononuclear cells. An exception is AHLE in which polymorphonuclear cells predominate. Also, especially early in the course of illness and hospitalization, CSF may be normal or show hypoglycorrhachia and a predominance of polymorphonuclear cells. Approximately 3% to 5% of patients with severe viral infections of the CNS have no CSF pleocytosis on initial CSF examination. While pleocytosis should not be attributed to status epilepticus until all other causes have been ruled out, a white blood cell count of more than 6×10^6 /L or one or more polymorphonuclear leukocytes have been found in 22% of these patients (12). While red blood cells may be suggestive of HSV infection or AHLE, they may be present or absent in these conditions (13).

While results of a second lumbar puncture 5 to 8 h after the first may demonstrate a shift in cells from polymorphonuclear to monocyte response, it is generally not considered clinically useful (14).

Electroencephalography: Electroencephalography may further support the diagnosis by showing general findings compatible with encephalopathy. Of particular value in herpes simplex encephalitis is its characteristic periodic high voltage spike wave activity in the temporal regions and slow wave complexes (intervals of 2 to 3 s).

MICROBIOLOGICAL TESTING

Obtaining an etiological diagnosis has been notoriously difficult in the past. A broad range of etiological agents are summarized in Table 3 while the diagnostic tests and potential for therapy are summarized in Table 4. With prompt, complete recovery within one to two days, testing may not be necessary.

Specimen collection: In general, CSF, blood, throat, stool and urine specimens should be obtained for viral studies. These specimens can be held in the hospital laboratory for immediate evaluation and possible subsequent analysis in a reference laboratory, depending upon the child's course. It is vitally important to collect and save adequate amounts of body fluids, specifically CSF and serum, should the need for confirmation of a diagnosis become imperative.

A minimum of 2 mL and preferably 3 mL of CSF is re-

TABLE 5: Minimal investigations to be considered after history and physical examination in a severely ill child or child who is not improving

Neuroimaging

- One or more of cranial magnetic resonance imaging (particularly if acute demyelinating encephalomyelitis is considered), computed tomography, brain scan

Cerebrospinal fluid

- Routine (protein, glucose, white blood cell differential, bacterial culture)
- Polymerase chain reaction (PCR) as indicated
- Hold 1 to 2 mL for possible future tests
- Paired sera (two to six weeks apart)
- Minimum 5 mL
- Arbovirus, herpes simplex virus, *Mycoplasma pneumoniae*, immunoglobulin M, *Bartonella henselae*, etc, as indicated
- Hold 3 to 5 mL acute sera for possible future tests

Viral detection (culture, PCR)

- Cerebrospinal fluid
- Throat, stool, urine, blood samples
- Other tissue, if applicable

Neurophysiological

- Electroencephalogram
- Evoked potentials as indicated

quired for virological studies. CSF is useful for the isolation of enterovirus and mumps. Although the cell lines used for viral isolation will also permit isolation of HSV, it is not usually isolated. Rapid diagnostic methods are being developed, most notably PCR for the herpes viruses and enteroviruses (14). The number of agents that can be detected by molecular methods is increasing rapidly, and physicians are encouraged to check regularly with their laboratory to determine what is available. These methods are usually available only at reference laboratories. Interpretation of both positive and negative results should be undertaken very cautiously because the sensitivity and specificity of these tests outside of research protocols remains to be determined.

Paired serology: In many patients, paired serology will ultimately be helpful to establish the diagnosis, either because of a protracted and complicated course or the presence of adverse sequelae. The importance of timely collection of acute serum cannot be overstated. A minimum of 5 mL of blood should be taken in the acute phase, followed by a second serum two to six weeks later. Testing of paired sera can confirm the etiology of the infection through demonstration of seroconversion or a fourfold rise in antibody titre. As well, IgM antibody testing can be done for certain agents, such as EBV, measles and arbovirus.

Determination of antiviral antibody synthesis in the CSF is usually not undertaken because it has not been considered useful in the diagnosis of HSV infections (14,15). Occasionally it might be useful to test for intrathecal synthesis of viral specific antibodies against other organisms, eg, measles in subcutaneous sclerosing

panencephalitis and Japanese encephalitis. It should be emphasized that additional amounts of CSF and serum must be obtained to allow for this testing when these diagnoses are suspected.

Of 145 patients admitted with encephalitis-like illness to The Hospital for Sick Children, Toronto in 1994 and 1995, 50 patients hospitalized 72 h or more underwent standardized microbiological investigations. A confirmed or very probable etiological agent was identified in 20 patients (40%); organisms included *M pneumoniae* (n=9), *M pneumonia* and enterovirus (n=2), HSV (n=4), EBV (n=1), human herpesvirus 6 (n=1), human herpesvirus 6 and influenza A (n=1), influenza A (n=1) and Powassan virus (n=1). In 13 cases (26%), a possible pathogen was identified based on lesser microbiological evidence, including nine *M pneumoniae* cases (17).

Brain biopsy: This should be reserved for patients who do not respond to acyclovir and supportive care and for whom there is an abnormality of unknown etiology on neuroimaging studies and a deteriorating clinical condition.

THERAPY

The infections for which there may be specific therapy are outlined in Table 4. The minimum investigations to be considered in the child who is severely or persistently encephalopathic are listed in Table 5. The efficacy of specific antiviral therapy has only been demonstrated for HSV, and questions about acyclovir dosage, duration of therapy, and detection and management of relapses remain. While

HSV is not the most common cause of encephalitis, empiric acyclovir therapy is justified until data from several sources (EEG, diagnostic imaging, clinical course) are available. The use of acyclovir in varicella depends on the timing of illness, with benefit likely only when the infection occurs before the rash or early in its course rather than as a postinfectious illness. The role of therapy in encephalitis caused by *M pneumoniae* and cat scratch disease is unproved. ADEM commonly responds to steroid therapy, as may vasculitis. In the child who fails to improve after several days of illness, the use of empiric steroids should be discussed with neurology colleagues. The importance of recognizing and treating continuous seizures and increased intracranial pressure cannot be overemphasized.

PROGNOSIS AND FOLLOW-UP

The spectrum of illness is highly variable and ranges from a short benign illness to a devastating one with severe sequelae and death. Physicians should understand that a child can make an apparently complete recovery following weeks of depressed consciousness in hospital. Persons taking part in bedside conversations should be aware that the child may make a full recovery with memory of such events. Conversely, children with apparently benign illness may show steady and profound deterioration in the subsequent weeks and months following hospital discharge. Both short term and long term follow-up of patients with encephalitis is important. The known risk of recurrence in patients with HSV encephalitis should be recognized.

REFERENCES

1. Johnson RT. Acute encephalitis. Clin Infect Dis 1996;23:219-26.
2. Fishman M. Infectious diseases. In: David R, ed. Pediatric neurology for the clinician. Norwalk: Appleton & Lange, 1992:249-267.
3. Grossman M, Azimi PH. An encephalitis syndrome in a seven year old. Pediatr Infect Dis 1995;14:550-5.
4. Scully RE, Mark EJ, McNeely WF, McNeely BU. Weekly clinicopathological exercises. N Engl J Med 1995;333:1485-92.
5. Marrie TJ, Purdy RA, Johnston BL, et al. Encephalomyeloradiculopathy of infectious or parainfectious etiology - a new entity? Clin Infect Dis 1995;20:945-53.
6. Whitley R. Viral encephalitis. N Engl J Med 1990;323:242-50.
7. Johnson R. The pathogenesis of acute viral encephalitis and postinfectious encephalomyelitis. J Infect Dis 1987;155:359-64.
8. Tselis AC, Lisak RP. Acute disseminated encephalomyelitis and isolated central nervous system demyelinating syndromes. Curr Opin Neurol 1995;8:277-9.
9. Somer T, Finegold S. Vasculitides associated with infections, immunizations and antimicrobial drugs. Clin Infect Dis 1995;20:1010-36.
10. Whitley RJ, Cobbs C, Alford CA Jr, et al. Diseases that mimic herpes simplex encephalitis: diagnosis, presentation and outcome. JAMA 1989;262:234-9.
11. Schlesinger Y, Brunstrom RS, Brunstrom JE, Moran CJ, Storch GA. Expanded spectrum of herpes simplex encephalitis. J Pediatr 1995;126:234-41.
12. Barry E, Hauser WA. Pleocytosis after status epilepticus. Arch Neurol 1994;51:190-3.
13. Koskineniemi M, Vaheri A, Taskinen E. Cerebrospinal fluid alterations in herpes simplex encephalitis. Rev Infect Dis 1984;6:608-18.
14. Jeffrey JKM, Read SJ, Peto TEA, et al. Diagnosis of viral infections of the central nervous system: clinical interpretation of PCR results. Lancet 1997;349:313-7.
15. Lakeman FD, Whitley RJ, the NIACA Study Group. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. J Infect Dis 1995;171:857-63.
16. Lipkin WI. European consensus on viral encephalitis. Lancet 1997;349:299-300.
17. Kolski H, Ford-Jones EL, Richardson S, et al. The etiology of acute childhood encephalitis: The Hospital for Sick Children, 1994-1995. Clin Infect Dis. In press.

Acute childhood encephalitis and meningoencephalitis

Answer the following questions by circling the letter of the correct answer.

1. The following statements correctly refer to acute demyelinating encephalomyelitis (ADEM) except for:
 - (a) generally follows acute non-neurological infectious illness by one to three weeks;
 - (b) disease of the white matter characterized by demyelination;
 - (c) encephalopathy (altered or fluctuating state of consciousness including profound lethargy) and variable neurological findings including ataxia, decreased deep tendon reflexes, urinary retention and bilateral optic neuritis are present;
 - (d) highly suggestive magnetic resonance imaging findings with variable cerebrospinal fluid (CSF) findings;
 - (e) lack of responsiveness to steroid therapy.
2. The following statements correctly refer to acute viral encephalitis:
 - (a) represents an uncommon response to a common infection;
 - (b) disease of grey matter;
 - (c) encephalopathy (altered or fluctuating state of consciousness including profound lethargy) and variable neurological findings including ataxia, decreased deep tendon reflexes, urinary retention, and bilateral optic neuritis are present;
 - (d) inflammation of the brain parenchyma manifest as CSF pleocytosis at some point in illness but not necessarily on admission to hospital;
 - (e) the outcome, favourable or otherwise, can be reliably predicted clinically within the first weeks of illness.
3. Contemporary management of the child with suspected acute encephalitis who is severely ill or fails to recover in 24 to 48 h includes the following except:
 - (a) neuroimaging;
 - (b) CSF examination;
 - (c) diagnostic testing of (1) blood collected acutely (5 mL) and in convalescence (two to six weeks later) and (2) viral detection with either culture or antigen detection (CSF, throat, stool, urine, blood as applicable);
 - (d) EEG +/- evoked potentials;
 - (e) no transfer to tertiary care centre.
4. Noninfectious conditions that can cause encephalopathy include the following except:
 - (a) endocrine and metabolic disorders;
 - (b) sprained ankle;
 - (c) hepatic or renal failure;
 - (d) intoxication;
 - (e) mitochondrial defects and inborn errors of metabolism.
5. Infections that can mimic viral encephalitis include the following except:
 - (a) bacterial sepsis;
 - (b) brain abscess and parameningeal infection;
 - (c) subacute bacterial endocarditis;
 - (d) tuberculosis;
 - (e) ringworm.
6. Therapy is available for encephalitis of the following etiologies except for:
 - (a) arbovirus;
 - (b) ADEM;
 - (c) cat scratch disease;
 - (d) herpes simplex;
 - (e) Lyme disease.

See page 56 for the correct answers