Chapter 17

Acute encephalopathy and traumatic brain injury

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Key messages

Acute encephalopathy

- – Altered level of consciousness is the essential clinical feature of acute encephalopathy.
- – In infants, look for disturbed behaviour, poor feeding, irritability, and high-pitched cry.
- – Recognize extraocular palsies, facial weakness, hemiparesis, and seizures.
- – Recognize decorticate or decerebrate (extensor) posturing, loss of pupillary reflexes.
- – Always measure blood glucose and ammonia.
- – Treat for bacterial meningitis, Herpes simplex encephalitis; consider anti-tuberculous therapy.
- – Emergency computed tomography or magnetic resonance imaging is essential.
- – Provide supportive intensive care, whatever the cause.
- – Seek specialist help when you suspect an inherited metabolic or genetic syndrome.

Traumatic and inflicted traumatic brain injury

- – Distinguish inflicted head injury from accidental traumatic head injury.
- – Inflicted injury requires multidisciplinary management.

Common errors

Acute encephalopathy

- – Missing meningitis/encephalitis is a very common error – beware!
- – Withholding antimicrobial treatment if infection is a possibility: if in doubt, treat.
- – Performing lumbar puncture without neuroimaging when Glasgow Coma Scale <9 or brainstem signs.

Definition

Acute encephalopathy refers to a state of rapid deterioration of brain functions, almost always presenting as an alteration in the state of conscious level, which may or may not be accompanied by focal neurological signs.

Causes

There are many possible causes of acute encephalopathy, the two most frequently encountered being traumatic brain injury (TBI) and infection. A recent study of 130 children from four resource-limited settings in Africa identified 45% of cases as TBI and 55% as infective encephalopathy. In this chapter, traumatic, metabolic, toxic, and

cerebrovascular causes are considered. Infection and post-infective causes are considered in Chapter 19; non-infectious causes that may mimic infection are considered in this chapter. It is important to note, however, that cases of acute infective encephalopathy with rapid deterioration, and even death, may occur without fever (e.g. there have been recent reports of this due to shigellosis and salmonellosis with only mild diarrhoea). Neoplastic and systemic conditions are also possible causes, but will not be considered in this chapter.

The initial differential diagnosis of acute encephalopathy is usually based on the presence or absence of fever and neuroimaging findings (Fig 17.1). However, remember that in infancy, sepsis may present with temperature instability rather than fever.

General principles of management

The key to rational assessment of the clinical state of the infant is systematic examination, with repeated recording of level of consciousness, pupillary responses, pulse, respiratory rate, and blood pressure. The simple AVPU scale (awake; responds to verbal stimulus; responds to pain; completely unresponsive) may be used in the emergency department but on admission to the paediatric department, assessment of consciousness should be based on observable behavioural responses to stimulation: eye opening, verbal response, and motor response that in combination make up the Glasgow Coma Scale (GCS). In infants the scoring is modified to be age-appropriate (Table 17.1). A total score is obtained by summing the scores on the eye opening, verbal, and motor subscales, but the three clinical observations that constitute the subscale scores are more informative than the total score.

Clinical assessment of a child with acute encephalopathy

History of the present illness and previous medical and family history, medication/access to medication in the household that may have been accidentally ingested, and history of illness in contacts are all potentially relevant. In the youngest children, the symptoms and signs may be subtle, such as poor feeding or poor social cognition, and easily missed by caregivers.
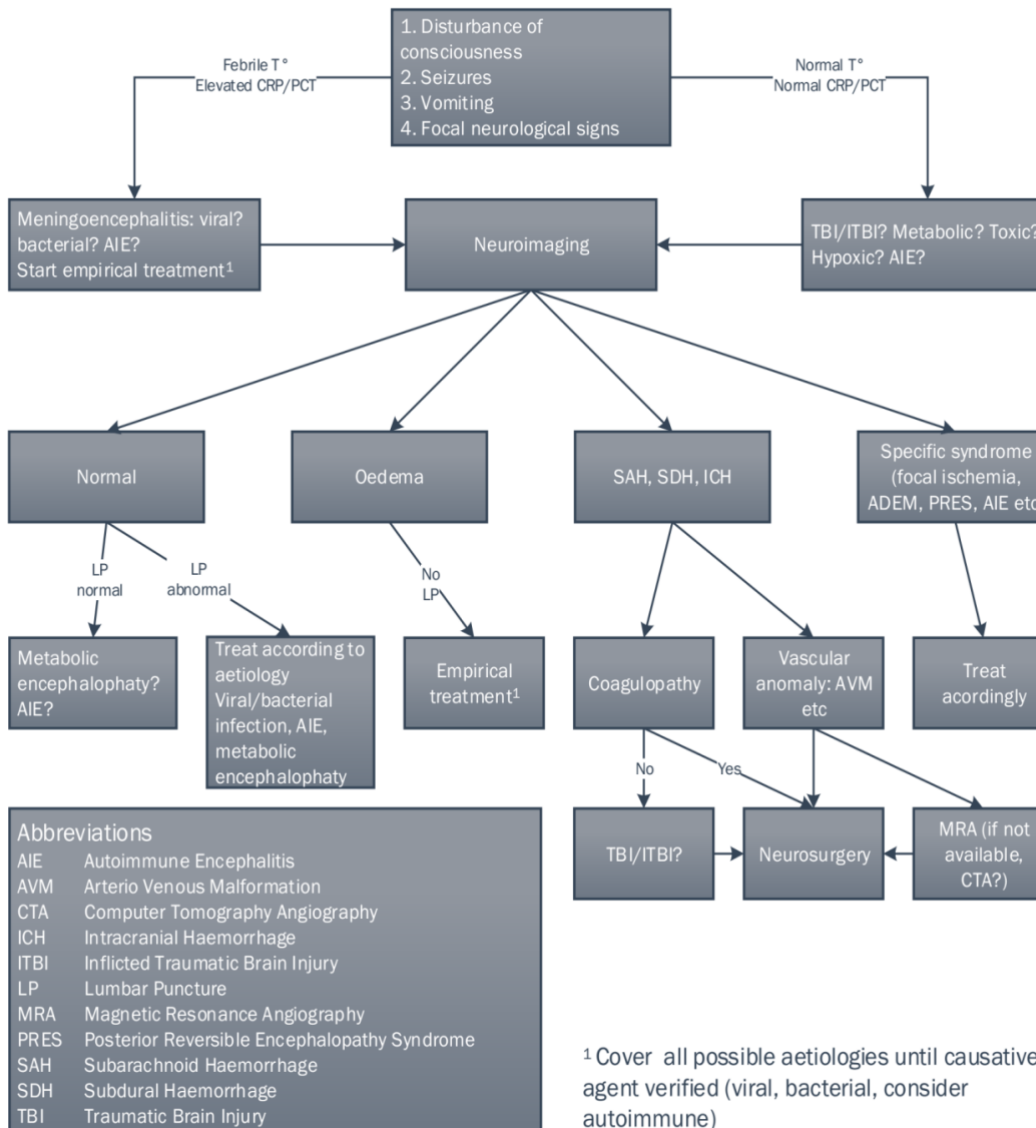

Figure 17.1 Algorithm in acute infantile encephalopathy

On examination, assess level of consciousness using the GCS. Assess airway, breathing, and circulation. Measure the blood pressure. In addition, look for a rash (purpuric in meningococcal infection or bleeding disorders, variable in viral infection); signs of inflicted injury or neglect; cardiac murmurs; signs of lower respiratory tract infection (tuberculosis, mycoplasma, pneumococcus); hepatosplenomegaly; any other diagnostic clues on general examination. Measure the occipito-frontal head circumference (OFC) with a disposable paper measuring tape and plot on the centile chart that is appropriate for age and sex: macro- or microcephaly are potentially relevant. Note any separation of the cranial sutures, which may signify intracranial hypertension. Fullness and firmness of the anterior fontanelle, examined, if possible, with the infant supported in a sitting position, can be a useful additional sign. The fontanelle may be sunken in several acute intracranial events.

Table 17.1 Glasgow Coma Scale modified for infants

Eye opening	Spontaneous	4
	To verbal stimuli	3
	To pain only	2
	No response	I
Verbal response	Coos and babbles	5
	Irritable cries	4
	Cries to pain	3
	Moans to pain	2
	No response	I
Motor response	Moves spontaneously and purposefully	6
	Withdraws to touch	5

	Withdraws in response to pain	4
	Pathological flexion in response to pain	3
	Extension in response to pain	2
	No response	1

Raised intracranial pressure (ICP) may accompany both traumatic and non-traumatic acute encephalopathies. Low cerebral perfusion pressure (CPP; i.e. arterial blood pressure minus ICP) leads to cerebral ischaemia and has consistently been shown to be an important determinant of outcome following TBI and non-TBI in children. Individualized autoregulation-guided CPP management in patients with severe TBI may be of benefit (Donnelly et al. 2017). Cerebral ischaemia itself causes cerebral oedema, which compounds the rise in ICP from other causes (e.g. trauma, metabolic derangement). A progressive, uncontrolled increase in ICP ultimately causes death by brainstem compression.

Persistent unexplained vomiting, loss of upgaze, or forced downgaze (sunsetting) may indicate increasing pressure on the tegmentum caused, for example, by hydrocephalus. If the infant is awake but drowsy, try to assess eye movements. Depressed level of consciousness may be associated with focal neurological signs or with abnormal posturing to noxious stimulation. This may be decorticate (flexion of the upper limbs and extension of the lower limbs, also referred to as pathological flexion) or decerebrate with extension of all four limbs. The emergence of such signs and/or abnormal respiratory patterns may indicate life-threatening deterioration.

Laboratory and radiological assessment of a child with acute encephalopathy

Remember the value of simple laboratory tests: white cell count (and increase in immature cells or 'shift to the left') may be seen in infection or prolonged seizure; acute-phase proteins such as C-reactive protein; cell count in the cerebrospinal fluid (CSF); CSF protein; paired plasma and CSF glucose (you cannot interpret one without the other); lumbar CSF pressure measured with a manometer or, more easily in an infant, with a tape measure held next to a vertically orientated, sterile, thin-bore flexible plastic tube (e.g. intravenous [IV] giving set), attached via a three way tap to the lumbar puncture needle.

Tests for non-infective causes of meningitis/meningo-encephalitis should include consideration of antibody-mediated illness (autoimmune encephalitis) and haemophagocytic lympho-histiocytosis (HLH). In practice, investigation for a possible infective cause (see Chapter 19) may also be required.

Ultrasound is good for defining the size of the cerebral ventricles, but less informative in describing extra cerebral and subdural spaces or abnormalities of the cerebral parenchyma. Therefore, computed tomography (CT) or magnetic resonance imaging (MRI) are needed to confirm ultrasound findings. MRI is the method of choice in children; CT has better availability and is often possible to perform without sedation, therefore, CT is used in acute settings for the rapid detection of intracranial blood and oedema. However, the risks of a high radiation dose must be kept in mind when evaluating young children. If the CT is normal, cranial MRI is mandatory in cases of acute encephalopathy, except when there is known trauma that is likely to explain the clinical condition of the child.

Clinical management of a child with acute encephalopathy

The GCS score (Table 17.1) and vital signs should be systematically monitored over time. If seizures are a feature, does the infant return to his or her usual self between seizures? Identify seizure type, duration, any localizing features, conscious level, and responsiveness between seizures. If the GCS is <8 or there is a decreasing level of consciousness, admit the patient to the intensive care unit

and manage airway. Restore normal circulating blood volume and manage seizures and CPP.

A child with encephalopathy needs empirical treatment at presentation, often several days before a definitive diagnosis is available. When an infective cause is suspected, an antimicrobial and aciclovir as an antiviral should be commenced. Recommended antimicrobial regimens include ampicillin and an aminoglycoside such as gentamicin. However, resistance of *Escherichia coli* to ampicillin has been reported. Cefotaxime is often added, although resistance to this antibiotic has also been reported.

If there is acute hydrocephalus, consider investigation and treatment for tuberculous meningitis in addition. Better outcome is associated with the starting of appropriate therapy before the conscious level deteriorates (see Chapter 19).

Table 17.2 Anticonvulsants used for seizures with acute encephalopathy

Drug	Route of administration	Paediatric dose administration
Drugs used as first line treatment of status epilepticus		
Diazepam Rectal	IV bolus	0.25–0.5mg/kg 0.5–0.75mg/kg*
Lorazepam	IV bolus	0.1mg/kg
Midazolam	Buccal, nasal IV	0.15–0.3mg/kg* 0.1mg/kg
Drugs in established status epilepticus or acute encephalopathy with seizures		
Phenytoin	IV infusion	20mg/kg at 1mg/kg/min
Phenobarbital	IV bolus	15–20mg/kg

Levetiracetam**	IV over 5 mins	40mg/kg

IV, intravenous. *May be repeated. **Lyttle et al. (2019).

Status epilepticus is less likely to be refractory to medical therapy if treated early with appropriate medication (Table 17.2) (see also Chapter 20).

Management of intracranial hypertension

Consideration of surgical placement of an ICP monitor is desirable but not possible in some clinical settings. Management aims to optimize CPP and reduce ICP. Methods include positioning (head straight, trunk and head at 30° to horizontal); temperature regulation to avoid fever (and, in post-hypoxic brain injury, controlled normo- or mild hypothermia to 33–34°C; see also discussion of hypothermia in Chapter 14; note that therapeutic hypothermia is not useful and may even be harmful in TBI); sedation with or without muscle relaxation; external ventricular drainage of CSF; operative decompression; osmotherapy with hypertonic saline or, for acute short-term management of an emergency, mannitol.

Hyperventilation is no longer recommended as the resulting vasoconstriction can worsen cerebral ischaemia. PCO_2 target should be set around 35mmHg, but lower values may be accepted for short period(s) of time, e.g. to gain time until surgery can be performed. Early consultation with neurosurgical colleagues is important for early discussion of ICP monitoring and/or surgical removal of space occupying causes of ICP (e.g. extradural haematoma, large tumour or drainage if hydrocephalus is present) and/or surgical decompression. There is possible benefit

of decompressive craniectomy (DC) in traumatic and non-traumatic coma for both survival rates and long-term outcome of survivors. Similarly, DC may result in improved outcome in children with elevated ICP regardless of underlying cause and even with unilateral or bilaterally dilated pupils present as a result of brain herniation. It may also be used as rescue therapy when maximal conservative measures for reduction of ICP have failed. However, as the operation is associated with complications, careful individual assessment of each situation is necessary. Boluses of glycerol or mannitol achieve transient reduction in ICP; there is, however, a risk of a significant 'rebound' (i.e. subsequent rise in ICP). The role of this treatment is, therefore, confined to severe acute deterioration due to raised ICP, to buy time to institute other measures to reduce ICP. Hypertonic saline has achieved faster and greater reduction in ICP and is associated with the most favourable effect on the cerebral circulation. In non-traumatic acute encephalopathy, hypertonic saline is associated with lower mortality when compared to mannitol or normal saline. The benefit is sustained for longer when given as a continuous infusion.

Specific non-infectious acute encephalopathies that may mimic infection
Infection and post-infective causes are considered in Chapter 19.

HLH may cause meningo-encephalitis and significant neurological sequelae. The term HLH encompasses the recessively inherited primary form, familial HLH (or FHL) – mostly affecting young children – and secondary HLH – predominantly associated with infections or malignancies. Common features are fever, pancytopaenia, hypertriglyceridaemia, hypofibrinogenaemia, and hepatosplenomegaly. The majority have a pronounced inflammatory response with high blood concentrations of cytokines and ferritin in association with deficient lymphocyte cytotoxic activity. Importantly, they also develop meningo-encephalitis that may be severe. About 66% will have neurological symptoms – with seizures, meningism, and irritability being the three most common – and/or

abnormal CSF findings at the time of diagnosis. CT and MRI findings of HLH are ring-enhancing parenchymal lesions (at times calcified), which are nonspecific and mimic abscesses. In the immunosuppressed child increased diffusion at the centre on diffusion-weighted imaging may help differentiate these lesions from an abscess, which has restricted diffusion at the centre. Prompt treatment (etoposide and marrow transplantation) of active HLH at onset or relapse may reduce neurological sequelae, and this is important to consider in undiagnosed encephalopathy.

In long-term survivors, neurological sequelae – usually neurodevelopmental impairment and epilepsy – are reported in approximately 15% of cases. Late sequelae affect approximately 25% of those with abnormal CSF at onset and are about three times as common as in those with normal CSF. Approximately 75% of children aged less than 12 months at the time of diagnosis have abnormal CSF without any neurological symptoms.

Aicardi–Goutières syndrome is a rare, genetically determined disorder with a phenotype classically characterized by episodic acute irritability with or without fever. It is associated with elevated levels of interferon in the CSF and often with an increased CSF white cell count. Chilblains and other skin manifestations may be seen (see also pp 208 and 265).

Acute necrotizing encephalopathy (ANE) is predominantly a disease of infants and young children. It is characterized by fever, acute encephalopathy, seizures, and rapid progression to coma within days of onset of a viral illness; more frequently influenza A, but also influenza B, parainfluenza, human herpesvirus 6, and others.

T2-weighted cranial MRI classically shows multiple symmetrical lesions affecting primarily the thalami but also the upper brainstem tegmentum, periventricular white matter, putamina and cerebellum (Fig 17.4 e1). A

genetic form of the disease, ANE1, is recognized with mutations in the gene Ran Binding Protein 2 (*RANBP2*; OMIM 601181). The thermolabile polymorphism in the Carnitine Palmitoyltransferase 2 (*CPT2*) gene is also associated with this condition and other acute encephalopathies.

Acute disseminated encephalomyelitis (ADEM) is a monophasic inflammatory multifocal demyelinating disorder of the CNS, usually appearing after an infection and by definition including a degree of encephalopathy (i.e. alteration/depression of conscious level). It is a rare disorder and very unlikely to present in the first year of life. There may also be focal neurological signs. MRI typically shows multifocal large areas of demyelination in white matter but grey matter involvement (e.g. lesions in thalamus and basal ganglia; Fig 17.4 d1) also occurs. Diagnosis is based on the combination of clinical and radiological features and exclusion of diseases that mimic ADEM. Treatment is with intravenous methylprednisolone 30mg/kg, up to a maximum dose of 1g/day, for 3 to 5 days (level of evidence, class III). Higher doses have been used in severe forms of steroid-resistant post-infectious encephalomyelitis. This is usually followed by oral steroid (prednisone 1mg/kg per day) tapered over 4 to 6 weeks, but might be unnecessary if symptoms improve. Monitor for hyperglycaemia, hypokalaemia, high blood pressure, and mood disorders. Outcome is usually favourable, with good functional recovery and mortality rates less than 5%. Recently, ADEM has been found to be associated with myelin oligodendrocyte (MOG) antibodies in over 50% of children under 11 years old. These children have a higher rate of relapse, or develop other demyelinating disorders (Hacohen and Branwell, 2019).

Posterior reversible leukoencephalopathy syndrome (PRES) is a condition also recognized on the basis of encephalopathy with the classic clinical signs such as seizures, visual disturbances, headache, impaired

consciousness, associated with high signal change (vasogenic oedema) on MRI, involving the white matter in parieto-occipital areas (with frequent involvement of the frontal lobe; Fig 17.4 c2, c3). Both hemispheres are usually affected, albeit often asymmetrically. Risk factors include hypertension, hypotension, treatment with tacrolimus, cyclosporin, cyclophosphamide, methotrexate, and some of the newer immunosuppressive and antineoplastic agents. It is very rare in the first year of life. PRES is most often associated with leukaemia/lymphoma (up to 72% of cases) complicating the course of 2.1% to 4.5% of children with acute lymphoblastic leukaemia, and less often associated with solid tumour or non-malignant diseases (HLH/thalassemia major/sickle cell disease [SCD]/Fanconi anaemia/congenital dyskeratosis/megakaryocytic thrombocytopenia).

Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) has been described in the context of viral and bacterial infections in children. The common neurological symptoms include seizure, behavioural changes, altered consciousness, and motor deterioration. The lesions may be in the splenium or other parts of the corpus callosum and show hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences with corresponding reduced diffusion (Fig 17.4 c1).

Vaccinations and acute encephalopathy

Recent reviews of cases of long-term neurological impairment with onset of acute epileptic encephalopathy immediately following diphtheria-tetanus-pertussis (DTP) vaccination have found that the majority of these had a *SCN1A* gene deletion. They were, in fact, cases of Dravet syndrome (see Chapter 20) and their neurological outcome was no different from those with the same gene deletion, and the onset of seizures was unrelated to vaccination. There are isolated reports of aseptic meningitis, without any known long-term sequelae, following

measles, mumps, and rubella (MMR) vaccination. The risk is less than 1 in 534 000 vaccinations. Research in the 1990s suggesting a link between vaccination and autism has now been discredited and the publications retracted. The resulting debate on this issue led to a large amount of high-quality epidemiological research that has provided reassurance that there is no such link. There is no evidence of increased risk of encephalopathy after DTP/Haemophilus influenzae B (Hib) or MenC vaccines 15 to 35 days after MMR vaccine.

Migraine

Migraine may present as encephalopathy, with or without hemiplegia, but it is a diagnosis of exclusion. There is usually a parent with migraine. Electroencephalography may be asymmetrically slow and diffusion-weighted MRI may show focal abnormality (Fig 17.4 a3).

TBI and inflicted TBI

Definitions

TBI results from external force being absorbed by cranial and intracranial structures. It may be closed or penetrating. It is a major cause of death and disability worldwide, especially in infancy and childhood. TBI is characterized by extra or subdural haemorrhages, often accompanied by cerebral contusion.

TBI including inflicted TBI

Causes in infancy include falls, or being a passenger in a road traffic accident, but the focus should always be on safe-guarding and whether the infant is the victim of deliberate inflicted TBI (ITBI). ITBI may be caused by direct impact or shaking, often accompanied by areas of hypoxia-ischaemia. Pathological data indicate that ITBI is probably a better term than the previously used 'shaken-baby syndrome' as it does not suggest that there is only a single mechanism by which brain injury

is caused. The level of violence used is recognized by others as excessive, dangerous, and likely to harm the child.

Caregivers at risk of abusive behaviour generally have unrealistic expectations of their children and may exhibit a role reversal whereby the caregivers expect their needs to be met by the child. Professionals should be aware that a crying infant is at higher risk of ITBI, especially when parents are complaining of excessive crying and are in a social position that could put pressure on the family situation. The actual duration of crying at a given moment seems to be less relevant than the parents' perception of the crying over the long term.

Epidemiology of TBI

The incidence of TBI in childhood is high and higher if measured prospectively rather than retrospectively (Table 17.3). TBI is an increasing cause of death in resource-poor countries and is the underlying cause in almost half of acute encephalopathies.

Table 17.3 Incidence of traumatic brain injury by region

Location	What is measured	Rate	
South West England and Wales	SDH under 1 year of age	21 per 100 000	Jayawant et al. (1998)
Scotland	SDH under 1 year of age (retrospective)	11.2 per 100 000	Barlow, Milne, and Minns (1998)
Scotland	SDH under 1 year of age (prospective)	24.6 per 100 000	Barlow and Minns (2000)
North Carolina, USA	Hospital surveillance (prospective)	29.7 per 100 000	Keenan et al. (2003)
Canada	Hospital surveillance (retrospective)	40 cases/year	King et al. (2003)
Germany	Estimation	100–200 per year	Matschke et al. (2009)

Switzerland	Nationwide	14 per 100 000 live births	Fanconi and Lips (2010)
New Zealand		14.7–19.6 per 100 000	Kelly and Farrant (2008)
Estonia	Retrospective	13.5 per 100 000	Talvik et al. (2006)
Estonia	Prospective	40.5 per 100 000	Talvik et al. (2006)

SDH, subdural haemorrhage.

Clinical approach

Take a careful and exact history. Look for consistency in accounts given by the different people involved. Does their version of events stay constant? Assess the injury: open, closed, or penetrating? Focal or diffuse? Associated soft-tissue trauma; damage to internal organs? Focal neurological signs? Are subtle seizures contributing to apparent depression of consciousness? ITBI is often seen in association with bruising, a torn frenulum, retinal haemorrhages, and fractures of long bones or ribs.

Investigation of TBI

- Blood clotting screen.
- Ophthalmoscopy (retinal haemorrhage in ITBI).
- Cranial CT scanning. CT to verify the possibility of intracranial haemorrhage (see Table 17.4) and brain oedema remains the first choice in all trauma patients with a GCS <15 or in a high risk category, including children (Shavit et al. 2019). Among 13 000 children with negative CT, no patient required operation later. If CT and clinical findings (in suspected ITBI also skeletal survey and retina) are normal no further investigations are needed.
- MRI. MRI of the head is needed within 2 to 5 days if CT is abnormal or if initial CT is normal but clinical evaluation is/remains abnormal or the patient presents in

the subacute stage. In case of suspected ITBI and spinal cord injury (e.g. flaccid quadriplegia), MRI of the whole spine may be required urgently. MRI must include T2*-weighted imaging or susceptibility-weighted imaging (SWI) sequences and diffusion-weighted imaging (DWI) that are sensitive to small haemorrhages. MRI is more sensitive than CT for evaluation of diffuse axonal injury with small haemorrhages, brain oedema and infarctions.

Note that between 5 to 10 days MRI and DWI findings may 'pseudo-normalize' and after 14 to 21 days longer-term changes, such as atrophy and encephalomalacia, may develop. Repeat the MRI despite normalized/normalizing clinical signs, if initial CT or MRI scans show abnormalities.

- Other imaging points
    - Spinal cord injury without radiographic abnormalities (SIWORA) is often seen in paediatric trauma patients. A large head compared to body size applies great forces to the neck in case of shaking or severe trauma.
    - Cranial ultrasound in young infants (screening), but should be followed by CT or MRI in suspected ITBI as subdurals are not excluded.
    - Skull X-ray is not recommended in TBI as it is unreliable in predicting the presence and degree of brain injury. In 15% to 30% of cases, skull fracture is associated with intracranial injury. Almost 50% of intracranial injuries occur without fracture and 21% of fractures detected with CT are missed by X-ray.
    - Skeletal survey in traffic trauma or suspected ITBI, including repeat chest X-ray at 7 days for rib fractures that are not apparent on initial X-ray; in 30% to 40% of children with inflicted injuries, signs of previous inflicted injury are present: e.g. old fractures, chronic subdural haemorrhage.
    - Ultrasound and/or CT of abdomen.

Management

Assess the level of consciousness with the GCS (Table 17.1). If GCS score is <8 or

there is a deteriorating conscious level, admit to the intensive care unit and manage the airway. Restore normal circulating blood volume and manage seizures and CPP. In possible ITBI, involve the interdisciplinary safe-guarding team, which will include not only relevant nursing and medical members of the hospital team but also a family doctor that knows the family, and other agencies that will keep the child safe at home. This will vary by country but may include a social worker and a police officer with specialist safeguarding training and experience.

Table 17.4 Causes of intracranial haemorrhage in infancy

Cause	Clinical or imaging feature	Possible other features	Comment/ management
Inflicted	SDH, ICH	External signs of abuse, inconsistent history, discrepancy between history and injury severity	Abdominal trauma, skeletal survey CT, MRI, surgery if necessary
Trauma	SDH, EDH, ICH,	External signs of trauma	CT, surgery if necessary
Haemorrhage	SDH, ICH, SAH	Signs of bleeding outside the CNS (e.g. nosebleed) and/or bruising, CNS parenchymal haemorrhage; bruises	Coagulation profile
Stroke including AVM/VST	SDH, ICH, SAH	Focal neurological signs	MRI, MRA
Infection	SDH	Fever; differentiate focal infection from meningitis (see Chapter 19) contraindicated	Enhancement with contrast, lumbar puncture if not
Metabolic disorder	SDH, ICH	Previous developmental impairment or arrest	MRI, metabolic screening

AVM, arteriovenous malformation; CNS, central nervous system; CT, computed tomography; EDH, extradural haemorrhage; ICH, intracranial haemorrhage; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SAH, subarachnoid haemorrhage; SDH, subdural haemorrhage; VST, venous sinus thrombosis.

Outcome of TBI and inflicted brain injury

The majority of children with ITBI have poor outcomes. About 20% die and only 20% survive without impairment. The remainder have impairments in their motor and cognitive abilities, language, vision, and behaviour. These impairments affect future educational and social attainment. The reasons for the poor outcomes in infants and children who sustain ITBI are not known but are probably attributable to associated ischaemia and hypoxia.

Acute metabolic encephalopathies

The clinical presentation in children with a metabolic encephalopathy is non-specific. In neonates it usually occurs after a symptom-free period following delivery. Poor feeding, vomiting, central hypotonia with limb hypertonia,

Figure 17.2 The urea cycle. AL, arginine-succinate lyase; AS, argininosuccinate synthetase; CPS, carbamyl phosphate synthetase; NAGS, *N*-acetylglutamate synthase; OTC, ornithine transcarbamylase.
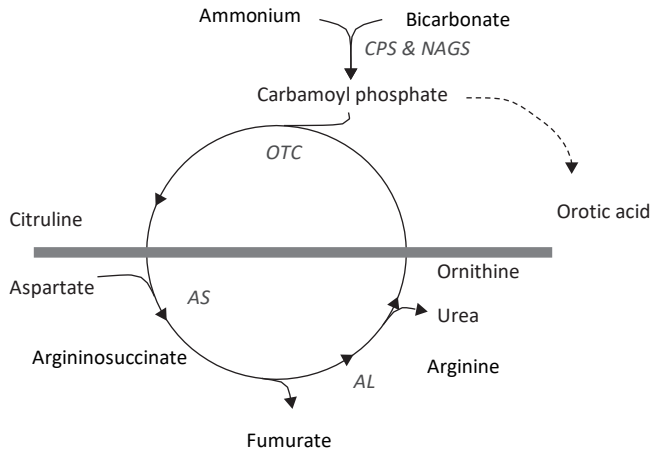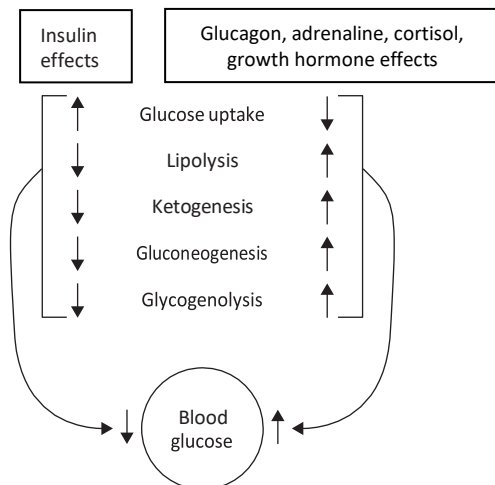
Figure 17.3 The principles of glucose metabolism

abnormal movements followed by seizures and coma may occur (see Chapter 15). In older infants, it may be associated with periods of metabolic stress (e.g. fasting, intercurrent infection). Inborn errors of metabolism should always be considered in children – and especially infants – with unexplained changes in their conscious level, alongside CNS infections (bacterial or viral), haemorrhage, hypoxia and/or ischaemia, or suspected poisoning.

Management

Supportive management is as for any child with an encephalopathy. Specific therapy depends upon the underlying disorder and the biochemical abnormalities. The three main biochemical disturbances associated with an encephalopathy due to inherited errors of metabolism are hypoglycaemia, hyperammonaemia, and metabolic acidosis. Therefore, the important investigations are ammonia, glucose, pH, serum lactate, and organic acids (see also Chapter 15 for a fuller discussion).

The most common causes of severe hyperammonaemic encephalopathy in children are enzyme deficiencies of the urea cycle (Fig 17.2), which functions to convert highly toxic ammonia arising from the catabolism of amino acids to non-toxic urea. Hyperammonaemia may also occur in children with organic acidaemias and, less commonly, in fat oxidation disorders. The outcome for children with hyperammonaemic encephalopathy is generally poor. However, permanent CNS damage can be limited by a rapid reduction in blood ammonia.

Although hypoglycaemia is a common non-specific feature of many sick infants, it may arise as a result of the following disorders:

- fat oxidation (most common),
- glycogen metabolism,
- gluconeogenesis,
- glucose transport,

- galactose and fructose conversion to glucose, or

- ketone metabolism.

Blood sugar must be measured in the laboratory as well as on BM stix or Dextrostix in any encephalopathic child with the following essential investigations:

- true blood glucose,

- lactate,

- free fatty acids, 3-hydroxybutyrate, acyl carnitines,

- insulin, urinary cortisol,

- organic acids,

- later: growth hormone.

Figure 17.3 shows the principles of glucose metabolism. Once identified the principles of management are

- glycogen storage disorders: maintain glucose with nocturnal enteral feeding;

- fatty oxidation defects: regular feeding, give carnitine supplements;

- gluconeogenesis defects: avoid fasting (tolerance increases with age);

- growth hormone/cortisol: replace as appropriate;

- organic acids/amino acids: may be vitamin-responsive, protein restriction;

- galactos-/fructosaemia (HFI): avoid galactose/fructose respectively;

- insulin excess: central venous line, glucose – at least 10% but sometimes requires higher concentrations; continuous enteral feeding with a glucose polymer, somatostatin, +/- diazoxide.

Metabolic acidosis is very common in sick infants and children and is most often caused by sepsis, poor tissue perfusion, and/or hypoxia. Severe metabolic acidosis is most often associated with the *organic acidaemias* (mainly propionic and

methylmalonic acidaemia) and *disorders of ketone body utilization*. The absence of acidosis does not exclude these disorders. In contrast to secondary causes of metabolic acidosis, sodium bicarbonate is usually a necessary part of therapy.

Some inborn errors of metabolism present with an acute encephalopathy without prominent biochemical abnormalities of blood glucose, ammonia, or acid/base balance and should still be considered in a child with an unexplained encephalopathy, even if initial biochemical investigations are normal. These include, for example, *pyridoxine-dependent seizures*, *maple syrup urine disease*, *sulphite oxidase deficiency*, and *glutaric aciduria type 1* (see Chapter 15). Identification and counselling for any underlying inherited error of metabolism will require the advice of a clinical geneticist.

Acute toxic encephalopathies

The most common cause of acute toxic encephalopathy is sepsis, but remember that the crawling infant may be able to access drugs or poisons in the home. Deliberate poisoning will rarely occur.
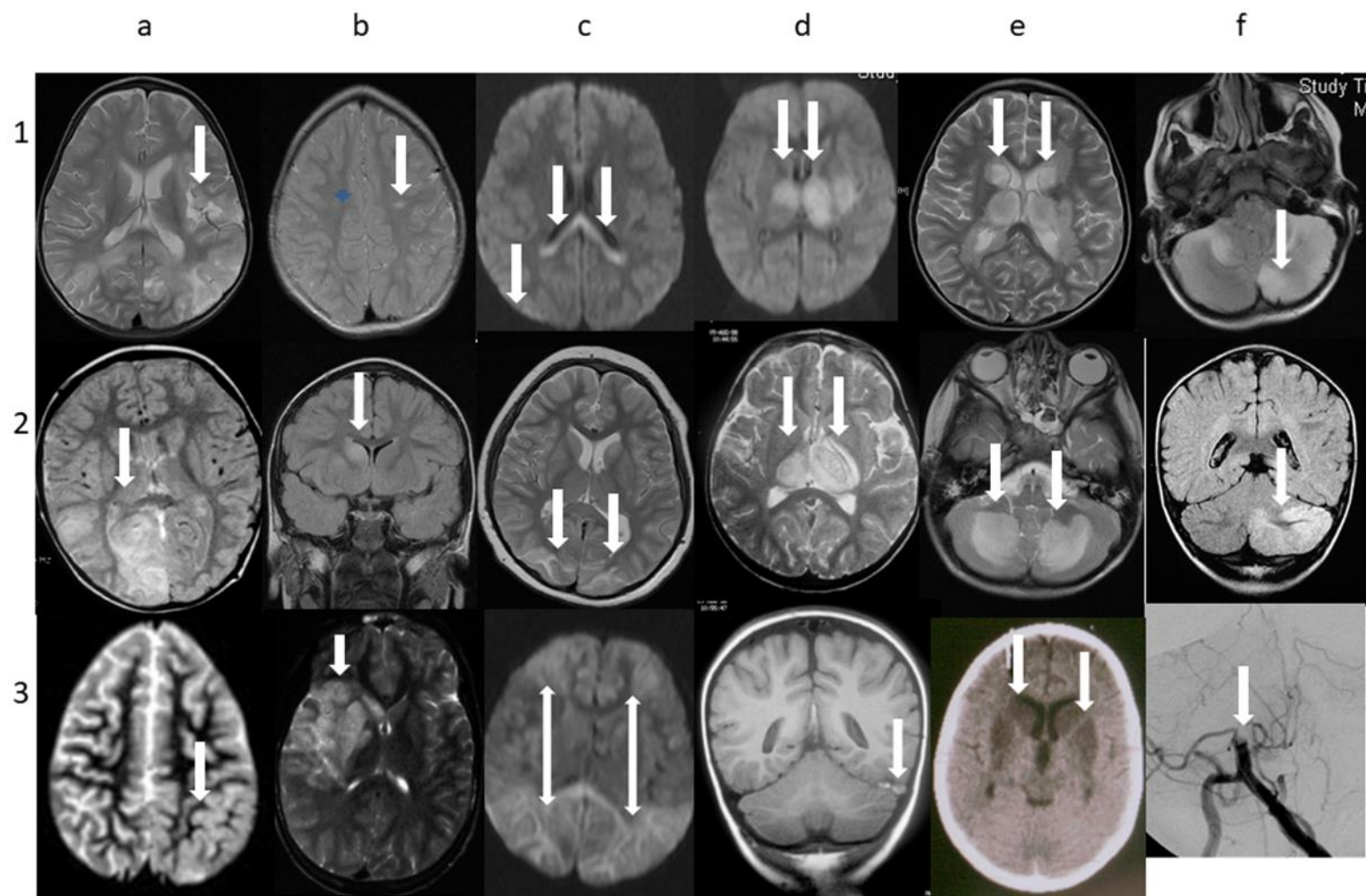
Figure 17.4 Imaging for diagnosis and differential diagnosis of encephalopathy. T2-weighted magnetic resonance imaging (MRI) unless stated. Viewed from below, i.e. left side is seen as right side of image.

Column a: (1) widespread focal cortical involvement (arrow) in Herpes simplex encephalitis in a neonate; (2) oedema/infarction (arrow) in sagittal venous sinus thrombosis secondary to iron deficiency anaemia; (3) parieto-occipital focal oedema consistent with reversible ischaemia (arrow; see also Fig 18.2b) in an unconscious child with unilateral slowing and a family history of hemiplegic migraine.

Column b: focal lesions (1) focus of high signal density in the left frontal white matter (arrow) in a child with anti-N-methyl-D-aspartate receptor antibody encephalitis who recovered after steroids, plasma exchange and cyclophosphamide; (2) right-sided high signal on T1-weighted imaging (arrow) in a child presenting with hemichorea and a raised antistreptolysin O titre, who recovered after 2 weeks of penicillin and prednisolone; (3) recent large infarct (arrow) in a child presenting with confusion and a reduced conscious level; small strokes rarely cause coma.

Column c: posterior involvement (1) abnormality of splenium bilaterally (arrows) on DWI in a child who recovered rapidly from acute coma; (2) posterior abnormality bilaterally (arrows) consistent with posterior reversible encephalopathy syndrome in an immunosuppressed male with juvenile chronic arthritis and hypertension in whom (3) bilateral border zone ischaemia was demonstrated on DWI (arrows) the day after a period of hypotension.

Column d: thalamic abnormality (1) bilateral thalamic involvement (arrows) in acute disseminated encephalomyelitis after acute otitis media; (2) bilateral thalamic ischaemia (arrows) in a child with (3) venous sinus thrombosis (arrow) and severe iron deficiency anaemia (haemoglobin 4g/dL) who recovered fully after anticoagulation.

Column e: widespread symmetrical abnormality. Fluid-attenuated inversion recovery MRI showing (1) bilateral symmetrical basal ganglia, thalamic, white matter (arrows) and (2) bilateral cerebellar involvement (arrows) in acute necrotizing encephalopathy in a child with acute sepsis for which the differential diagnosis includes (3) Leigh syndrome with bilateral symmetrical basal ganglia involvement (arrows) on computed tomography.

Column f: Cerebellar involvement in (1) cerebellitis with descent of the cerebellar tonsils (arrows) in the context of rising titres to Epstein–Barr virus (2) unilateral infarction (arrow) in a child with (3) basilar occlusion (arrow) which was thrombolysed 11 hours after presentation with good outcome.

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