Hypothalamic hamartoma, precocious puberty and gelastic seizures

This is a rare syndrome in which a hypothalamic hamartoma is accompanied by precocious puberty and intractible seizures which are often gelastic, i.e. laughing seizures. Such seizures are sudden brief outbursts of unusual laughing which does not seem to be pleasurable for the patient. There may be sudden grimacing and vocalization that is qualitatively different from normal laughing. This syndrome is difficult to treat; the lesion is not removable by surgery and does not usually respond to radiotherapy. Seizures may be very resistant to drug treatment.

Status epilepticus

Status epilepticus is defined as a continuous epileptic state. This can be further defined as a single continuous seizure or series of seizures between which the patient does not regain consciousness (Hauser 1983). The duration of a seizure before it is defined as status epilepticus is generally taken to be from 30 min to 1 h.

Status epilepticus is more common in childhood than in adult life. Aicardi & Chevrie (1970) reported that 16% of children diagnosed as having epilepsy under the age of 15 years would have an episode of status epilepticus. The majority of cases of status epilepticus occur in the first 2 years of life. The episode of status epilepticus is often the first epileptic seizure.

Status epilepticus can be classified in the same way as single seizures. Thus they can be generalized, partial, tonic clonic, clonic, myoclonic or tonic. Likewise non-convulsive status epilepticus (absence status epilepticus) may occur. The most common form of status epilepticus is convulsive status epilepticus with tonic clonic or clonic seizures which may be generalized or focal.

The causes of status epilepticus can be divided into cryptogenic or symptomatic and the symptomatic cases further divide into acute and chronic. Overall 50% of cases will be cryptogenic of which half will be cases of febrile convulsions. In other words 25% of cases of status epilepticus in childhood are due to febrile convulsions (Aicardi & Chevrie 1970, Maytal et al 1989). Chronic CNS disorders such as cerebral palsy, ischaemic anoxic brain damage, malformations, tumours and progressive diseases account in total for a further 25% of cases. The remaining 25% are due to acute encephalopathies such as CNS infection, electrolyte disorders, metabolic and toxic causes, trauma and cerebrovascular accidents. Sudden withdrawal of antiepileptic drugs in epileptic patients is another important cause.

Effects of status epilepticus

Following generalized or unilateral status a postictal hemiplegia is common. During the status there is often hypoventilation, hypoxia and hypertension (later hypotension). Tachycardia is present at first but bradycardia may ensue if the seizure is not controlled. Hyperthermia is common and hyperglycaemia is usual unless seizures are due to hypoglycaemia. There is also muscle ischaemia and damage due to continuous muscle contractions and this will raise levels of lactate and CPK in the blood. Even if systemic factors are controlled there is much evidence that excessive neuronal activity itself will eventually lead to neuronal damage. There is a fourfold increase in cerebral blood flow and similar increase in cerebral metabolic rates. These may initially be compensated for but eventually decompensation occurs leading to a series of metabolic derangements that may in themselves or collectively lead to neuronal damage and death.

There is thus a mortality and morbidity from status epilepticus. Interestingly the incidence of sequelae for status epilepticus appears to have decreased markedly over the last 20 years. Thus Aicardi & Chevrie found a mortality of 11% in 239 children studied in 1970. This contrasts with mortality of 3.6% in 193 patients reported by Maytal et al in 1989. In this study all deaths occurred in patients with acute CNS insults or progressive CNS disease.

The morbidity has changed also in the past 20 years. Aicardi & Chevrie reported a 4% incidence of neurological sequelae and a 48% incidence of mental deterioration for 44% incidence of epilepsy. This compares with a recent figure of Maytal et al where only 9% of the whole group had new neurological or cognitive problems on follow-up. Approximately 10% of patients developed epilepsy following the status.

The incidence of sequelae relates primarily to the cause of the status, the majority of sequelae occurring in those with acute CNS dysfunction. In the earlier studies some patients with cryptogenic status had sequelae and the incidence was markedly higher in the younger age groups. However, in recent studies virtually all the sequelae occurred in patients who had acute or progressive CNS disease.

The nature of sequelae varies but includes hemiplegia, ataxic and extrapyramidal syndromes and mental retardation. Hemiplegia following a prolonged hemiconvulsion which used to be a relatively common observation has become very rare. The reasons for this change are almost certainly due to better first aid management of seizures, particularly with widespread use of rectal diazepam and improved intensive care facilities for the patients after admission.

Management of status epilepticus (Table 14.12)

The management of status epilepticus involves prompt stopping of the seizure followed by the determination of the underlying cause and treatment of this where possible.

Table 14.12 Management of status epilepticus

1. Assess airway, respiration, circulation and neurological state
2. Give facial O_2 and suck out pharynx (i.p.p.v. if necessary)
3. Insert i.v. canula and take blood for urea, electrolytes, glucose, calcium, full blood count, culture and anticonvulsant levels
4. Check blood sugar with BM or dextrostix
5. If low treat with glucose (1–2 ml/kg 50% dextrose)
6. Give 0.2–0.3 mg/kg diazepam by slow intravenous injection
7. If still fitting after 10 min give second dose diazepam
8. If fit stops load with phenytoin 10–20 mg/kg i.v.
9. If still fitting after 10 min give phenytoin 10–20 mg/kg i.v. no faster than 1 mg/kg/min. Watch ECG
10. If still fitting after phenytoin give paraldehyde 1 ml/year of age + 1 ml by deep i.m. injection into anterior thigh (no more than 5 ml in each leg)
11. Give mannitol 20%, 7 ml/kg by slow infusion
12. If still fitting after 20 min give phenobarbitone 15–20 mg/kg intravenously. Watch pulse, BP and support BP if it falls
13. If still fitting arrange transfer to ITV, EEG monitoring and either general anaesthesia with thiopentone or lignocaine or chlormethiazole

As with resuscitation in other conditions initial attention should be given to the airway, breathing and circulation (ABC). The airway should be cleared by suction. Facial oxygen is given or bag and mask ventilation if the patient is not breathing. Pulse and blood pressure should be monitored and the need for circulatory support determined. An ECG monitor should be started if possible. Blood sugar using a glucose stick should be estimated.

A brief examination of the patient should then be carried out noting the conscious level of the child, the pupillary reactions and eye movements, the presence of focal signs and observations of the pattern and site of convulsive movements.

All the above should be completed in under 5 min and efforts should be directed to stopping the seizures.

An i.v. cannula should be inserted, blood taken for future analysis and a bolus of diazepam 0.2–0.3 mg/kg given over 1–2 min. In aproximately 80% of cases the seizure will stop after diazepam. If after 10 min there has been no response a further dose of diazepam can be given. If after this there is no response then further doses of diazepam should not be given as they will merely depress respiration and blood pressure and will not have any effect on the seizure. If there is no response to diazepam then a loading dose of 15–20 mg/kg of phenytoin by slow intravenous infusion (no faster than 1 mg/kg per min) is given. Peak brain penetration with phenytoin will occur within 5–6 min after the start of the infusion.

In most cases of status our personal practice is to load the patient with phenytoin after the diazepam even if the seizures have stopped. This is to provide continued anticonvulsant cover over the next few hours. Status occurring in a patient already taking oral phenytoin is not a contraindication to intravenous phenytoin. If at the end of the phenytoin infusion seizures are still present, intramuscular paraldehyde in a dose of 1 ml/year of age +1 given by deep intramuscular injection into the lateral thigh (not the buttock) can be used. No more than 5 ml should be given into one site. Paraldehyde is an extremely effective anticonvulsant and side effects or complications are very uncommon.

In some instances, particularly in an obese toddler where difficulties are encountered in finding veins and in whom rectal diazepam therapy has been tried, paraldehyde would be an appropriate first line drug.

There are very few seizures that paraldehyde will not stop. If after 20 min seizures are still present then consideration should be given to phenobarbitone 10–20 mg/kg by slow intravenous infusion. Although very effective, hypotension is a real risk and if intracranial pressure is raised this may have disastrous effects. Close attention should be paid to blood pressure and heart rate and if hypotension occurs it should be treated aggressively with plasma or ionotropic drugs.

Seizures may cause rises in intracranial pressure that may persist after the seizure has stopped. Radiological evidence has shown cerebral oedema in the acute phase of status epilepticus that disappears on recovery. The response to mannitol is often impressive and the patient's conscious level may improve markedly following the infusion of 7 ml/kg of 20% solution.

Seizures which are still uncontrolled at this stage require third line management and the child should be transferred to the intensive care unit where further therapy can be tried under continuous EEG control. There are various therapeutic options at this point. The most aggressive and probably most effective is to undertake general anaesthesia with thiopentone and electively ventilate the patient. It is possible to use thiopentone infusions without ventilating the patients but this should be done only where facilities for easy intubation or ventilation are available. The main risk again is hypotension. CVP and arterial pressure should be monitored and treated appropriately. If the patient is anaesthetised or paralysed, EEG monitoring is essential to determine that seizure activity is abolished. In addition, in acute encephalopathies after control of clinical seizures, a stage of electroclinical dissociation may occur with continuous electrical seizures occurring without clinical accompaniment. This can be associated with continued raised intracranial pressure. If consciousness is not regained ICP monitoring may be required. Treatment with lignocaine and/or chlormethiazole may on occasions be effective.

In our experience the use of diazepam, phenytoin, paraldehyde and mannitol allows the vast majority of cases of status to be treated outside the intensive care unit.

Rectal diazepam has revolutionalized first aid treatment of status and has undoubtedly resulted in a reduced morbidity and mortality rate. Rectal diazepam is absorbed rapidly and reaches peak levels within 4–10 min. A higher dose is needed than for intravenous diazepam (0.5 mg/kg). If two doses of rectal diazepam have failed one further dose of intravenous diazepam is justified before a change to a different drug as respiratory depression can occur. All new cases of status should have a check on blood urea and electrolytes, calcium, magnesium, full blood count, blood culture and urine and blood should be kept for toxicology and metabolic screening. It is essential to consider and rule out CNS infection, thus the decision about whether or not to do a lumbar puncture always arises. If the seizures stop and the child is showing signs of waking up and there are no other signs of raised intracranial pressure then a lumbar puncture should be done. If the seizure has been unilateral then a hemiplegia on that side is not a sign of structural cerebral damage and if there are no other indications of raised intracranial pressure it is not a contraindication to lumbar puncture. If the child does not wake up or does not stop fitting then he should be managed as for any other acute encephalopathy and a CT scan carried out before a lumbar puncture. This may mean treating with broad spectrum antibiotics before the lumbar puncture is done and a retrospective diagnosis made using countercurrent immunoelectrophoresis when lumbar puncture is safe. Urine and blood should be sent for antigen testing against haemophilus, meningococcus and pneumococcus.

If the patient is already on antiepileptic drugs then blood levels should be taken on arrival to hospital. Sudden withdrawal of antiepileptic treatment is a not uncommon cause of status in older children. If episodes are recurrent or the patient is not recovering then urinary organic acids, amino acids, blood lactate, ammonia and a blood gas test should be carried out to exclude a metabolic cause.

Non-convulsive status epilepticus

This refers to a continuous non-convulsive seizure such as absences or complex partial seizures. The most common form in childhood is atypical absence status and this has been discussed in the context of the Lennox Gastaut syndrome above. This form is also common in Angelman's syndrome. Treatment of atypical absence status is very difficult and many cases are resistant to benzodiazepines (Livingston & Brown 1987). They should how-

as occasionally there is a dramatic response. Many drugs have been tried and in individual cases these may be ive. However, often one has to wait until the episode ends aneously.

lex partial status

is not common in childhood. However, it should always be d for in children or young adults with bizarre behaviour, iorating school performance or confusional states, particu- if there is a past history of complex partial seizures. The symptoms are only slightly impaired consciousness, emo- al disturbance, delayed reaction times, disorientation, ability and poor concentration. There is usually great fluctua- in the severity of these symptoms during an attack. The ent may swing in and out of periods of unreactiveness and ods of partial reactiveness.

he EEG must show focal abnormalities at some point. How- r, again the EEG may fluctuate showing generalized abnormal- s on occasions and on others focal continuous abnormalities illar to those seen in complex partial seizures.

In rast to atypical absence status, complex partial status ually responds rapidly and well to intravenous diazepam with without phenytoin.

REATMENT OF EPILEPSY

e would not recommend initiation of anticonvulsant therapy tomatically after a first seizure but would adopt the more usual beit arbitrary approach of starting treatment after two or more izures have occurred. This approach however must be flexible. or example, if seizures are separated by greater than a year then t may not be necessary to treat if the parents and patients are in greement. On the other hand a teenager experiencing a tonic lonic seizure at school may not want to run the risk of it hap- pening again and may opt for immediate treatment even though it may never happen again.

The type of seizure is also of importance in the decision. In- frequent absences or complex partial seizures may not interfere with the patient's life in any way and especially if there is any doubt about the diagnosis treatment can be safely deferred. However, these types of seizure are usually quite frequent and do interfere with the patient's life. Exclusively nocturnal seizures or sleep related seizures again may not pose a great problem to the child if infrequent. Benign rolandic seizures are often infrequent and the patient may only have two or three seizures in the whole illness. A trial of witholding treatment in this group may be justified. Petit mal absences once started tend to continue and increase in frequency.

When to stop the treatment is again a controversial subject. It is usual to consider discontinuing treatment 2 years after the last seizure had occurred.

Antiepileptic drugs (see Table 14.13)

Sodium valproate

Sodium valproate is completely absorbed following oral administration. Its mode of action is not certain. It is highly bound to plasma protein and binding is reduced by free fatty acids, hypoalbuminaemia, liver and renal disease. It is almost completely metabolized prior to excretion mainly by conjugation in the liver. The plasma half-life is around 12–13 h. Although this would suggest a twice or thrice daily dosage would be required there is evidence that patients can be well controlled on a once daily regime.

Valproate does not induce hepatic metabolism but acts as a non specific inhibitor of drug metabolism. There appears to be no relation between plasma valproate levels and seizure control. Thus blood levels are only of value in determining if the patient is compliant and taking the drug and in cases of intoxication.

Side effects. Nausea, vomiting and anorexia are not uncommon and may be avoided by giving the drug after meals. Weight gain can be troublesome causing marked obesity. Reversible alopecia is not infrequent. Tremor and thrombocytopenia are the only dose related side effects. No consistent effect on behaviour has been found and in some studies alertness and concentration improve on the drug. A severe, sometimes fatal, hepatic toxicity has been described as a side effect (Dreifuss et al 1987). It is not dose-related. It usually comes on in the first 3 months of therapy and is more common in children with neurological dysfunction who are on polytherapy. It usually comes on without warning and

T 14.13 Main antiepileptic drugs

Drug	Total daily dose (mg/kg)	No. of daily doses	Main indication (see text)	Main side effects
Sodium valproate	20–50	1 or 2	Absence epilepsy, generalized tonic/clonic epilepsy, myoclonic seizures, photosensitivity	GI, weight gain, tremor. Rare hepatotoxicity
Carbamazepine	10–20	2 or 3	Generalized toxic/clonic epilepsy, all partial epilepsies	Rashes, ataxia diplopia
Ethosuximide	20–40	2 or 3	Typical absence epilepsy, some myoclonic epilepsy	GI, hiccups, sedation
Phenytoin	5–10	2	Generalized tonic/clonic epilepsy, partial epilepsy	Ataxia, hirsutism, gum hypertrophy, sedation, cognitive difficulties
Phenobarbitone	2–5	1 or 2	Generalized tonic/clonic epilepsy, partial epilepsy	Sedation, overactive behaviour, cognitive effects
Clobazam	0.51	2 or 3	Add on therapy for any resistant seizures	Sedation, behaviour difficulties, cognitive effects, hypotonia
Clonazepam	0.1–0.2	2 or 3	As above	As above
Nitrazepam	0.5–1	2 or 3	As above, infantile spasms	As above plus excess secretions

early symptoms are vomiting, lethargy, weakness and drowsiness. Liver function tests and ammonia are usually normal before the onset of this complication.

The exact incidence of this condition is unknown but it has been suggested that it is around one in 85 000 patients receiving valproate but one in 500 under 3 years. Some of the patients who had this reaction undoubtedly had hepatic diseases such as hepatitis or a urea cycle abnormality.

Hyperammonaemia is a common occurrence on valproate therapy and is asymptomatic and not related to the severe hepatic failure syndrome.

Carbamazepine

Carbamazepine is a tricyclic compound closely related in structure to imipramine. Its mode of action is uncertain but it shares many of the actions of phenytoin and as such is thought to work by inhibiting sustained high frequency firing of neurones. It is absorbed slowly and erratically from the gut, absorption being inversely related to dose.

The half-life in chronically treated patients is around 12 h, but in new patients is much longer. This needs to be taken into account when starting therapy and the dose built up gradually. Likewise because of autoinduction the level may fall after a few weeks.[2]

It is only 70–80% protein bound and other drugs do not seem to influence this. Carbamazepine is largely metabolized into a stable epoxide metabolite. The epoxide is pharmacologically active but its exact role in seizure control or side effects are not clear. Carbamazepine is further hydroxylated then excreted in the urine. There is little correlation between dose and blood levels. However, there is a relationship between blood levels and seizure control. Some patients are controlled below the therapeutic range and occasional patients may be controlled without side effects at levels above the so-called toxic range. Carbamazepine is usually given twice daily but occasionally better control may be obtained by more frequent daily doses. Carbamazepine can induce the metabolism of valproate, phenytoin and benzodiazepines, likewise phenytoin, primidone or phenobarbitone can lower levels of carbamazepine.

Adverse effects are not uncommon but are rarely severe. The most common are dose related occurrence of dizziness, ataxia, blurred vision or diplopia. These often occur early in treatment and are usually transient. Skin rashes occur in at least 3% of cases and usually come on early in treatment and are often transient. However, more severe allergic reactions do occasionally occur. Transient leucopenia is not uncommon early in therapy. However, very rarely aplastic anaemia may occur. Pulmonary eosinophilia is a rare severe allergic response. Hyponatraemia can occur early in therapy with carbamazepine.

Carbamazepine does not have major effects on cognitive function and in some cases seems to have a positive effect both on mood and performance.

Oxcarbazepine

This is a new carbamazepine analogue which has equal efficacy as an anticonvulsant with carbamazepine. Its benefit appears to be a lower incidence of side effects and that it does not cause the same allergic reactions as carbamazepine.

Ethosuximide

This has been used in the treatment of absence seizures for over 25 years. It has a highly selective action against experimental seizures but in spite of this its mode of action is unknown.

It is rapidly and completely absorbed from the gut with peak levels in 1–4 h. It is not protein bound and CSF and saliva levels are similar to those in plasma. It is metabolized in the liver and excreted as glucuronide. Only 20% of the drug is excreted unchanged. The half-life is 20–40 h and thus once daily dosing is possible. However gastrointestinal side effects with large doses may make a twice daily regime necessary. Control of seizures is related to the plasma level and the therapeutic range is considered to be 200–300 μmol/l. However, in some cases improved control may be achieved without side effects at a much higher level.

Interactions are not usually a problem. However, valproate may cause elevation of ethosuximide levels and toxicity.

Ethosuximide is a well-tolerated drug. Dose related side effects such as nausea, abdominal discomfort, drowsiness and anorexia are not uncommon. These usually respond to dose reduction. Protracted hiccups may occur. Skin rashes including erythema multiformae and Stevens Johnston syndrome have been described. Acute psychotic episodes have been described early in treatment.

The above drugs are the first line anticonvulsants and should be tried alone or in combination in most seizure disorders before going on to try the drugs that are considered below. Phenytoin and phenobarbitone are both extremely effective anticonvulsants but because of their relatively high incidence of adverse effects they should now be considered second line drugs.

Phenytoin

Phenytoin is still one of the most commonly used anticonvulsant drugs and one of the best studied. In spite of this its main mechanism of action remains elusive. It reduces sodium ion conductance, blocks repetitive burst firing and enhances GABA mediated inhibition and reduces excitatory transmission.

The absorption of phenytoin is dependent on the preparation. The acid form is poorly absorbed whereas the sodium salt is readily absorbed. In newborns and young infants phenytoin is absorbed slowly and incompletely whereas in older children absorption is efficient with peak levels reached in 2–6 h. Phenytoin should not be given intramuscularly as absorption is erratic and uncertain and considerable muscle damage may occur.

It is highly (90%) protein bound, mainly to albumen though less in neonates. It is very lipid soluble and diffuses rapidly into tissues including the brain.

Phenytoin is metabolized by hydroxylation in the liver. This hepatic metabolism is under genetic control and varies between individuals. Phenytoin also exhibits zero order or saturation kinetics. This means that the enzymes are saturable within the therapeutic range of concentrations, the liver being unable to increase its rate of metabolism proportionately as the blood level rises. It thus moves towards a situation where a fixed amount of drug is removed regardless of the increase in serum levels. For this reason small changes in dose can produce large fluctuations in serum level resulting in either toxicity or sudden breakthrough of seizures if the drug level becomes subtherapeutic. This also means that the half-life of the drug will increase with higher blood levels in a non-linear way. The half-life in neonates is long but becomes shorter in infancy and in general twice daily dosing

is usually employed. There is thus a great variability in the r[illegible]ship between dose and concentration and for this reason mo[illegible]oring of serum levels is essential.

The therapeutic range of phenytoin serum concentration is 40–80 μmol/l, however some patients may be controlled with levels below this and rare patients may achieve improved control without side effects with levels above 80 μmol/l.

There are numerous interactions between phenytoin and other drugs. Phenytoin is a potent inducer of hepatic enzymes thus leading to lower levels of antiepileptic drugs that are metabolized by the liver. Drugs which inhibit phenytoin metabolism include chloramphenicol, isoniazid and valproate. Dose dependent side effects include vertigo, tremor, ataxia, dysarthria, nystagmus and headache.

Long-term phenytoin has been shown to impair cognitive function (Thomson et al 1981). More severe effects may occur resulting in a reversible encephalopathy characterized by intellectual deterioration, depression, behavioural problems and psychomotor slowing. These changes are usually associated with high phenytoin levels. Occasionally dyskinesias, e.g. choreoathetosis may occur. Several reports have suggested that chronic phenytoin treatment has led to irreversible cerebellar damage with loss of [illegible]inje cells. However, it is not proven that such features are due to the phenytoin and not part of the underlying disease.

Peripheral neuropathy and rare hepatic hypersensitivity-type reactions have been described. Megaloblastic anaemia, aplastic anaemia and leucopenia and decrease in IgA levels may occur and hypocalcaemia and osteomalacia have been described. One of the most disturbing chronic side effects, particularly for girls, is coarsening of facial features, hirsutism and gum hyperplasia and this may be a reason for discontinuing the drug.

Phenobarbitone

This was the first generally effective antiepileptic drug to be used. It is thought to act by enhancement of GABA mediated inhibition and diminishing glutaminergic and cholinergic excitations.

It is well absorbed in the gut with peak levels in 1–6 h. Brain penetration is slow. It is 45% bound to plasma proteins. Phenobarbitone is partly excreted unchanged in the urine and partly metabolized in the liver. The plasma half-life is long, 30–70 h, thus once daily dosages are effective. The half-life is much longer in neonates. The serum concentration is proportional to the dose. Therapeutic range is wide with levels between 40 and 130 μmol/l generally being regarded as therapeutic. The main drug interaction is due to induction of hepatic enzymes with lowering of blood levels.

Serious systemic side effects are rare. However, neurobehavioural side effects are common. In children hyperactive behaviour with poor concentration may occur in up to 50% of cases. The children most at risk are those with brain damage syndromes.

Cognitive function may be markedly affected with memory and learning difficulty. Dependence develops and withdrawal effects are common.

Megaloblastic anaemia has been described. Biochemical rickets may occur. Skin rashes are rare.

Primidone

Primidone is a desoxybarbiturate that is metabolized to phenobarbitone and phenylethylmalonamide (which has antiepileptic activity itself). It may be more effective than phenobarbitone in some patients, particularly those with complex partial seizures.

Benzodiazepines

Benzodiazepines are the most potent agents for the emergency treatment of seizures and are extremely effective drugs against experimental seizures. However, their value in the treatment of chronic epilepsy is severely limited by:

1. The development of tolerance to their antiepileptic effects which will occur in up to 60% of cases within 1 year
2. Relatively high incidence of behavioural side effects in children.

There are four benzodiazepines in current use in the treatment of epilepsy: diazepam, nitrazepam, clonazepam and clobazam. Oral diazepam does not have a role in the chronic treatment of epilepsy.

The benzodiazepines act by enhancement of GABAergic transmission by the effect of their binding to the benzodiazepine receptor which exists as a complex with the GABA receptor and chloride ionophore. Usually resistance or tolerance to one benzodiazepine means that there is also tolerance to the other. However, this is not always the case when sometimes an improved response may be obtained by changing from one to the other.

The benzodiazepines are rapidly absorbed with peak levels in 1–4 h for nitrazepam, clonazepam and clobazam. They are all quite slowly metabolized with long half-lives ranging from 20 to 60 h. Diazepam and clobazam have active metabolites which have even longer half-lives, thus accumulation of sedative effects may occur.

Monitoring of serum concentrations is unhelpful because of the poor correlation between serum concentration and response. The major side effects are behavioural with clobazam and clonazepam causing overactivity, aggression, sleep disturbance and poor concentration in many children. In some children excessive sedation occurs. In young children, particularly those with motor problems, hypotonia may be troublesome.

Nitrazepam may cause bronchial hypersecretion and drooling. Other side effects are rare. Tolerance severely limits the usefulness of these drugs. However, they are potent anticonvulsants and may be the only effective drugs in some patients. When tolerance occurs the patient needs to be gradually weaned off benzodiazepine and allowed a drug holiday of 2 weeks to 1 month or more. If seizures remain troublesome reintroduction of the benzodiazepine will often be effective for a further period.

Dependence is common and withdrawal seizures or behavioural changes are common on coming off treatment. Thus stopping benzodiazepines can be very difficult and should be done slowly with small decreases in dose occurring no more often than once every 2 weeks.

Acetazolamide

This has anticonvulsant properties itself but is particularly useful when used in conjunction with carbamazepine. The mechanism of this interaction is unknown. It may be useful used in this manner in the treatment of complex partial seizures.

Steroids

The use of different corticosteroids has been discussed above in relation to infantile spasms. Steroids do not have a clear place in the treatment of other epilepsies in childhood. They have however been tried in the Lennox Gastaut syndrome and Landau Kleffner syndrome.

Ketogenic diet

The observation that some epileptic patients become seizure free during febrile episodes led to the introduction of the ketogenic diet in an atempt to mimic the ketotic state occurring during illness.

Various diets have been devised and the palatability of these has been improved by medium chain triglyceride oils (Schwartz et al 1983). Widely varying claims as to the success of the diet have been made but no control data are available.

Some patients undoubtedly respond to the diet and any patient with intractable epilepsy, particularly infantile spasms or Lennox Gastaut syndrome, should be given a trial of the diet. In some patients it is very difficult to achieve ketosis. In others diarrhoea is troublesome. Monitoring the plasma blood level of ketones has been advocated as a better way of achieving controls.

New antiepileptic drugs

There has been much recent research into developing new antiepileptic drugs that will be effective in some of the resistant types of epilepsy or which will be free from troublesome side effects. In the last 10 years many new agents have been investigated, some modifications of existing drugs but many novel compounds. The first of these drugs to become available is vigabatrin. This is a tailor-made drug which is an irreversible inhibitor of GABA transaminase, the enzyme which metabolizes GABA. It is thus thought to act by increasing GABAergic inhibition. Studies in children have shown it to be particularly effective against resistant partial seizures with some effect against generalized seizures and a surprising effect on infantile spasms, particularly those due to tuberous sclerosis (Livingston et al 1989, Luna et al 1989). The main side effect in children is agitation which in most cases goes away on decreasing the dose.

Lamotrigine is a new drug that has shown promise in preliminary studies for control of refractory seizures including childhood epilepsy. It is thought to act by inhibiting glutaminergic excitation.

Surgical treatment of epilepsy

There are four main types of surgical procedure used in the treatment of epilepsy.

Lesionectomy

If a lesion is identified that corresponds to the site from which seizures are arising then removal of the lesion may cure or markedly improve the severity of the seizures. This is the case with arteriovenous malformations, tumours and abscesses.

Anterior temporal lobectomy

Complex partial seizures most commonly arise from the anterior temporal lobe. If this can be confirmed on EEG and the side of the habitual seizure determined, then removal of that anterior temporal lobe or amygdalohippocampectomy may cure or markedly improve the severity of the seizure. For this to be effective and safe, strict selection criteria are necessary. The seizures must be truly intractable and causing disruption to the patient's life. They must originate in a well-circumscribed region of the brain that can be removed without producing a major neurological handicap. Localization of the origin of the seizures can be determined from the history, clinical features of the attack and neuroradiological and EEG data. Surface EEGs may show a localized abnormality but this may be misleading. For this reason more intensive forms of EEG monitoring employing special electrodes such as sphenoidal, foramen ovale or chronically implanted depth electrodes may be necessary to demonstrate the focus. Ideally both ictal and interictal recordings should be done. The most difficult patients to evaluate are those in whom there are bilateral independent foci demonstrated. Positron emission tomography (PET) or single photon emission computerized tomography (SPECT) may be helpful in demonstrating interictal hypometabolism at the site of the focus. Prior to surgery detailed neuropsychological assessment is necessary to determine laterality of speech, handedness, and memory function.

Hemispherectomy

Patients with dense hemiplegias and intractible epilepsy that is arising from the abnormal hemisphere may benefit markedly by removal of the abnormal hemisphere without significant deterioration in the degree of motor or intellectual function. Patients who may benefit from hemispherectomy are those with congenital or acquired hemiplegias and epilepsy, Sturge Weber syndrome and chronic focal encephalitis of Rasmussen.

Division of the corpus callosum

Division of the corpus callosum has been shown to be effective in suppressing drop attacks and other secondarily generalized seizures. The mode of action is not clear but the limitation of spread of the seizure discharge from one hemisphere to the other is a likely mechanism. Although various neuropsychological abnormalities can be demonstrated after corpus callosum section clinically significant problems are uncommon. The exact role of this procedure in the treatment of childhood epilepsy is not yet established. At present it is usually considered for intractable drop attacks, but it may also be of value in hemiplegic epilepsy where the hemiplegia is not dense and hemispherectomy therefore not indicated.

PROGNOSIS OF EPILEPSY

Mortality

There is an excess mortality for epileptic children. This has been estimated as 5% during the first 10 years after onset of seizures with a further 3% risk in the next 10 years. There is an increased risk in accidents such a drowning or falling and sudden unexplained death can occur.

Morbidity

The prognosis of epilepsy is measured in terms of continuing

Table 14.14 Reasons why epilepsy may be erroneously thought to be intractable

Incorrect diagnosis
Inappropriate treatment
Non-compliance
Inadequate trial of anticonvulsant
Drug induced seizures
Progressive disease
Psychosocial factors

seizures, social and emotional adjustment, educational attainment and employment prospects.

One of the most important prognostic indicators will be the type of epilepsy; a widely different prognosis may be expected, for example, between petit mal epilepsy and the Lennox Gastaut syndrome.

Studies which have looked at large populations have not separated different epileptic syndromes and have included both adults and children. Some generalizations however are possible.

Overall the likelihood of remission of seizures is between 50% and 70% (Annegers et al 1979, Sillanpaa 1983). There are a number of reasons why epilepsy may be thought to be intractable (Table 14.14). Most relapses will occur during withdrawal of therapy or in the first 1–2 years after stopping treatment.

Individual factors that indicate a high chance of remission are absence of neurological abnormalities or brain lesion, normal intelligence, onset of seizure after the age of 3–4 years, low seizure frequency, brief duration of epilepsy prior to control, generalized tonic clonic seizures, typical absence seizures or simple partial seizures, no episodes of status, normal EEG background and normalization of EEG after onset of therapy (Aicardi 1986).

Prognosis for cognitive function in epilepsy

In general the same factors that indicate a good prognosis for seizure control will indicate a good prognosis for educational and social outcome. Patients with epilepsy will tend to score slightly lower on IQ tests when compared with normal siblings; 50–70% of patients will have normal IQ.

Overall, IQ scores are misleading in that a much larger proportion of children with epilepsy have learning difficulties. A recent study demonstrated significant difficulties in reading, spelling and arithmetic in up to 30% of epileptic children with normal or low normal IQ (Seidenberg 1989). Some authors have suggested that the problems relate to abnormal activity in the dominant hemisphere and correlate with left sided spikes seen on the EEG. However, this has not been confirmed by others. The learning problem may be due to the same brain damage that causes the epilepsy but not a result of the seizures. Antiepileptic drugs themselves may affect learning, particularly chronic treatment with phenytoin, primidone or phenobarbitone.

Some patients appear to show decreasing IQ as their epilepsy continues. This has particularly been noted in the Lennox Gastaut syndrome but has been described in other children with epilepsy. The role of non-convulsive status epilepticus in the dementia that occurs in the Lennox Gastaut syndrome has been extensively discussed. An effect of chronic toxic levels of anticonvulsants has been suggested particularly with phenobarbitone (Bourgeois et al 1983).

Social and behavioural outcome

Around 20–30% of children with epilepsy will experience behavioural or psychiatric problems. The causes of this are many but important factors are the degree of seizure control, type of epilepsy, the use of polytherapy and the family response. This illustrates that the behavioural outcome is the complex interaction between biological and psychosocial factors (Hermann et al 1989).

The overall prognosis may be good for populations of children with epilepsy. A poor outcome is often associated with a constellation of several problems, i.e. low intelligence, poor control of seizures and behavioural abnormalities. For optimal management of chronic epilepsy therefore three main areas need to be evaluated each time the child is seen:

1. The medical aspects of the disease
2. The educational and social development of the child
3. The response and adjustment of the family to the child with epilepsy.

Collaboration therefore with many other professionals is essential, including psychologists, psychiatrists, social workers and teachers.

ACUTE ENCEPHALOPATHIES

DEFINITION AND CLASSIFICATION

Acute encephalopathy denotes a non-specific brain insult in a patient manifested by a combination of coma, seizures, decerebration and, less commonly, ataxia, hemiplegia or cardiorespiratory arrest. Coma and seizures may be seen as neurological complications of many children's diseases, for example scalds and burns (Emery & Reid 1962), cardiac bypass surgery (Seshia et al 1979), leukaemia (Hanefeld & Riehm 1980), hepatic failure in fibrocystic disease (Conomy & Swash 1968), diabetic ketoacidosis (Frier et al 1980), and coeliac and nephritic crises.

Acute encephalopathies may be classified as:

1. Anoxic ischaemic
2. Infectious and parainfectious
3. Haemorrhagic
4. Traumatic (accidental and non-accidental)
5. Toxic
   a. Exogenous
   b. Endogenous
6. Epileptic.

AETIOLOGY

Infection accounts for approximately one-third of cases presenting with acute encephalopathy and coma. The causes are seen in Table 14.15. Most organisms are capable of invading the nervous system (with the direct effects of cerebral oedema, cerebritis, encephalitis, cerebral congestion, hydrocephalus, subdural effusion and empyemas, ventriculitis, thrombophlebitis, and abscess), but encephalopathy may also result from the effects of extracranial infection by inappropriate ADH, inflammatory brain oedema, thrombophlebitis, status epilepticus, severe endotoxaemic shock and circulatory failure and DIC.

As an example, tuberculous meningitis may present as an acute hemiplegia resulting from vasculitis, or as an acute encephalopathy with raised intracranial pressure from acute ventricular dilatation or multiple tuberculomata.

Table 14.15 Causes of infectious encephalopathies

acterial or fungal meningitis/encephalitis
Cortical thrombophlebitis
Cerebral abscess (including immunocompromised patients)
Meningitis with septicaemia (*Meningococcus*/B haemolytic *Streptococcus*)
Viral encephalitis (e.g. herpes simplex encephalitis)
Parainfectious demyelinization
Subacute sclerosing panencephalitis (acute presentation)
Meningoencephalitis (protozoal, helminthic and rickettsial), e.g. *Toxoplasma*
Cerebral malaria
Acute disseminated encephalomyelitis

On some occasions multiple factors may contribute to the encephalopathy. An example is viral gastroenteritis which may cause a direct invasive encephalitis following viraemia (enteroviruses) or meningitis from systemic *Salmonella* infections. *Shigella* and *Campylobacter* may both secrete a neurotoxin which causes fits and coma and is therefore a true toxic encephalopathy. There may be accompanying dehydration and hyperviscosity with venous sludging and cerebral venous thrombosis adding to the problems of gastroenteritis. Additionally osmotic imbalance or biochemical disorders (e.g. hypocalcaemia) may also result in seizures. The haemolytic uraemic syndrome may have an associated encephalopathy as a result of disseminated intravascular coagulation affecting intracranial vessels.

Viruses may result in an acute encephalopathy by virtue of their neurotropic nature or they may attack specific parts of the central nervous or peripheral system, e.g. polio and the anterior horn cells, chicken-pox and the cerebellum or mumps and the aqueduct of Sylvius. Viruses may also produce an acute encephalitis or perivascular demyelination as a result of myelinoclastic antibodies produced by the leucocytes involved in perivascular cuffing.

A reversible encephalopathy from virus invasion of neurones may result in the the 'pyrexial convulsion syndrome'. Virus infection may also result in a catabolic stress and precipitation of inborn errors of metabolism such as maple syrup urine disease or Leigh's syndrome (from pyruvate decarboxylase deficiency), biotinidase deficiency, cytochrome oxidase deficiency, or other complex mitochondrial cytopathies.

Hypoxic ischaemia

This is a common and frequently irremediable cause of acute encephalophathy. The pathogenesis of hypoxic ischaemic injury begins with hypoxia followed by a build up of $PaCO_2$, lactic acid, and a decreased pH. There follows a two-pronged insult:

1. To the brain cell membrane with inhibition of membrane ion pumps, resulting in accumulation of extracellular K^+ and intracellular Na^+ and Ca^{2+} and in depletion of ATP and phosphocreatine. The result is a cytotoxic oedema which contributes to the raised intracranial pressure and infarction.
2. To the cardiac muscle (as well as lung, liver, kidneys and gut) with a resultant systemic pressure failure below the limits of cerebrovascular autoregulation. This results in failure of cerebral perfusion and infarction. The low systemic pressure additionally adds a degree of vasogenic brain oedema.

Table 14.16 Hypoxic–ischaemic causes of acute encephalopathy

Perinatal asphyxia
Pulmonary disease (upper airways obstruction, laryngeal TB, epiglottitis)
Alveolar hypoventilation
CO poisoning
Methaemoglobinaemia
Anaemia
Status epilepticus
Near miss SIDS
Post cardiac arrest (any cause)
Cardiac bypass surgery
Near drowning
Cardiac dysrhythmia
Congestive cardiac failure
Hypotension
Disseminated intravascular coagulation
Hypoglycaemia
Vitamin or cofactor deficiency (B_{12}, B_6, folate etc.)
Anaesthetic accidents

The brain is able to withstand hypoxia without ischaemia (for example cyanotic congenital heart disease) but is especially sensitive to ischaemia. In hypoxia alone there is reversion to anaerobic metabolism with glucose converted to lactate and pyruvate. If the circulation is intact these metabolites are removed and later converted back to glucose in the liver when oxygen becomes available. With ischaemia (for example from raised intracranial pressure and reduced cerebral perfusion pressure), especially if there is plentiful glucose, glycolysis continues with an accumulation of lactate which is not cleared and causes intracellular acidosis. This prevents enzyme action and causes the lysosomes to rupture. Although status epilepticus is considered a separate cause of encephalopathies, the end result of uncontrolled and decompensated status epilepticus is cerebral oedema and hypoxic ischaemic injury with depleted ATP and PCr and increased lactate, and diminished cerebral blood flow. The hypoxic ischaemic causes of encephalopathy and coma are seen in Table 14.16.

Toxic and metabolic disorders

These may result in an exogenous or endogenous encephalopathy. The exogenous causes are seen in Table 14.17. Occasionally these may be non-accidentally delivered as part of the Munchausen's syndrome by proxy (Meadow 1977). Endogenous sources of toxins include liver and renal failure, carbon dioxide narcosis, and other causes seen in Table, 14.18.

Non-traumatic intracranial haemorrhage

This may be responsible for an acute encephalopathy, for example haemorrhage into a benign astrocytic cyst. Other causes are listed in Table 14.19.

Table 14.17 Causes of toxic encephalopathy (exogenous)

Amines
Anticholinergics
Anticonvulsants
Antidepressants (tricyclics and phenothiazines)
Antimetabolites (vincristine, cyclophosphamide, methotrexate, asparaginase, vinblastine, cranial irradiation, cytosine arabinoside)
Hypnotics and analgesics (barbiturates, paracetamol, benzodiazepines and salicylates)
Antibiotics (penicillin, nalidixic acid)
Anti-inflammatory agents (steroids, cimetadine)
Abused drugs (alcohol, solvents, amphetamines etc.)
Environmental toxins (H_2S, CO, phosphates, DDT, iron, lead, hexachlorophane, aflatoxin, venoms, insecticides/pesticides, plants and minerals, heavy metals, hypothermia and heat stroke)

Table 14.18 Endogenous causes of acute encephalopathy

1. Fluid balance	—	Water intoxication Hypo- or hypernatraemia Hypo- or hypermagnesaemia Hypo- or hypercalcaemia Hypo- or hyperphosphataemia Acidosis/alkalosis Trace metal deficiency Scalds
2. Endocrine	—	Diabetes mellitus/hypoglycaemia Hypo- or hyperthyroidism Hypo- or hyperparathyroidism Hypopituitarism Hyperbilirubinaemia
3. Organ failure	—	Liver Kidneys Pancreas Intestinal/volvulus Hypertensive encephalopathy
4. Inborn errors of metabolism	—	Aminoacidopathies — branched chain ketoacidosis Organic acidaemia — propyl, malonyl, isovaleric and betaketothiolase Galactosaemia Urea cycle defects Carnitine deficiency Porphyria Medium chain acyl dehydrogenase deficiency

Table 14.19 Intracranial haemorrhage

Arteriovenous malformation
Ruptured aneurysm
Arteriovenous occlusion — thrombotic or traumatic a. Infection (focal or widespread) b. Cardiac c. Haemotological (sickle cell, polycythaemia or idiopathic thrombocytopenic purpura) d. Collagen (lupus erythematosus) e. Metabolic (diabetes mellitus) f. Moya moya
Intracranial venous thrombosis which may be sterile or secondary to thrombophlebitis

Trauma

Trauma may be accidental or non-accidental. Accidental head injury is discussed elsewhere (pp. 905–910). The young child who presents with an acute encephalopathy with retinal haemorrhages but little evidence of external trauma should be suspected of having had a 'whiplash shaking injury' (disciplinary injury). The shaking, with rotation of the head, results in subdural and petechial brain haemorrhages, cerebral oedema and retinal haemorrhages.

INVESTIGATION OF COMA

After the initial resuscitation of the cardiovascular and respiratory system and treatment of seizures, after a history has been obtained of the events leading to the coma, and after an examination of the child, the clinician's approach to investigating the comatose child is twofold. First, investigations are aimed at making a diagnosis (Table 14.20) and second, supportive investigations are necessary regardless of the aetiology (Table 14.21). The coma state will require monitoring itself. Initially one of the coma scales is used, such as the original Glasgow coma scale (Table 14.22) (Teasdale & Jennett 1974), or the modified Glasgow coma scale (Table 14.22) (Jennett et al 1977). Alternatives are the Adelaide scale (Simpson & Reilly 1982), the 0–IV scale (Huttenlocher 1972, Seshia et al 1977) (Table 14.22), the 'Jacobi scale' (Gordon et al 1983), the children's coma scale (Raimondi & Hirschauser 1984), and the children's orthopaedic hospital and medical centre scale (Morray et al 1984). We favour the Adelaide scale and the 0–IV scale, but once the patient is paralysed and ventilated, all scales are insufficient for following the progress of coma, and the coma state then needs monitoring by means of:

1. Occular examination (pupils, eye movements, etc.)
2. Bulbar reflexes
3. Temperature, pulse rate, respiratory rate and blood pressure.

MANAGEMENT

Whatever the cause of the encephalopathy, there are common factors responsible for the mortality and morbidity. These have led

Table 14.20 Strategy for coma management: diagnostic investigations

Obvious causes	Non-obvious causes
Hypoxic ischaemic	CT–ultrasound
Diabetic ketoacidosis	LP (incl. immunofluorescence etc.)
Poisoning	EEG
Infections	Toxicology (barbituates, toluene, benzodiazepines, salicylates, iron, lead, anticonvulsants, antidepressants)
Drowning	
Burns/scalds	Metabolic (NH_3, LFTs, porphyrins, amino acids, dicarboxylic acids, urine sugars, lactate/pyruvate/acidosis, urea/creatinine, calcium, T_4/TSH)
CVA	Tuberculin test
	Virology
	Technetium scan
	X-rays (skull, skeletal)
	Brain biopsy

Table 14.21 Strategy for coma management: supportive investigations (independent of cause of coma)

* Gases (4 hourly)
* Pulse oximeter (O_2 sat.)
CVP −/+ Wedge
* Dextrostix (4 hourly)
* Osmolality (8 hourly)
* Calcium and phosphate (bd)
EEG (continuous)
ICP/CPP (continuous) (mean pressure, pulse pressure, periodic waves)
* BP arterial (continuous)
Coagulation (once then prn)
* Temperature
* Fluid balance (vs output, weight, labstix)
* Blood count and haemoglobin
* CXR (portable)
Weight
Anticonvulsant levels
* ECG (continuous)
* Urea and electrolytes (twice daily)
* Infection screen
Visual evoked potentials
Brain stem evoked potentials
Liver function tests (once/day)
Arteriovenous oxygen difference or jugular venous oxygen saturation
Cerebral blood flow (initial + change) (autoregulation, CO_2 respiration and perfusion)
Cerebral blood flow velocity (continuous, intermittent daily)
Monitoring neurology and coma state
1. Glasgow coma scale
2. Ocular (pupils, external ocular movements, etc.)
3. Bulbar reflexes
4. Temperature, pulse rate, respiratory rate and blood pressure

* All coma regardless of cause.

:o a philosophy of management of 'treating the treatable' which ncludes:

1. Treatment of infection
2. Control of seizures
3. Detection and treatment of raised intracranial pressure (maintenance of cerebral metabolism and blood flow)
4. Maintenance of homeostasis
5. Removal of circulating toxins.

·eatment of infection

The treatment of bacterial meningitis, cerebritis, encephalitis and hrombophlebitis is appropriate high dose intravenous antibiotic herapy or, in the case of herpes simplex encephalitis, acyclovir.

The cytological technique of cyctocentrifugation and millipore ilter collection of cells has improved the identification of cell ypes in the CSF. The technique is useful in CNS leukaemia, as well as in acute and chronic spinal meningitis (Kontopolous et al 1986). It is particularly useful in cases of mild CSF pleocytosis. There is a significant discordance between lymphocytes and macrophages in the CSF and the ability to recognize the recovery phase of pyogenic CSF infection, by an increased macrophage count, is useful while treating meningitis or ventriculitis.

Antibiotics vary in their ability to penetrate the CSF. Antituberculous drugs penetrate well but the aminoglycosides as a group show very poor CSF penetration and need to be given intrathecally. Intrathecal therapy may also be necessary in cases of pneumococcal infection and cases of pyogenic meningitis with loculation of CSF. If intrathecal therapy is used then it is important to monitor the CSF levels of antibiotic as well as the cell count. Antibiotic serum levels should also be routinely monitored. Low 'peak levels' of antibiotic indicate that the frequency of administration needs to be increased while low trough levels indicate that the dose should be increased. It is important to ensure the antibiotic is instilled at the appropriate locus to be effective, as antibiotics injected into the lumbar CSF may not reach the basal cisterns if there is loculation, and very little will reflux back into the ventricles. In such situations a ventriculostomy reservoir may usefully be inserted for administration of the antibiotics.

In the case of tuberculous meningitis with coma the ideal management is first to obtain a CT scan, and since tuberculous meningitis is frequently accompanied by an acute hydrocephalus in children, this is followed by the insertion of a ventriculostomy reservoir into the frontal horn of the right lateral ventricle. The intracranial pressure is then measured and relief of the supratentorial pressure obtained by removal of CSF. With the intracranial pressure normal, a lumbar puncture is performed for lumbar CSF collection. The spinal meningitis is not necessarily accompanied by an increased cell count in the ventricular CSF. Persistent raised intracranial pressure needs to be treated by tapping the reservoir or by external drainage from the reservoir while at the same time sterilizing the CSF with the appropriate antituberculous medication.

Control of seizures

It is important to control seizures to prevent secondary hypoxic ischaemic damage and routine EEG monitoring (preferably continuous display) should be carried out. A single fit during an acute encephalopathy requires only short-term prophylactic anticonvulsants. Phenytoin is the anticonvulsant of choice. For epileptic encephalopathy, intravenous diazepam and intravenous mannitol with or without paraldehyde may be required.

Paraldehyde can be given in modern 'plasti-pak' syringes. It is usually given intramuscularly in a dose of 0.05 ml/kg or 1 ml/year of age. The half-life is approximately 6 h (range 6–9 h). It can in an urgent situation be given intravenously, but is not routinely recommended. The dose should be reduced in the presence of hepatic or pulmonary disease. Much care is needed with intravenous injections because of serious hepatic necrosis or pulmonary haemorrhage which may result. The rectal route is a satisfactory alternative, if given in a 10% solution with normal saline or mixed with equal quantities of oil. The dose of the 10% solution is 0.5 ml/kg. Estimation of blood levels of paraldehyde can be performed in some laboratories and the therapeutic range is 300–400 mg/ml (Curless et al 1983).

Intravenous phenytoin may be given as a 'slow epinutinization' or 'rapid epinutinization' regimen. For encephalopathies the rapid

Table 14.22 Coma scales for use in children

0–IV Scale (Seshia et al 1977, Huttenlocher 1972)	Children <5 years (Simpson & Reilly 1982)	
0 — Arouses spontaneously and to stimuli	Eye opening	— 4 (same) — 3 — 2 — 1
I — Stuperose. Spontaneous arousal rare. Roused readily but briefly by stimuli. Cough/gag present	Verbal response	— 5 oriented — 4 words — 3 vocal sounds — 2 cries — 1 nil
II — Spontaneous arousal absent. Semipurposive/avoidance motor response to stimuli. Cough/gag depressed	Motor response	— 5 (same) — 4 — 3 — 2 — 1
III — Arousal in form of motor response only to intense, sustained, painful stimuli. Cough/gag absent	(Normal developmental milestones taken into account)	
IV — Not aroused even by intense/sustained painful stimuli. Cough/gag absent	0–6 months	9 points
	>6–12 months	11 points
	>1–2 years	12 points
	>2–5 years	13 points
	>5 years	14 points

regime is required — 10 mg/kg intravenously slowly at a rate of 10 mg/min, followed 1 h later by 5 mg/kg with a further 10 mg/kg in divided doses over the next 24 h. The blood level must be measured daily and maintained in a therapeutic range. In the newborn there is a large dose range (between 2 and 25 mg/kg) and blood level should be regularly checked. The dose required may change acutely in the second week of life. At high doses phenytoin may become epileptogenic and produce seizures which are resistant to benzodiazepines and paraldehyde. Prolonged thiopentone or chlormethiazole may result in enzyme induction and low phenytoin levels. The commonest reason for failure to control seizures in acute encephalopathy is failure to achieve adequate plasma concentrations of the drug.

Diazepam is useful to control seizures in the acute presentation of encephalopathies although some children may be diazepam resistant and have an exacerbation of seizure activity. With continuous EEG monitoring the benzodiazepine sensitivity can be readily assessed. There is a slight cerebral vasoconstrictor effect and therefore intracranial pressure is lowered. Following the first dose, if the fits have not ceased and provided the pupils have not dilated and blood pressure has not dropped, and the child is not benzodiazepine resistant, it may be repeated. The intravenous preparation should not be diluted for injection or a white precipitate may form in the mixture, which is irritant. It should not be mixed with other drugs and should be injected at a rate of 1 mg/min. Fast injection may cause apnoea or laryngeal spasm and hypotension. Other benzediazapines, such as clonazepam, are more likely to produce hypotension and bronchorrhoea. Peak brain levels of diazepam occur 1 min after injection but the drug leaves the brain rapidly and fits may recur after 20 min. The dose is 0.25–0.4 mg/kg (age in years plus 1). An intravenous infusion is possible for those cases responsive to diazepam.

Lignocaine, thiopentone and chlormethiazole are other alternative anticonvulsants for use with encephalopathies. With thiopentone the aim is to stop seizures and not to produce anaesthesia. One gram is dissolved in 500 ml of normal saline and the infusion is commenced at 5 ml/kg i.v. infused to keep the patient awake but seizure free.

The concentrations in the bottle may be reduced and the patient is weaned off 24 h after the last fit. Apnoea, hypotension and laryngospasm may all occur from fast infusion.

Detection of raised intracranial pressure

The methods and sites for monitoring the intracranial pressure are seen in Table 14.23 (Minns 1990). In children with encephalopathies, the preferred method of monitoring the intracranial pressure will depend on whether ventricular dilatation

Table 14.23 Sites for ICP monitoring

Ventricle	Catheter (percutaneous through the anterior fontanelle) Catheter (via burr hole) Reservoir Transducer (camino) Telemetry (± inline with shunt)
Subarachnoid (and subdural)	Bolt (Beeds, Richmond, Newell, Philly, Bolt) Catheter (cordis via burr hole) Catheter (Teflon via anterior fontanelle) Transducer (catheter tipped-gaeltec ICTb) Transducer (miniaturized, fitment to burr hole) Lumbar space (at LP or cannula)
Extradural	Catheter tip transducers Transducer (similar to subdural) Sensors (Ladd)
Brain parenchyma	Fibreoptic transducer (brain tissue pressure)
Fontanelle	Fontanometers (aplanation especially pneumatic)
Tympanic membrane	Impedance test of tympanic membrane tension

is present or whether the ventricles are small and shifted as a result of the brain swelling.

For the infant with a patent anterior fontanelle, and with ventricular dilatation, the ventricles can be punctured percutaneously. If ICP monitoring is needed continuously for long periods, then a ventriculostomy reservoir is neurosurgically inserted or a ventricular transducer placed in situ. For the infant with cerebral oedema it is possible to continuously monitor the intracranial pressure by the use of a subdural or subarachnoid Teflon catheter placed percutaneously through the anterior fontanelle. A ventricular transducer may be inserted which will record either the ventricular pressure or if not in the ventricle the brain parenchymal pressure. For the older child with acute ventricular dilatation it is Edinburgh practice to insert a ventriculostomy reservoir or, in the oedematous brain, to monitor the intracranial pressure from the brain surface by means of a 'Cordis fluid filled catheter' coupled to a pressure transducer.

Intracranial pressure

A common factor in children with encephalopathies and cerebral oedema is the secondary brain shifts which cause ischaemic brain damage. These are responsible for the mortality and the morbidity. They come about by a critical reduction in the vascular perfusion pressure to the brain produced usually by an increase in intracranial pressure.

Because of the need to compare the intracranial pressure with arterial blood pressure the same units of measurement are usually used. These are mm of mercury (1 mmHg = 1.36 cm of water) or if SI units are used ICP is expressed as kilopascals (1 kPa = 7.5 mmHg). The normal ICP in adults is 0–15 mmHg (0–2 kPa). In children the upper limit of normal ICP is lower and for the newborn levels should not be in excess of 3.5 mmHg, for the older infant 5.5 mmHg, and for the toddler 6.5 mmHg (Minns et al 1989).

Brief rises in the intracranial pressure may occur during coughing, straining, and crying, as well as other physiological activities that increase the central venous pressure. Sustained elevations or intermittent rises in pressure in the form of pressure waves may also occur (Fig. 14.28). Several wave forms have been described including the 'A' waves or plateau waves which show a rapid rise in ICP to 50 mmHg or more which last from 5 to 20 min. The second common type is the 'B' wave which consists of a series of sharply peaked waves lasting 30 s to 2 min. Both are thought to result from cerebral vasodilatation. In the 'A' waves this occurs against a background of reduced craniospinal compliance in which small increments of volume result in large increases in pressure. 'B' waves, on the other hand, may result from fluctuations in the cerebral vascular dimensions corresponding to alterations in arterial CO_2 tension. The third type of abnormal ICP wave form is the 'C' wave which consists of rapid sinusoidal fluctuations of about 6 per min corresponding to the Traube–Hering–Mayer fluctuations in the systemic arterial tree.

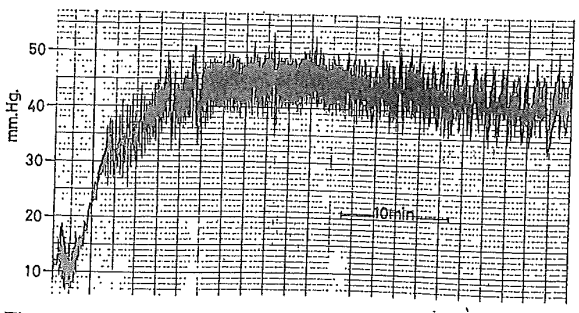

Fig. 14.28 Plateau or A-wave indicating reduced cerebral compliance in the presence of intact cerebrovascular autoregulation (mmHg = ventricular CSF pressure).

Table 14.24 Clinical features of brain herniations

Tentorial
Sunsetting
Dilated pupils
VI nerve palsy
Cortical blindness
Hemiplegia
Extensor motor pattern (decerebrate)
Coma
Respiratory irregularity
Systemic hypertension
Tonic seizures
Cingulate gyrus herniation
Diplegia or hemiplegia
Visual symptoms
Foramen magnum cone
Cardiorespiratory arrest
Bulbar palsy
Neck stiffness
Hypotonia
Stridor
Spinal flexion
Hypotension
Hyperthermia

An increase in the intracranial pressure may come about as a result of increasing either the brain, blood or CSF contents of the skull. The actual increases in ICP that result from a given increment in volume will depend on the intracranial pressure–volume status. Miller & Leech (1975) described the pressure–volume response (PVR) as an increase in ICP in mmHg/ml of CSF volume added or withdrawn in 1 s. Normal values were 0–2 mmHg/ml; values of 3 mmHg or more at baseline ICP levels indicated reduced craniospinal compliance (or increased elastance). Marmarov et al (1975) defined a pressure–volume index (PVI) as a volume which if added to the CSF would produce a 10-fold increase in the intracranial pressure. The normal range of PVI in an adult is 25–30 ml. In a child it is from 12 to 25 ml.

As a result of the increased intracranial pressure in encephalopathies with cerebral oedema, and because the brain is virtually incompressible, there is a resultant brain shift. The cingulate gyrus herniates under the lower margin of the falx as the midline is shifted. The medial part of the temporal lobe also herniates through the tentorial hiatus between the free edge of the tentorium and the mid-brain. At the same time the brain stem is shifted downward to the foramen magnum which tends to cut off the blood supply to the stem from the perforating branches of the basilar artery and this results in ischaemia. The signs of a cingulate gyrus herniation, tentorial herniation and foramen magnum cone are seen in Table 14.24.

Cerebral perfusion pressure

With increasing ICP there is an increase in the cerebral venous

re. This remains about 3 mmHg below the ICP so that cerebral circulation continues. The cerebral perfusion pressure is defined as the difference between the mean systemic arterial pressure (SAP) and intracranial pressure (ICP), i.e. CPP = mean SAP — ICP.

The relationship between intracranial pressure and cerebral perfusion pressure is complex. Raised intracranial pressure may be caused by an increase in cerebral blood flow or it may be the limiting factor producing a reduction in cerebral blood flow. In encephalopathies the brain is frequently pale and devoid of blood flow as a result of the raised intracranial pressure producing ischaemia. A cerebral perfusion pressure of 60–70 mmHg is normal and there is a progressive fall in perfusion to the brain with decreasing cerebral perfusion pressures down to 40 mmHg. Below this there is an absolute fall in the brain perfusion and levels of less than 18–20 ml/100 g of brain per min will result in ischaemic infarction.

Cerebral blood flow

The earliest measurements of blood flow involved the Fick principle with a method which involved inhalation of a metabolically inert gas that diffused freely in and out of brain tissue. The normal value in man is 50 ml/100 g per min. The normal cerebral arteriovenous oxygen content difference is 6 ml/100 ml of blood and therefore the normal cerebral oxygen uptake rate is 3 ml oxygen/100 g per min. Methods of measuring the cerebral blood flow are listed in Table 14.25. There is ordinarily coupling between cerebral blood flow and brain metabolism but in coma the cerebral metabolic rate consuming oxygen falls as well as the cerebral blood flow.

The determinant of cerebral blood flow is the arterial $PaCO_2$ level. Increases in the arterial $PaCO_2$ increase the cerebral blood flow and a fall in arterial $PaCO_2$ reduces the cerebral blood flow due to cerebral vasoconstriction. Changes in cerebral blood flow cause changes in the cerebral blood volume and this influences the ICP. Inducing hypocapnia by hyperventilation the ICP can be reduced (if the raised ICP had been due to cerebral vasodilatation). If, however, the cerebral blood flow is already low from cerebral oedema then hyperventilation will result in worsening ischaemia. CO_2 responsiveness may be lost globally or regionally.

The cerebral blood flow remains constant over an arterial pressure level of 60–140 mmHg in normal adults. With low systemic arterial pressures, below the limits of cerebrovascular autoregulation there is a fall in cerebral blood flow and with blood pressure rises above 140 mmHg there is a breakthrough of autoregulation (break point) with progressive cerebral oedema. Autoregulation, therefore, can be defined as a maintenance of the cerebral blood flow by alteration of the cerebral blood volume in response to large changes (increases or decreases) in the systemic perfusion pressure. Autoregulation can also be lost globally or regionally.

Table 14.25 Methods of measuring blood flow, velocity or perfusion

1. Flow meter
2. Electrical impedance
3. Doppler ultrasound
4. Magnetic resonance imaging
5. Single photon emission computerized tomography
6. Positron emission tomography
7. First pass (MTT)

Treatment of raised intracranial pressure

Removal of CSF is possible if a ventricular cannula is in situ but this is not always possible with small shifted ventricles and cerebral oedema. Despite this, for some conditions such as tuberculous meningitis this may be the optimal method of managing the raised intracranial pressure.

Steroids have a number of important actions on the brain — an immunosuppressant effect, an anti-inflammatory effect, and the reduction in CSF formation. The main actions are to tighten the endothelial junctions of the blood–brain barrier, stabilization of lysosomal activity, and restoration of the microcirculation. Other actions include inhibition of the release of free radicals, fatty acids, prostaglandins, and the products of catecholamine metabolism. Steroids also cause glial uptake and transcapillary efflux of water with resolution of oedema. Steroids cross the blood–brain barrier to reach neuronal receptor sites. There is an additional direct effect on cerebral metabolism with increased neuronal function and stimulation of glucose consumption.

Steroids are of little use in controlling the raised intracranial pressure in Reye's syndrome. They are most useful in reducing the perifocal oedema surrounding mass lesions. They may be positively harmful in hypoxic ischaemic brain damage and their use in herpes simplex encephalitis is debatable. Mannitol in combination with dexamethazone will prevent the unwanted escape of mannitol across the blood–brain barrier. Mannitol reduces brain water by controlled hyperosmolar dehydration, it reduces blood viscosity, and increases cerebral vasoconstriction (the cerebral blood flow remains normal while the cerebral blood volume is decreased). Mannitol also scavenges free radicals. If mannitol and frusemide are used together, the circulating volume is decreased and, depending on the central venous pressure, volume expansion may be necessary. Mannitol is given in a dose of 7 ml/kg of a 20% solution or 0.21 g/kg per dose.

Hyperventilation should not be used prophylactically in encephalopathies to control raised intracranial pressure. Its use should be restricted to episodic increases in intracranial pressure because the cerebral vasoconstriction, changes in pH, bicarbonate, and CO_2 reactivity are not maintained if hyperventilation is continued for longer than 24 h. Prolonged hyperventilation can lead to ischaemia. During episodes of raised intracranial pressure the $PaCO_2$ level should be reduced no lower than 3–3.5 kPa.

Barbiturates produce a concomitant reduction in the cerebral metabolic rate and cerebral blood flow. Their use is restricted to those patients unresponsive to mannitol, hyperventilation and steroids. It is important to carefully monitor the systemic blood pressure during their use for fear of reducing the cerebral perfusion pressure.

Other measures, such as decompression craniotomy or hypothermia, have some support in some units but, as with barbiturates, their use where first line methods have failed is less likely to be successful.

CEREBROVASCULAR DISEASE AND MIGRAINE

Intracranial and intracerebral haemorrhage is a common problem at the extremes of life in the neonatal period and in old age. In the postneonatal period the commonest cause of intracranial

haemorrhage is head trauma and this is considered on page 905. Cerebrovascular disease presenting as either stroke or an acute intracerebral haemorrhage is relatively rare and affects only about two per 100 000 of the childhood population. Intracranial haemorrhage is usually either subarachnoid or intracerebral with subdural bleeding being extremely rare other than from trauma. Infarction of the brain may result from many causes and may be due to vascular thrombosis, cerebral embolism, watershed zone lesion infarction, vascular compression or vascular injury.

The presentation is usually that of acute hemiplegia with a stroke, or sudden onset headache and vomiting with meningism or coma.

In 27 cases of intracerebral haemorrhage presenting after the neonatal period arteriovenous malformations were responsible for haemorrhage in 37% and aneurysm in 11%. Haemophilia and coagulopathies result in individual cases. Hypertension is a rare cause of primary intracerebral haemorrhage in children but haemorrhage into a tumour, particularly cerebellar astrocytomas, is responsible for 20% of cases. This may be the presenting feature so that haemorrhage into a benign astrocytic cyst may mask the underlying neoplasm.

INTRACRANIAL HAEMORRHAGE

Subarachnoid haemorrhage

Subarachnoid haemorrhage is most commonly due to a bleed from an arteriovenous malformation or an aneurysm. It presents classically in the older child with sudden onset of headache, vomiting, loss of consciousness with bilateral sixth nerve palsy, and possibly hyloid haemorrhages in the fundus.

Although diagnosis rests on finding blood stained CSF on lumbar puncture it should be stressed that lumbar puncture should never be performed on a child presenting with decreased conscious level without a prior CT scan. Since computerized tomograms are the most useful way now of diagnosing subarachnoid haemorrhage in most cases one can demonstrate the bleed on the scan without the need for a lumbar puncture. Only very small leaks may not show enough change in the density pattern of the CSF to be picked up on a CT scan and lumbar puncture is then necessary.

The CSF is found to be blood stained and after 6 h xanthochromia appears, the red cells are crenated and if there is any doubt as to whether one is dealing with a true subarachnoid haemorrhage or a traumatic puncture then spectrophotometry of the fluid is indicated. This will show a bilirubin peak together with haemoglobin in a true subarachnoid haemorrhage whilst the oxyhaemoglobin peak will predominate in a traumatic tap. There are still cases of subarachnoid haemorrhage in children missed with label of traumatic lumbar puncture who then have a fatal second bleed before the diagnosis is established.

In addition to arteriovenous malformations and aneurysm one can have the presentation of subarachnoid haemorrhage or a primary intraventricular haemorrhage such as haemorrhagic disease of the newborn, thrombocytopenia and rarely haemophilia secondary to bleeding from a coagulation disorder. Subarachnoid bleeding may also be prominent in non-accidental shaking injury.

Cerebral aneurysms

These are usually of the berry or saccular type but fusiform aneurysms can occur when there is a uniform dilatation of the blood vessel with a mycotic basis.

Aneurysms may occasionally be familial. Mycotic aneurysms secondary to bacterial endocarditis should be borne in mind, and a complete examination inclusive of the cardiovascular system is always mandatory. Aneurysms are associated with coarctation of the aorta, associated with Ehlers Danlos syndrome, polycystic disease of the kidneys and occasionally with abnormalities of the cerebral vessels themselves, such as a common trunk anterior cerebral artery with aneurysm of the pericallosal vessels. Vasculopathies occur in pseudoxanthoma elasticum. Although Kawasaki disease is associated with a vasculopathy and secondary aneurysm formation in the heart it is a very rare cause of cerebral aneurysms.

Between 1% and 3% of all aneurysms occur in children. They tend to occur under 2 years or over 10 years of age. In 23 aneurysms described by Heiskenen (1989), 10 were at the carotid bifurcation and 8 on the anterior communicating artery. Those on the middle cerebral artery are often on the distal part of the vessel.

Diagnosis is nearly always because of presentation with a subarachnoid haemorrhage. Occasionally calcification in an aneurysm is seen on a plain skull film. Local pressure on the third nerve presenting as an isolated third nerve palsy or on the hypothalamus with diabetes insipidus can occur but is unusual. The bleeding may occasionally be intracerebral as well as subarachnoid.

Bleeding into the subarachnoid space results in intense vasospasm which can itself result in secondary cerebral infarction. Occasionally posterior fossa aneurysms of the basilar artery or posterior inferior cerebellar artery occur in children and are more common in children than adults. Multiple aneurysms are rare, but in very young children under 2 years of age the aneurysms may reach quite a large size.

Arteriovenous malformation

These are of several types.

The capillary or telangiectasia type of capillary haemangioma. Characteristic of the Sturge Weber syndrome. Although this lesion may be extensive it rarely bleeds. Rarely as a result of status epilepticus it may thrombose and so cause infarction of the hemisphere with onset of a hemiplegia. This type of lesion has no large feeding vessels and may not show at all on angiography, but is shown well on isotope scan or MRI imaging.

Cavernous haemangiomas. These occur particularly in the neonatal period and may be part of a syndrome of multiple haemangiomas. They have small feeding vessels but large blood filled sinusoids reaching 1 mm in diameter which form a honeycomb (Herter et al 1988). There may be a familial occurrence of haemangiomas or blood vessel abnormalities elsewhere such as the eye, skin or viscera. These lesions have no capsule but have well-defined limits. They are not invasive and do not metastasize. They behave as hamartomas and may grow with the child so that presentation may be of a space occupying lesion with headache, focal signs and raised intracranial pressure with papilloedema as well as with the classical features of haemorrhage, which may be intracerebral, subarachnoid or intraventricular. Fits are often a symptom before a bleed occurs. Seventy-five per cent are supratentorial and 25% infratentorial, and they are most common in the territory of the middle cerebral artery.

When removed at surgery nearly all show evidence of repeated

small bleeds with haemosiderin deposits and cyst formation so that recurrent small bleeds may herald a large bleed. CT scan shows a hypo- or hyperdense area. Angiography may not show the lesion because of stagnation with little flow and because the feeding vessels are small unlike the commoner arteriovenous malformation — see below (Suarez & Viano 1989).

Venous arteriovenous malformations. These usually constitute an abnormal plexus of veins at the base of the brain which may form one large sinus such as an aneurysm of the vein of Galen. The blood flow in this type of malformation may be torrential so that the child presents with a large head, hydrocephalus, a loud bruit and high output heart failure.

Arteriovenous fistulae. These are the more common type of arteriovenous malformation and consist of a direct arterial to venous connection with no capillary between. They usually have large feeding vessels, they are usually unilateral and occur more in males than females. More than 50% are in the parietal area with the frontal lobe and basal ganglia next in frequency. They may occur in the posterior fossa or brain stem. Presentation is by fits or a sudden subarachnoid and intracerebral bleed. An intracranial bruit is not a reliable sign as it may be absent in the presence of large arteriovenous malformations. A loud bruit may be heard in the head of normal children and any cause of a rise in intracranial pressure results in a systolic bruit over the fontanelle and orbits. Diagnosis is by CT scan and angiography which will demonstrate the extent of the abnormality and the feeding vessels. If the child presents with fits there is a 25% chance of a bleed during childhood, and the mortality if a bleed occurs is between 10% and 20% so that treatment is always warranted. Even without seizures the presence of an arteriovenous malformation means that there is a 2–3% chance per year of a bleed. The mortality from surgery is thought to be less than 2% (Fong & Chan 1988).

Management of intracranial haemorrhage

1. Hypertension should be avoided and if present treated.
2. Straining at stool and anything producing a Valsalva manoeuvre should be avoided.
3. There should be bed rest with no exercise.
4. Sedation with diazepam is useful and an anti-emetic should be given if vomiting is occurring.
5. Analgesia is important for the headache.
6. Control of seizures with intravenous phenytoin may be indicated.
7. Monitoring of intracranial pressure is performed in almost all neurosurgical centres.
8. The use of anti-fibrinolytic agents is not recommended in children.
9. Surgery: in children who present with a subarachnoid or intracerebral bleed due to an aneurysm or arteriovenous malformation surgery is the management of choice. If the child is in coma, if angiography shows the aneurysm is fusiform or if there is any question of a mycotic aneurysm then conservative medical management is indicated. In the case of berry aneurysms surgery should be carried out preferably within the first week using microsurgical techniques in order to get a clip round the neck of the sac. If it is impossible to clip the base of the aneurysm then it is sometimes wrapped or the feeding vessel itself is clipped. Arteriovenous malformations or large fusiform aneurysms may nowadays be treated by inserting a balloon catheter into the feeding vessel and embolizing it or occluding it using a detachable balloon or a suitable glue.

The prognosis overall for cerebral haemorrhage in childhood is poor with a 54% mortality. Aneurysms presenting with subarachnoid haemorrhage without intracerebral extension carry a 30% mortality (Livingston & Brown 1986, Heiskenin 1989).

Stroke in childhood

An acute cerebrovascular accident may be caused by a sudden intracerebral haemorrhage as already discussed but more frequently may be the result of a vascular occlusion (Wanifuchi et al 1988, Roach & Riela 1988). The causes of acquired hemiplegia can be discussed under several headings.

Vascular lesions

The vessels in the neck can be traumatized at birth, by blows on the shoulder, accidental hanging, following puncture at angiography or by falls on objects, e.g. a pencil in the mouth which penetrates the tonsillar fossa. In these cases there is often an interval between the injury and onset of hemiplegia probably due to formation of a thrombus at the site of the trauma which eventually loosens and becomes a cerebral embolus. In some cases when the child falls on an object in the mouth, the tear of the vessel wall causes a dissecting aneurysm to form and secondary occlusion may then follow.

Roughened areas of endothelium may be seen on angiography of the internal carotid artery in the tonsillar fossa. It is postulated that arteritis secondary to adjacent tonsilitis roughens the endothelium allowing platelet adhesion and subsequent embolization.

The carotid artery can occasionally be elongated into redundant loops and these may kink with neck movement.

Arteritis due to immune mechanisms is rare in childhood but large vessels are involved in Takayasu's disease, polyarteritis, and in disseminated lupus erythematosus. The vessels are abnormal in Menkes disease which along with homocystinuria and Fabry's disease represent metabolic diseases which can present with cerebrovascular accidents. Certain of the mitochondrial disorders may also present with seizures and stroke (e.g. Melas syndrome). Moya moya is the name given to a peculiar leash of small vessels which is seen on angiography in children who have sustained a stroke. This is said to resemble a puff of smoke and is much more common in Japanese children. It may be seen in any child who has a stenosis or occlusion in the terminal carotid or proximal middle cerebral artery. An idiopathic fibromuscular hyperplasia may be seen in Japanese children which may affect the cerebral vessels in the same way as the more commonly described lesions in the renal arteries. It can present with transient ischaemic attacks or as an established stroke.

Arteriosclerosis is rare in children except in familial hypercholesterolaemia.

Vascular spasm is a more difficult diagnosis to prove with certainty although it is suggested that in cases of spasm following subarachnoid haemorrhage one can now demonstrate this with pulsed Doppler. Whether this will be applicable in migraine remains conjectural. Migraine is a classical model for recurrent spasm and hemiplegic migraine certainly occurs in children. The alternating hemiplegia syndrome is a separate entity which is familial. The occasional occurrence of a hemiplegia after severe

tends to cause renal excretion of hydrogen ions in exchange for sodium, whilst conserving potassium. Associated with this is the transfer of hydrogen into the intracellular space and the movement of potassium into the ECF. The final result is an increase in the plasma concentration of potassium. Conversely, an alkalosis will promote the production of hypokalaemia without any immediate intracellular potassium deficiency occurring.

One situation where the result of these changes may manifest itself with potential danger to the patients is where intravenous therapy is employed to correct severe dehydration and possible associated acidosis. The initial plasma potassium concentration can be normal but falls rapidly as normal glomerular function is restored and potassium migrates intracellularly. In such circumstances, the use of potassium-free fluids should be avoided.

Most of the clinical upsets resulting from potassium depletion can be attributed to associated hypokalaemia without any immediate intracellular alteration in the membrane potential. One possible exception is the condition of adynamic ileus which seems to be due to intracellular potassium depletion. Balance studies have shown that in the adult, of a total body potassium of 3500 mmol, it is possible to have a deficiency as great as 1500 mmol (>20 mmol/kg) following prolonged vomiting. Even with this magnitude of deficiency the membrane potential is affected less than where a change from 5 to 2 mmol/l occurs in the plasma concentration. The clinical symptoms of potassium depletion include muscular weakness, hypotonicity and paralysis, although tetany is occasionally observed. Polyuria due to renal tubular dysfunction is another well-recognized sign of potassium deficiency. Cardiac upsets occur including arrhythmias, tachycardia, hypotension and even ventricular fibrillation. Electrocardiographic changes observed comprise ST depression, prolonged QT interval and prominent U wave, T wave inversion and the appearance of bifid U waves.

Potassium intoxication is caused by the hyperkalaemia almost invariably present rather than by an excess of total body potassium. This can be demonstrated by employing measures designed to cause the movement of potassium from the ECF to the ICF. Clinical improvement follows such therapy. The occurrence of hyperkalaemia is always associated with a failure or overwhelming of the renal excretory mechanisms. The renal failure may be real as in glomerular or tubular disease or related to the lack of steroid hormones in Addison's disease. On the other hand it may be relative and due to excessive entry of potassium into the ECF. The latter situation is found in states of haemolysis, acidosis, infections, and injudicious potassium therapy. Cardiac arrest may occur if the plasma concentration exceeds 7.5 mmol/l, but this is very variable.

The electrocardiographic changes associated with hyperkalaemia include peaked T waves, a prolonged P–R interval and ventricular slowing. These are valuable confirmatory signs of potassium intoxication but the clinical decision to employ treatment for hyperkalaemia should be based largely on the result obtained for the plasma potassium determination. An exception to this statement is the description of electrocardiographic changes normally associated with hyperkalaemia, but found in the presence of a normal plasma potassium concentration. These findings can be induced by administering potassium supplements too rapidly to patients with severe intracellular potassium depletion and hypokalaemia. The hypokalaemia is quickly corrected, but the intracellular potassium depletion persists. The membrane potential is altered to a value similar to that obtaining where a normal intracellular potassium concentration and hyperkalaemia coexist.

THE LOW SODIUM SYNDROME AND WATER INTOXICATION

Whilst sodium depletion is often associated with hyponatraemia, the occurrence of hyponatraemia does not necessarily imply sodium depletion; it can be due to dilution. Unless this fact is appreciated, serious errors in therapy will result. The following (after Black 1968) are causes of hyponatraemia:

1. True sodium depletion
2. Water intoxication
3. Diuretic-resistant oedema, with or without uraemia
4. Inappropriate secretion of ADH
5. New 'steady states'
6. Dilution of plasma sodium by excess glucose, fat or protein.

Categories 1 and 6 have already been mentioned (pp. 477–478).

Water intoxication

Water intoxication is the state which results when excretion of water is unable to keep pace with intake and production of water. It is especially liable to occur when prompt diuresis by the kidney fails to occur. It may be found in infants (relatively inadequate tubular function), following operations (increased ADH), in adrenocortical insufficiency (lack of cortisol), or when parenteral hypotonic fluid is given in excess of requirements. Clinical manifestations may appear when water amounting to between 5 and 10% of the body weight has been retained. The excess water is distributed between the ECF and ICF causing reductions in the concentration of plasma sodium and in plasma osmolality. Hypokalaemia is also likely to be present unless renal failure is severe. The PCV is theoretically normal, whilst haemoglobin level and plasma protein concentration tend to be low. Anorexia, weakness, nausea, vomiting, headache, confusion and coma have all been reported in this syndrome. That these upsets are due to intracellular overhydration can be proved by infusing a small volume of hypertonic saline, following which water moves from the ICF to the ECF, and clinical improvement results. The finding of a normal plasma sodium concentration excludes the presence of water intoxication.

Oedema

Diuretic-resistant oedema may occur in renal or cardiac failure and implies that renal excretion is impaired in spite of the possible presence of an increased ECF volume. The total body sodium may be increased but water retention is even more marked, resulting in hyponatraemia. The sequence of events leading to this syndrome is complicated and involves excessive secretion and/or diminished inactivation of aldosterone and ADH together with possible changes in capillary permeability. The outcome is an increase in the volume of interstitial fluid but a decrease in plasma volume. This results in pre-renal azotaemia which is further aggravated by sodium restriction. The therapeutic use of hypertonic saline in this syndrome often causes improved renal function with a decrease in the uraemia even if the oedema may not be diminished.

The syndrome of inappropriate antidiuretic secretion (SIADH)

Inappropriate secretion of ADH produces a clinical picture similar to that observed in water intoxication. The fundamental fault is that the secretion of ADH persists even in the presence of a reduced osmolality. This may be associated with head injury where the ADH is of posterior pituitary origin, or it may be found with certain tumours where a vasopressin-like polypeptide is elaborated by the neoplastic tissue.

Treatment of this condition involves water restriction together with any specific therapy against the tumour if such is practicable.

Steady states

New 'steady states': there are some patients, especially in the older age group, whose plasma sodium concentrations are habitually about 132 mmol/l. They have no signs of sodium deficiency and are not suffering from water intoxication. Given hypertonic saline they neither achieve normal plasma sodium concentrations nor do they derive any benefit. Readjustment of the distribution of sodium in their bodies with the appropriate alterations in the feedback regulation mechanisms appears to have occurred.

TREATMENT OF FLUID AND ELECTROLYTE DISTURBANCE

To sustain life, the basic principles involve the correction of deficit or excess of fluid and electrolytes, compensation for abnormal loss by whatever route and maintenance of a physiological balance. Where a patient has severe dehydration with attendant shock and peripheral vascular collapse the first move is to expand the plasma volume. To this end, immediate intravenous infusion of citrated plasma or suitable plasma substitute at 20 ml/kg may be life saving. Even in the above dramatic situation all fluids supplied to a patient will basically contain water, solutes and calories.

Water and solutes are usually required in more than normal amounts but when parenteral nutrition is limited to a few days an intake of 20–35% of the average calorie requirement will normally suffice.

The treatment of mild dehydration of the hypotonic, isotonic or hypertonic type does not necessarily require intravenous therapy. Mild gastroenteritis will yield to gastric lavage followed by oral half-strength physiological saline in liberal amounts, and the water-deprived hypernatraemia to adequate oral intake of quarter-strength physiological saline. Moderate diarrhoea may be treated away from hospital by reconstituted oral solutions such as those of WHO, Armour (Dioralyte) or Searle (Rehidrat). Their composition in mmol/l is shown:

	Sodium	Potassium	Chloride	Bicarbonate	Glucose (g/l)
WHO	90	20	80	30	20
Dioralyte	35	20	37	18	40
Rehidrat	50	20	50	20	16.4

Rehidrat also contains sucrose (32.3 g/l), citric acid (1.76 g/l) and fructose (1.76 g/l). The higher sodium concentration (WHO) is good for high sodium loss as in cholera, but less good for young infants for whom it may be diluted. Monosaccharides are beneficial but disaccharides less so and lactose may be harmful.

Table 10.14 Average daily requirements for maintenance of fluid and electrolytes per kg body weight at various ages

Age	Water (ml)	Potassium (mmol)	Sodium (mmol)
Day of birth	50	0	0
Infant	150	3	3
Older child	50	2	2

Provided that renal function is good it is relatively difficult to overload these infants and 150–200 ml/kg body weight/day are necessary save for the neonatal period when less is required. The widespread use of such 'stock' solutions has produced a dramatic fall in mortality in malnourished infants suffering from diarrhoea. Recourse to the intravenous route demands knowledge of daily requirements of fluid and electrolytes. Normal daily requirements for water and electrolytes are listed in Table 10.14 but provided renal function is good, wide tolerance exists.

In a few patients parenteral magnesium (as magnesium chloride) at 0.5 mmol/kg/day in 5% dextrose is required, therapy being governed by measuring plasma magnesium concentration.

Over and above the need to maintain hydration is the need to correct existing deficits. In a considerably dehydrated child the water deficit will lie between 30 and 150 ml/kg body weight and the deficit of sodium and/or potassium between 5 and 20 mmol/kg body weight.

Solutions for fluid and electrolyte replacement are given in Table 10.15.

Although the principles involved in the control of fluid and electrolyte therapy are not complicated, it must be appreciated that only meticulous care by all concerned in the management of such patients will result in the achievement of the ultimate degree of success.

ISOTONIC AND HYPOTONIC DEHYDRATION

These are by far the commonest patterns of dehydration resulting from sodium and water loss, with or without concomitant potassium loss. In general terms the water requirement relative to the solute is higher in infants than in older children. For this reason, fluids lower in sodium content are usually administered to infants as quarter- or half-strength physiological saline. Physiological (isotonic) saline tends to be used for older children. Energy is generally provided as 5% dextrose and a stock solution of half-strength physiological saline in 5% dextrose solution is a very useful fluid. The rate of infusion will be calculated to counteract continuing losses, to maintain fluid and electrolyte balance and to replace existing deficits. The aim should be to restore water and sodium deficiencies in 24–36 h and potassium deficit, if large, in 5 days.

It is important to stress to all attendants that because a target for administration over a 24-h period may be calculated this must not be divided by 24 and given at a standard rate for the first 24 h. Severe dehydration may require urgent partial correction, continuing diarrhoea or vomiting increase the rate of flow required, or renal dysfunction mandate the reverse. The infusion should be started at a relatively fast rate for several hours at least, and progress reviewed on the clinical and biochemical findings.

Thus, in moderately severe dehydration a 1-year-old infant given 150 ml/kg body weight of half-strength 5% dextrose–saline in the first 24 h receives in this 150 ml water, 11.5 mmol sodium

espiration, a consumptive asphyxia may result: the part of the rain giving rise to the convulsions will be the most damaged, as has the greatest oxygen demand, so a permanent hemiplegia an result from inadequately treated convulsions.

Trauma

Birth trauma has been discussed as a cause of congenital hemiplegia but trauma occurring in postnatal life from non-accidental injury may also cause hemiplegia. Shaking an infant with the head unsupported can cause tears of the bridging veins with a resultant acute subdural or subarachnoid haemorrhage and retinal haemorrhages. Hemiplegia with visual difficulty is the commonest long-term neurological sequel to non-accidental injury.

Iatrogenic trauma from attempts to needle the lateral ventricle may cause bleeding into the internal capsule. A rise in intraventricular pressure in the presence of a ventriculoperitoneal shunt may result in a puncture porencephaly with a hemiplegia that may appear only at the time of raised pressure.

Accidental injury is the commonest cause of acquired hemiplegia in children and may be due to pressure from an external clot such as an extradural or subdural haematoma. An acute subdural haematoma is nearly always associated with a severe contusion of the underlying cortex and persistent focal neurological signs are more likely to follow than following an extradural haematoma. Cerebral contusion or contracoup injury can cause a cortical hemiplegia. A tentorial cone from any cause of raised intracranial pressure may compress one of the cerebral peduncles causing an ipsi or contralateral brain stem hemiplegia. Occasionally rare conditions such as a pneumatocele from a fracture into the frontal sinus or obstruction of the foramen of Monro on one side may cause a hemiplegia with an easily remediable cause.

Anoxic ischaemic encephalopathy

With abnormal anatomy of the circle of Willis there may be differential flow in the six main vessels supplying the cerebral cortex. These are end arteries so that in hypotensive states the territory between the adjacent arterial territories (watershed zones) are more liable to infarction. Thus a generalized insult such as hypotension will not affect all regions of the cerebral cortex equally. Fits further compound the effect by increasing local demand and localized oedema also interferes with the microcirculation. Once the damage has occurred loss of vessel reactivity to carbon dioxide as well as release of thromboplastin from damaged brain (causing thrombosis in the veins draining the area) create a complex set of intermediate pathological mechanisms whereby hypoxic ischaemic damage can cause a focal cerebral infarction. Later in life anoxic ischaemic brain damage is likely to occur from status epilepticus, head injury, cardiac arrest, poisoning, drowning, carbon monoxide poisoning, anaesthetic accidents, acute hypotension from blood loss or endotoxic shock, cardiac bypass surgery, or respiratory obstruction from foreign bodies or laryngeal obstruction. In most cases when hemiplegia occurs this is against a picture of more widespread damage with ataxia, dystonia, mental handicap and epilepsy with or without cortical blindness.

Neoplasia

A glioma may rarely present with acute hemiplegia when haemorrhage occurs into it. Although this can occur in a benign tumour (cystic astrocytoma) haemorrhagic necrosis is usually a sign of severe malignancy. Leukaemia is the commonest malignancy of childhood and with modern treatment prolonged survival is possible so that neurological complications are common. Haemorrhage in leukaemia may occur in the acute or terminal stages from thrombocytopenia. Multiple haemorrhagic infiltrations can cause a 'cherry cake' brain and following treatment, when a very high CSF white cell count exists there may be a hyperviscosity syndrome which may cause multiple infarcts.

Meningeal leukaemia was common prior to the use of radiotherapy which has almost abolished CSF leukaemia. Now however, radiation vasculitis and late stroke must be added to the list of complications along with possible risk of microgliomas of the brain. Immunosuppressive drugs may predispose to infections with cytomegalovirus, toxoplasma and measles virus. Malignant glands in the neck may rarely infiltrate the internal carotid artery to give a hemiplegia.

Management of the child with acute onset hemiplegia

Management of the individual conditions causing the hemiplegia (meningitis, hyperosmolar dehydration, haemolytic uraemic syndrome etc.) is considered in the relevant sections of the book. In this section we will confine ourselves to the management of the acute focal ischaemic brain insult.

Fits. Fits must be treated energetically but ensuring that no drop in cerebral perfusion pressure is caused from drug induced hypotension. It is essential that an EEG is performed in all cases. In ideal circumstances continuous EEG monitoring will provide early warning of cerebral dysrhythmia. Electrical status epilepticus with a resultant increase in oxygen requirement of the convulsing brain may occur with only minor clinical ictal activity. Diazepam should be given intravenously during the EEG if there is any abnormality to see whether it is due to infarction or an arrhythmia. Intravenous diazepam has a duration of action of less than half an hour so that phenytoin should also be commenced as background therapy. Paraldehyde given intramuscularly should be used if the fits are not benzodiazepine sensitive and in intractable seizure activity may be given on a regular basis by the rectal route mixed with arachis oil.

Raised intracranial pressure. The three common types of cerebral oedema, i.e. vasogenic, toxic and osmotic, may all be present together in the same patient. The area infarcted from ischaemia is associated with opening of tight endothelial junctions which allows fluid and protein into the intercellular space.

Steroids are now back in favour in the management of meningitis. They are thought to stabilize lysosomal membranes inhibiting cell lysis, tighten endothelial junctions preventing albumen escaping and to have a vasodilator effect possibly improving microcirculation. Fluid should be restricted to 50–60% of calculated requirements to prevent water intoxication from inappropriate antidiuretic hormone secretion. If there is hyperosmolality and hyperviscosity which require fluids the circulation must be maintained by use of plasma expanders and extracellular dehydration treated with normal saline so that there is no change in osmolality. If the child has any impairment of consciousness or change in neurological state, intracranial pressure should be

monitored. If it is found to be raised treatment with mannitol, hyperventilation, frusemide and colloid may be given appropriately.

Maintain the microcirculation. Blood pressure is maintained by the use of plasma expanders or dopamine depending on the cause of shock. Polycythaemia is treated by venesection, plasma exchange or mannitol. In the experimental situation anaemia is extremely beneficial as a low haematocrit improves the microcirculation far better than any other measure provided blood pressure and oxygenation are maintained. Mannitol may exert its beneficial effect not only as an osmotic diuretic reducing cerebral oedema but also as a plasma expander improving the microcirculation. It is thought in addition to have an antioxidant effect. Some centres try and maintain haemodilution in cerebrovascular disorders over several days by the use of low molecular weight dextrans. Hyperviscosity from hyperlipidaemia requires urgent treatment in diabetes. Acidosis should be corrected and there is a theoretical preference for tris-hydroxyaminomethane (THAM) as it will treat the intracellular acidosis in the damaged area and not cause hypernatraemia which may occur with the overzealous use of sodium bicarbonate.

The adhesion of platelets to damaged endothelium causing local thrombosis may further block the microcirculation. Liberation of thromboplastin from the damaged brain also tends to encourage secondary thrombosis in the veins draining the damaged area, further aggravating the situation. Aspirin can be given in very small doses to try and prevent platelet stickiness and in the cases of vascular damage (e.g. in neck trauma or recurrent vascular spasm) it can be continued on a long-term basis. Anticoagulants such as warfarin or heparin are only rarely indicated in children unless there is a known focal arterial lesion or possibly in protein C or S deficiency. They are contraindicated once cerebral infarction has actually occurred because of the risk of bleeding into the infarct.

Cerebral protection. Barbiturates reduce the cerebral metabolic demands and reduce cerebral oedema. Theoretically they should reduce neuronal oxygen demands, stabilize membranes, reduce fits and prevent local oedema. This ideal has some support in limiting the extent of infarction in vessel occlusion in the experimental animal (Steer 1982). If intracranial pressure is being monitored one can give a test dose of thiopentone in order to see whether this will reduce the intracranial pressure but if there is any depression of blood pressure one is likely to lose more by reducing cerebral perfusion pressure than one gains by reducing metabolism. Large doses of barbiturates in many cases drop the intracranial pressure directly proportional to the drop in blood pressure. If the child is breathing spontaneously they may depress respiration and continuous PCO_2 monitoring is desirable. One cannot use the EEG to monitor barbiturate dose in small infants as burst suppression may not occur before dangerous doses have been given.

Maintain homeostasis. The sick child may show the syndrome of inappropriate antidiuretic hormone secretion inability to excrete a water load. Water intoxication with oedema and hyponatraemia may result if intravenous fluids are given at the normal rate. Hypoglycaemia may occur at any stage and blood glucose estimation must be done 3 hourly in any child with an acute neurological problem. Alternatively, raised intracranial pressure causing secondary brain stem compression may result in hyperglycaemia, i.e. cerebral diabetes. The blood glucose may also rise in the presence of seizures to levels seen in diabetes. Insulin must be avoided in children showing central hyperglycaemia as severe hypoglycaemia may result. Hypocalcaemia is a common problem in infants with acute neurological disease and this may itself aggravate the situation by causing seizures. Respiration may be depressed or there may be central neurogenic hyperventilation. There may be vasoparalytic shock requiring dopamine or severe hypertension which may cause fits and retinal haemorrhage. Regular monitoring of blood gases is necessary due to the potent cerebral vasodilator effect of carbon dioxide which will cause severe intracranial hypertension. Monitoring should also include electrolytes, osmolality, haematocrit, acid–base status and continuous blood pressure.

Surgery. Surgery is the treatment of choice in children with bleeding from aneurysms or arteriovenous malformations. Subdural haematoma, abscess, or haemorrhage into tumours also merit early surgical intervention. The use of surgery in the established stroke and cerebral thrombosis is limited.

HEADACHE AND MIGRAINE IN CHILDREN

Headache is a common problem in children with about 10% of children at the age of 10 years complaining of a periodic headache.

Classification

Headache can be divided into four main varieties.

Vascular headache

Vascular headache is used synonymously with migraine.

Organic neurological headache

This is usually worse after sleep or upon awakening in the morning. It is aggravated by lying down, tends to be a daily occurrence and not periodic, there is no family history and one would expect other neurological abnormalities. The commonest concern when a child is referred to hospital with a headache is to exclude a cerebral tumour. Certain tumours such as cystic astrocytoma or haemangioblastoma may be very chronic and may cause a headache over a period of a year or more. Raised intracranial pressure characteristically causes a headache which may be worse when the child wakens in the morning or may awaken him in the night as a result of the rise in pressure that occurs with rapid eye movement sleep. Apart from cerebral tumour, hydrocephalus, chronic subdural haematoma and benign intracranial hypertension may all result in a child presenting with a headache. One must be aware of benign intracranial hypertension in the obese child at puberty which can easily be falsely labelled as migrainous or psychogenic in origin. The other disorders which may cause a vascular-type headache on the basis of an organic pathology are arteriovenous malformations. These may cause a headache in their own right or as a result of small bleeds, raised intracranial pressure or as a result of pain from the blood vessels themselves.

Barlow (1984) gives the following criteria for considering CT scanning:

1. Neurological lateralizing signs
2. Persisting visual problems
3. Increase in occipital circumference

Table 18.9 Causes of diabetes insipidus (data from Crawford & Bode 1975, Czernichow et al 1985, Niaudet et al 1985, Perheentupa 1989)

Hypothalamic tumour 38% — craniopharyngioma 23% (usually postoperative); germinoma 6.5%; optic neuroma rarely
Idiopathic 23% — autoimmune factors may be important
Congenital renal 23%
Histiocytosis X 8%
Cerebral malformations 3%
Primary polydipsia 3%
Traumatic 2%

salt or glucose) is readily excluded from the history and by testing the urine for glucose. Habitual polydipsia most often develops in response to fluids being offered to pacify a demanding infant or young child. Such primary polydipsia of 'psychogenic' origin is suggested by fluctuating symptoms, evidence of psychological difficulties in the child or family, and a refusal of water (as opposed to juice!) if waking thirsty in the night. A morning plasma osmolality in the normal range (cf. in DI) often contrasts with a low value in the evening.

A history of head injury or meningitis or encephalitis should be sought. Poor growth suggests either inadequate appetite or food intake relating to the polydipsia or an associated anterior pituitary lesion with TSH, GH, Gn or ACTH deficiencies. TSH or ACTH deficiency may temporarily conceal DI until thyroxine or cortisol replacement is given. Headaches, vomiting and visual disturbances must be taken seriously as indicators of raised intracranial pressure secondary to tumour.

Synchronous measurements of plasma and urinary osmolality are very valuable provided that accurate assays are available. If not, plasma sodium (not specific gravity) should be substituted. A finding that urinary osmolality is inappropriately low when plasma osmolality is raised confirms the diagnosis of DI and charts aiding the interpretation of plasma and urinary osmolalities have been produced in preliminary form in children (Richman et al 1981). To achieve this mismatch a water deprivation test may be necessary (see below). Plasma AVP assays are increasingly available but their value in the diagnosis of central DI in children is not established (high, diagnostic, values are found in children with nephrogenic DI).

The water deprivation test is potentially both dangerous and misleading if not adequately supervised and, for both reasons, a strict protocol should be adhered to. Several protocols are available — Hughes (1989a) and Perheentupa (1989) are readily accessible. Specific additional endocrine and neuroradiological investigations may be necessary in many cases.

Provision of adequate water with free access to solute-free fluid at all times is vitally important. Treatment with AVP has been much simplified by the availability of a synthetic AVP analogue 1-desamino-8D-arginine vasopressin (DDAVP, desmopressin) which is administered intranasally. The convenience and simplicity of administration (the solution is blown into the nose via a soft plastic tube) outweigh problems such as the variable therapeutic effect and duration of action with each dose (Robinson & Verbalis 1985). A reasonable starting dose would be 0.25 μg (in neonates), 0.5–1.0 μg (infants) and 2.5 μg (children). Therapeutic effect is seen within 1 h. The dose is adjusted so as to provide an anti-diuretic effect for 8–12 h and is generally given 2 or 3 times daily. The dose may need increasing during episodes of rhinitis.

Special care must be taken with infants who do not have free access to water and children with an impaired sense of thirst. Water intoxication is a risk with overdosage or if water is given inappropriately. A card, disc or talisman detailing the disease and its therapy should be carried or worn at all times.

Poor control of DI is associated with nocturia, enuresis, irritability and poor behaviour and school performance. Appetite and growth velocity may be poor. Polyuria may lead to secondary enuresis. If treatment is optimal, the prognosis reflects the underlying condition in secondary DI and in primary DI the outlook for growth and development should be normal.

DI, diabetes mellitus, optic atrophy, deafness syndrome ('DIDMOAD' syndrome, Walfram syndrome)

See later.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Causes are listed in Table 18.10. Excessive AVP secretion results in water retention, hypo-osmolality and dilutional hyponatraemia. Inhibition of aldosterone with continuing AVP secretion leads to paradoxically high urinary sodium levels and concentrated urine. AVP levels may not be above the normal range but are inappropriately high for the expanded extracellular volume and hypo-osmolality.

Table 18.10 Causes of inappropriate ADH secretion

CNS disease/disorder
Meningitis/encephalitis
Trauma
Tumour
Haemorrhage
Hypoxia
Ischaemia
Malformation
Guillain–Barré syndrome
Obstructed ventriculoatrial shunt
Lung disease
Pneumonia
Tuberculosis
Pneumothorax*
Asthma*
Cystic fibrosis*
Ventilation
Postoperative (including mitral valvotomy*, ductus arteriosus ligation*)
Drugs (e.g. analgesics, sedatives, anaesthetics)
Malignancy
Trauma/burns
Endocrine/metabolic
Hypothyroidism
Adrenocortical failure
Hypoglycaemia
Idiopathic

*May be secondary to reduced left atrial filling.

In paediatric practice, SIADH is usually seen either in newborn infants in association with birth asphyxia (Feldman et al 1970), hyaline membrane disease or intraventricular haemorrhage (Moylan et al 1978), or in the older child in association with meningitis, encephalitis or CNS tumours (Kaplan & Feigin 1980). It occasionally complicates pneumonia or pulmonary tuberculosis (Rivers et al 1981), vincristine or cyclophosphamide therapy, and is a common, temporary (up to several days) complication of surgery requiring general anaesthesia (Kennedy et al 1978). It may be a particular problem in burns and trauma patients (Shirani et al 1983).

The first signs and symptoms are often masked by, or taken as manifestations of the underlying problem — anorexia, confusion, headaches, muscle weakness and cramps. Eventually, there is vomiting, convulsions or coma. There is no oedema. Diagnosis depends on a high clinical index of suspicion and the finding of the abnormalities in blood and urine described above.

Treatment is by water restriction to between one-third and one-half maintenance and sodium replacement to compensate for the secondary sodium losses. Correction should be gradual (over several days). In situations where this cannot be achieved drug therapy may be indicated. Lithium and demethylchlortetracycline have serious side effects in children and should not be used. Frusemide (with adequate sodium replacement) is useful (Decaux 1983) and AVP antidiuretic analogues may become the treatment of choice (Kinter et al 1985).

For further discussion of disturbances of salt and/or water metabolism, see Chapter 10.

DISEASES OF THE ADENOHYPOPHYSIS

GH insufficiency and excess

See earlier.

ACTH excess

Hypercortisolism in children is most usually the result of excessive glucocorticoid medication. Endogenous adrenocortical overactivity is rare whether due to adrenal tumour (benign or malignant), hyperplasia, to ectopic tumour ACTH production, or to pituitary dependent ACTH secretion (Cushing's disease). Cushing's syndrome includes all pathological states secondary to excessive glucocorticoid production and is discussed later. Cushing found a basophil pituitary adenoma in only six of his original 12 patients (Cushing 1932) and it is now thought that bilateral adrenal hyperplasia secondary to excessive ACTH secretion of pituitary origin is not a single entity and may be due to a variety of hypothalamic, pituitary or even CNS (neurotransmitter) abnormalities (Forest 1989a).

The classical clinical features of hypercortisolism (hypertension, striae, truncal obesity, moon face, osteoporosis) are less obvious in children than in adults and are discussed more fully later. Growth failure is usually marked but there can be temporary growth acceleration (due to excess adrenal androgen secretion) in the early stages.

For the investigation of suspected hypercortisolism see later. The utopian aim in treating Cushing's disease is to control cortisol overproduction (if appropriate by removing the source of ACTH hypersecretion) whilst avoiding permanent endocrine deficiencies and dependence on replacement therapy. In practice, the treatment of Cushing's syndrome in children is far from ideal and still controversial — understandably so given its poorly understood and diverse aetiological basis. Options include surgery to the adrenals or pituitary, pituitary irradiation (conventional or with radioactive implants), or medical management with dopaminergic agents or serotonin antagonists. For a full discussion see Forest (1989a).

ACTH deficiency

ACTH deficiency is usually associated with other anterior pituitary hormone deficiencies which may be congenital, idiopathic, due to brain malformations or pituitary hypoplasia or to tumours such as craniopharyngioma (especially following surgery and/or radiotherapy).

Isolated ACTH deficiency is rare (Odell et al 1960, Aynsley-Green et al 1978), may be congenital (Stempfel & Engel 1960) and may have an unexplained association with primary hypothyroidism (Stephens et al 1985) with thyroxine therapy precipitating adrenal insufficiency (thyroxine increases the metabolic clearance of cortisol).

Congenital panhypopituitarism (see Fig. 18.17) is associated with severe neonatal hypoglycaemia (see earlier) but isolated ACTH deficiency does not usually produce such severe adrenal hypofunction as is seen in primary adrenal insufficiency (see later). Glucocorticoid and adrenal androgen secretion is impaired but aldosterone secretion is normal. Nevertheless, collapse with associated salt loss may occur during severe intercurrent illness or general anaesthesia. Treatment is with appropriate glucocorticoid replacement.

TSH deficiency

Congenital hypothyroidism due to decreased TSH stimulation of thyroid hormone secretion may be due to abnormalities of hypothalamic or pituitary development, isolated TRH or TSH deficiency (familial or idiopathic) or panhypotituitarism. Congenital primary hypothyroidism is some 15- to 30-fold commoner.

TSH deficiency may present in later childhood, almost always in association with other anterior pituitary hormone deficiencies and secondary to tumours (especially craniopharyngioma), cranial irradiation or meningitis. Symptoms and signs due to the associated deficiencies usually predominate.

The differential diagnosis of primary, secondary (pituitary) and tertiary (hypothalamic) hypothyroidism and management is discussed later.

Gonadotrophin (Gn) deficiency

Isolated Gn deficiency may occur without underlying anatomical abnormality. Usually congenital abnormalities of brain development give rise to hypothalamic GnRH deficiency, either isolated (e.g. Kallman's syndrome, a familial condition with associated hyposmia or anosmia) or associated with other hypothalamic disturbances. Gn deficiency may be associated with other pituitary hormone deficiencies in pituitary aplasia or hypoplasia, craniopharyngioma etc. For discussion of the differential diagnosis and management of delayed sexual maturation see Ch. 8.

Hyperprolactinaemia

Moderately raised PRL levels are an early non-specific sign of neuroendocrine disturbance and particularly of suprasellar or

Table 22.8 Antibiotics used in treatment of childhood septic meningitis

Antibiotic(s)	Dosage	Advantages	Disadvantages	Reference
Benzylpenicillin	240 mg/kg/day ×6	*S. pneumoniae* and *N. meningitidis* sensitive	Uncommon *S. pneumoniae* resistance	Standard combination against which newer antibiotics evaluated
Or ampicillin	200 mg–400 mg/kg/day × 6		*H. influenzae* resistant in 15%	See references below
And chloramphenicol	100 mg/kg/day × 4 75 mg/kg/day after 48 h	Extremely good CSF penetration Oral absorption good Inexpensive	Aplastic anaemia in 1/50 000 courses Blood chloramphenicol levels should be estimated	
Cefotaxime	200 mg/kg/day × 4	Single agent Good CSF penetration		Odio et al 1986
Ceftazidime	150 mg/kg/day × 4	Single agent Good CSF penetration for Gram-negative enteric pathogens		Rodriguez et al 1986
Ceftriaxone	100 mg/kg/day × 1	Good CSF penetration Single daily dose	Diarrhoea	Del Rio et al 1983 Congeni et al 1986
Cefuroxime	225 mg/kg/day × 3	Single daily dose	Slow clearance of *H. influenzae* from CSF	Marks et al 1986

hourly for 4 days) reduces the risk of sensorineural hearing loss (Lebel et al 1988).

Skilled nursing should be available and regular neurological observations performed. Although vomiting may be a presenting symptom of meningitis, dehydration is unusual and fluid overload associated with inappropriate ADH secretion is a more frequent occurrence. Plasma and urine electrolytes should be carefully monitored and fluids restricted until there are clear signs of recovery.

Anticonvulsants such as phenobarbitone and phenytoin should be used if fits occur. The unconscious child may need referral to a neurosurgeon for intracranial pressure measurement and treatment with mannitol and dexamethasone.

COMPLICATIONS

Incomplete notification of meningitis by clinicians makes assessment of mortality difficult but this is probably around 5%. Convulsions occur in 20–30% of children, in most within the first 48–72 h of hospitalization. Persistence of fits is associated with a poor prognosis. Subdural collections of fluid are common particularly during infancy. Presenting features include fever, irritability, vomiting and a bulging fontanelle and rapidly enlarging head. A diagnosis may be made from abnormal transillumination of the head. In one series subdural fluid could be aspirated from nine out of 59 children with meningitis under the age of 2. All were less than a year old and as might be expected most were associated with *H. influenzae* infection. In only two infants were cultures positive (Dodge & Swartz 1965). Persistent fever during treatment may also be associated with thrombophlebitis and viral infection. Hydrocephalus may develop and is characterized by irritability, vomiting, a tense fontanelle (if still patent) and rapidly enlarging head. Investigations such as ultrasound or CT scan may be required for diagnosis of both subdural collections and hydrocephalus. In some cases hydrocephalus can be arrested by isosorbide (2 g/kg dose four times a day) over several weeks (Lorber 1975). Unfortunately it causes vomiting in a significant proportion of infants.

The commonest long-term complication of meningitis is sensorineural deafness. All children should undergo audiological assessment after recovery from infection. A number of studies have shown either unilateral or bilateral hearing loss in about 10% of children. In one series deafness occurred in 31% of children following *Strep. pneumoniae*, 10% following *N. meningitidis* and 6% following *H. influenzae* meningitis. Bilateral hearing loss occurred in about half of the children (Dodge et al 1984).

Other complications of meningitis are cerebral palsy, epilepsy and cranial nerve palsies. In a prospective study of children with *H. influenzae* meningitis, 28% had major handicaps: 10% deafness, 15% impaired speech, 10% mental retardation, 3–7% motor abnormality and 2–8% fits. The mean IQ of these children was 11 points less than the controls (Sell 1983). This group appears to have been a highly selected one. Other studies have been unable to determine a significant effect of illness on IQ (Tejani et al 1982).

There is little evidence that the duration of illness prior to hospital admission has any relationship to development of long-term sequelae. Focal neurological signs present on admission may be prognostic of a low intelligence quotient at follow-up (Feigin et al 1976).

MENINGOCOCCAL MENINGITIS

Caused by a Gram-negative diplococcus it is the commonest type of meningitis in children. Over recent years there has been an increased incidence with very high rates in certain areas.

In cases associated with meningococcaemia the typical petechial or purpuric rash is seen often preceded or accompanied by a maculopapular erythematous eruption. The symptoms and signs of meningitis are as described above.

The antibiotic of choice remains benzyl penicillin given intra-