NEUROLOGY

METABOLIC ENCEPHALOPATHIES

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Abstract: *The etiologies of metabolic encephalopathy are often diverse in children. Encephalopathy could result from lack of glucose, vitamin cofactors or oxygen and end organ failure. Inborn errors of metabolism, hypoglycemia, dyselectrolytemia, endocrine disorders and Reye syndrome are the reported causes of metabolic encephalopathies in children and adolescents. The clinical manifestations, biochemical parameters and radiological findings vary according to the etiology. Early diagnosis and management lead to reversal of symptoms and can prevent long-term neurological sequelae.*

Keywords: *Metabolic encephalopathy, Inborn error of metabolism, Osmotic demyelination syndrome, Hepatic encephalopathy, Uremic encephalopathy.*

Encephalopathy refers to altered mental status that includes "disorientation, short-term memory impairment, inattentiveness and abnormal state of arousal".[1] Intracranial or extracranial pathologies that interfere with the cerebral functions would result in encephalopathy. The common causes of encephalopathy are systemic or central nervous system infection, trauma, toxin exposure, metabolic disorders, organ failure, anoxia, endocrine dysfunction, nutritional deficiencies and neoplasms.[1] The term 'metabolic encephalopathy' was coined by Kinnier Wilson.[2] 'Metabolic encephalopathy' refers to a "clinical state of global cerebral dysfunction induced by systemic stress varying in clinical presentation from mild executive dysfunction to deep coma".[2] 'Acute toxic-metabolic encephalopathy' is characterized by altered level of consciousness, behavioural changes with or without seizures. It is suspected when central nervous system infection, inflammation or structural brain disease are excluded.[3] Clinical features, evaluation and management of the major causes of metabolic encephalopathy excluding hypoxic ischemic and toxin / drug induced encephalopathy are discussed here.

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Pathophysiology

A regulation of balance of water, electrolytes and other metabolic substrates is needed to maintain the local milieu of neurons in the presence of adequate blood flow, temperature and pH.[4] The possible mechanisms of cerebral dysfunction in metabolic encephalopathies are cerebral edema, endogenous accumulation of toxic metabolites, vasogenic or cytotoxic edema, dysregulation of neurotransmitter function, disruption of neurotransmission and energy depletion.[2,3]

Causes

The metabolic encephalopathies could result from lack of glucose, oxygen and vitamin cofactors and organ failure such as hepatic or uremic encephalopathy.[5] The metabolic disturbances may be transient or permanent. The causes of metabolic encephalopathies (Box 1) might vary depending upon the age of presentation.

Box 1. Metabolic encephalopathy - Causes

- Electrolyte disturbances: hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, hypophosphatemia, hypomagnesemia, hypermagnesemia
- Inborn errors of metabolism: Organic acidemia, urea cycle disorders, mitochondrial cytopathy, Reye syndrome
- Organ failures: Hepatic encephalopathy, uremic encephalopathy, hypoxic and hypercapnic encephalopathy
- Endocrine causes: Hypoglycemia, diabetic ketoacidosis, adrenal crisis, hypothyroidism, hyperthyroidism
- Nutritional deficiency: Wernicke encephalopathy
- Posterior Reversible Encephalopathy Syndrome (PRES)

Dyselectrolytemia - Related encephalopathy

Electrolyte disturbances such as hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, hypophosphatemia, hypomagnesemia and hypermagnesemia often result in encephalopathy. Clinical symptoms may be directly related to electrolyte disturbances or iatrogenic resulting from an inappropriate correction. The laboratory cut-off values above or below which encephalopathy may occur include sodium less than 125 mmol/L (hyponatremia), sodium more than 160mmol/L (hypernatremia), ionized calcium less than 0.5 mmol/L (hypocalcemia), ionized calcium more than 3 mmol/L (hypercalcemia), phosphorus less than 0.5 mmol/L (hypophosphatemia), magnesium less than 0.5 mmol/L (hypomagnesemia) and magnesium more than 2 mmol/L (hypermagnesemia).[2]

Hyponatremia contributes to hypoosmolar stress that drives water into the intracellular space by osmotic forces thereby resulting in cerebral edema. However, a rapid shift of electrolytes and organic osmolytes occurs from the intracellular space to prevent cerebral edema. Severe hyponatremia attributes to failure of adaptive mechanisms resulting in clinical manifestations. Clinical symptoms include headache, lethargy, seizures, vomiting, behavioral symptoms and coma. Hypernatremia leads to hyperosmolar stress that activates the shift of water and electrolytes out of the intracellular compartment resulting in shrinkage of oligodendroglial cells.[2] Clinical symptoms in these patients are altered sensorium and seizures. Dysregulation of calcium homeostasis affects the neuronal excitability, synaptic transmission and function of various organelles. The precise mechanism of encephalopathy in patients with hypomagnesemia is not clear, though it is postulated to result from an influence on the calcium homeostasis. Neurological manifestations in patients with hypocalcemia, hypercalcemia, hypomagnesemia, hypermagnesemia and hypophosphatemia are cognitive disturbances, psychiatric symptoms, seizures, muscle weakness, cramps, hemiparesis, aphasia, extrapyramidal symptoms and respiratory compromise.[2]

Osmotic demyelination syndrome is a rare cause of encephalopathy in children and adults. It has been reported in patients with rapid correction of hyponatremia, malnutrition, burn injuries, cirrhosis, pituitary surgeries, prolonged use of diuretics, hypophosphatemia and folate deficiency.[6] The underlying pathophysiology is impaired ability of brain cells to respond to sudden osmolality changes with resultant intracellular dehydration, energy depletion and axonal damage.[6] Sites of involvement in osmotic demyelination syndrome are pons and extra pontine sites such as basal ganglia, cerebral cortex, hippocampi, lateral geniculate bodies and white matter. Clinical manifestations include altered sensorium, coma, seizures, memory disturbances, dysphagia, flaccid quadriparesis, mutism, tremor, ataxia, dysarthria, dystonia, horizontal gaze paralysis and parkinsonism.[6,7]

Hypoglycemic encephalopathy

Hypoglycemia is one of the common causes of encephalopathy in infants and children. In symptomatic cases, hypoglycemia is defined as blood sugar less than 50 mg/dL and 60 mg/dL in neonates less than 48 hours and after 48 hours of life respectively.[8] Hypoglycemia may occur due to low birth weight, sepsis, hyperinsulinism, inborn errors of metabolism, growth hormone deficiency, adrenal insufficiency and medications. Clinical symptoms in hypoglycemic patients that result from the activation of sympathetic nervous system are tachycardia, sweating, hypothermia, anxiety and tremors. Neuroglycopenic symptoms in these patients include lethargy, headache, seizures and altered sensorium.[8]

Inborn errors of metabolism (IEM)

IEM may be broadly categorized into 3 groups.[9] Group 1 disorders include amino acidopathies, organic acidemia, porphyria and metal intoxication. In group 1 disorders, proximal to the block in metabolic pathways, the metabolites accumulate resulting in acute or progressive intoxication. Group 2 disorders are those resulting from defects in energy production or utilization. Disorders under this group are mitochondrial energy defects such as pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, fatty acid oxidation defects, ketone body

Box 2. Clinical clues for diagnosis of inherited metabolic disorders in neonates and infants

Neurological

Lethargy, coma, poor sucking, apnea, myoclonic seizures, hypotonia or hypertonia, involuntary movements, hiccups, fast breathing

Gastrointestinal

Hepatosplenomegaly, Cholestatic jaundice

Others

Hypothermia, sepsis-like presentation with no response to antibiotics, abnormal urine odor, dysmorphic features, hydrops fetalis

Table I. Specific diagnostic markers for inherited metabolic disorders in general physical and neurological examination

Features	Metabolic disorders
Microcephaly	Sulfite oxidase deficiency, molybdenum cofactor deficiency, untreated phenylketonuria
Facial dysmorphism	Glutaric aciduria type II, peroxisomal disorders
Sparse hypopigmented hair	Biotinidase deficiency, multiple carboxylase deficiency, vitamin B12 deficiency
Hair shaft abnormalities	Arginosuccinic aciduria, Menkes disease
Alopecia	Biotinidase deficiency, multiple carboxylase deficiency
Hypertrichosis	Mitochondrial complex deficiency
Skin rashes	Biotinidase deficiency, multiple carboxylase deficiency
Fat maldistribution	Congenital disorder of glycosylation
Cyanosis	Methemoglobinemia due to cytochrome b5 reductase deficiency
Petechiae	Ethylmalonic aciduria
Anemia	Vitamin B12 deficiency
Ocular findings - Cherry red spot, retinitis pigmentosa, nystagmus, optic atrophy, supranuclear gaze paralysis, strabismus, oculogyric crisis, lens dislocation	Tay-Sachs disease, Niemann Pick disease, mitochondrial cytopathy, homocystinuria, sulfite oxidase deficiency, Gaucher disease, neurotransmitter defects
Spasticity	Nonketotic hyperglycinemia, sulfite oxidase deficiency, molybdenum cofactor deficiency, multiple carboxylase deficiency
Extrapyramidal signs (dystonia, choreoathetosis, tremors)	Glutaric aciduria, Leigh syndrome, biotin thiamine responsive basal ganglia disease, neurotransmitter defects, homocystinuria
Ataxia	L-2-hydroxyglutaric aciduria, vitamin B12 deficiency, cobalamin disorders, mitochondrial complex deficiency

utilization defects and respiratory chain disorders. Group 3 disorders involve the defects in the synthesis or catabolism of complex molecules such as lysosomal storage disorders, peroxisomal disorders, congenital disorders of glycosylation (CDG) and disorders of cholesterol metabolism. Group 1 and 2 disorders usually manifests with acute encephalopathy. Disorders categorized under group 3 manifest with chronic progressive course and episodic decompensation with intercurrent illness may rarely occur in some of these disorders. Hypoglycemia, dyselectrolytemia, cytotoxic edema and energy failure could possibly attribute to encephalopathy in children with various inborn errors of metabolism.

Clinical manifestations of IEM in neonates are often non-specific. Neonates with IEM usually manifest with poor feeding, lethargy, vomiting, failure to thrive, respiratory distress and coma. Other symptoms include neurological deterioration, seizures, jaundice, cardiac failure or refractory hypoglycemia.[9] A full term neonate with no apparent antenatal or perinatal risk factors presenting with sudden neurological deterioration must be evaluated for IEM. Clinical clues for consideration of IEM in full term neonates and infants are summarized in Box 2.[9]

Disorders that exhibit lethargy and progressive neurological deterioration are maple syrup urine disease

(MSUD), methylmalonic acidemia (MMA), propionic acidemia (PA), isovaleric acidemia (IVA), multiple carboxylase deficiency (MCD) and urea cycle disorders (UCD).[9] Seizures are predominantly observed in pyridoxine dependent epilepsy, biotinidase deficiency, folinic acid responsive seizures and hypomagnesemia. Hepatic failure has been reported in galactosemia, tyrosinemia, fructose intolerance, CDG type 1b and bile acid synthesis defects. Cardiac failure and rhythm disturbances have been observed in neonates with fatty acid oxidation defect (FAOD). Disorders of glycogenolysis, hyperinsulinism and FAOD must be considered in neonates with persistent hypoglycaemia.[9]

IEM must be suspected in children of any age with developmental delay, seizures, consanguinity, positive family history, stroke like episodes, vision deterioration, hearing dysfunction, peripheral neuropathy, extrapyramidal signs, ataxia and neurological worsening with intercurrent illness.[10] The clinical markers for diagnosis of inherited metabolic disorders are summarized in Table I.[10]

Nutritional deficiencies

Children with nutritional deficiencies of vitamins such as thiamine, vitamin B12, folic acid and niacin would manifest with altered level of consciousness, memory disturbances, seizures, ataxia and involuntary movements.

Wernicke encephalopathy results from thiamine deficiency and though common in alcoholic patients, it has been reported in infants born to thiamine deficient mother, children with malignancies on chemotherapy, nephrotic syndrome, gastrointestinal surgeries, prolonged hospitalization, magnesium deficiency and inherited thiamine transporter deficiency.[11] The classical triad described in Wernicke encephalopathy consisting of encephalopathy or memory disturbances, ataxia and ophthalmoplegia are not observed in majority of cases. Other uncommon clinical manifestations in Wernicke encephalopathy are seizures, hallucinations, behavioral disturbances, dyskinesias, coma, hypotension and hypothermia.[11] Thiamine deficiency leads to impaired functioning of transketolase, pyruvate dehydrogenase, alpha ketoglutarate dehydrogenase and branched chain ketoacid dehydrogenase resulting in energy depletion and neuronal injury.

Hepatic encephalopathy (HE)

Hepatic encephalopathy occurs commonly in children with fulminant hepatic failure due to viral hepatitis, drug toxicity or inborn errors of metabolism. HE may be acute or chronic. The acute HE would result from liver cell dysfunction and cerebral edema while chronic HE predominantly results from portosystemic shunting.[2] Hyperammonemia, dyselectrolytemia, generation of aberrant neurotransmitter-like molecules, manganese deposition in brain and production of abnormal ligands could explain the neurological symptoms in children with HE.[12,13] The precipitating factors of HE are infection, variceal bleeding, constipation, dehydration, dyselectrolytemia, hypoglycemia, excessive intake of dietary protein, use of sedative drugs and renal failure.[14] There are four types of HE namely type A associated with acute liver failure, type B associated with portosystemic bypass, type C associated with cirrhosis and type D associated with urea cycle disorders.[14] Common IEM responsible for liver failure are tyrosinemia, galactosemia, urea cycle disorder and neonatal hemochromatosis. The clinical stages of HE are summarized in Table II.[15, 16]

Table II. West Haven grading of hepatic encephalopathy[15,16]

Grade	Clinical features
1	Lack of awareness Decreased attention span Impaired calculation Euphoria or anxiety
2	Lethargy or apathy Disorientation of time or place Personality changes Inappropriate behavior Impaired calculation
3	Hypersomnolence Disorientation Stupor
4	Coma

Reye syndrome

Reye syndrome was first described by R.D.K Reye in 1963.[17] It is an acute non-inflammatory encephalopathy that typically manifests with vomiting, lethargy and progression to coma.[17] The criteria to be fulfilled for the diagnosis of Reye syndrome is given Box 3.[18]

Reye syndrome may be precipitated by viral or bacterial pathogens such as influenza virus, varicella zoster virus, coxsackie virus, parainfluenza virus, adenovirus, Epstein-Barr virus, hepatitis virus, chlamydia, bordetella, mycoplasma and shigella. Ingestion of salicylates has also been associated with the occurrence of Reye syndrome. These bacterial / viral pathogens and aspirin appear to cause

Box 3. Reye syndrome – Diagnostic criteria[18]

"Acute noninflammatory encephalopathy that is documented clinically by a) an alteration in consciousness and, if available b) a record of cerebrospinal fluid (CSF) containing less than or equal to 8 leukocytes/cu.mm or a histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation.

Hepatopathy documented by either a) a liver biopsy or an autopsy considered to be diagnostic of Reye syndrome or b) a threefold or greater increase in the levels of the serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) or serum ammonia. No more reasonable explanation for the cerebral and hepatic abnormalities."[18]

Box 4. Clinical stages of Reye syndrome[19]

- Stage 0- Alert, wakeful
- Stage I- Lethargy, drowsy
- Stage II- Delirious, combative
- Stage III- Unarousable, decorticate posturing
- Stage IV- Unarousable, decerebrate posturing
- Stage V- Unarousable, flaccid paralysis, areflexia, dilated and fixed pupils

hepatic mitochondrial injury thereby leading to inhibition of fatty acid oxidation metabolism. Hyperammonemia, hypoglycemia, coagulopathy, cerebral edema and hypoxia are the important determinants of clinical severity. The clinical stages of Reye syndrome may be categorized as shown in Box 4.[19]

Uremic encephalopathy

Children with acute or chronic renal failure may develop uremic encephalopathy with a progressive decline in the estimated glomerular filtration rate. The etiologies for acute or chronic renal failure in children are often diverse. Clinical features of uremic encephalopathy are anorexia, drowsiness, restlessness, poor attention span, cognitive disturbances, bizarre behavior, emotional instability, seizures, stupor and coma.[20]

Involvement of cranial nerves, hyperreflexia, asterixis and focal motor deficits may occur in these patients. The causes of CNS injury in uremic patients are accumulation of uremic metabolites, guanidino compounds and cystatin C, hypertension, dyselectrolytemia, secondary hyperparathyroidism, thiamine deficiency, graft rejection, hyperhomocystinemia, oxidative stress, chronic inflammation, aluminium-related encephalopathy and dialysis disequilibrium syndrome.[21]

Pulmonary encephalopathy

Pulmonary encephalopathy is caused by hypercapnia or hypoxemia due to respiratory insufficiency of varied etiology. Hypercapnia results in encephalopathy due to CSF acidosis, cerebral vasodilatation and impaired neuronal excitability. Clinical manifestations are headache, agitation, poor attention, drowsiness, stupor and coma.[2]

Posterior reversible encephalopathy syndrome (PRES)

PRES was first described in 1996 by Hinchey et al.[22] Other terminologies that are used to describe PRES are reversible posterior leukoencephalopathy, reversible posterior cerebral edema, reversible occipitoparietal encephalopathy and hypertensive encephalopathy. PRES occurs in children and adults with uncontrolled hypertension of varied etiology, use of immunosuppressive drugs and antiretroviral drugs, blood transfusion, hypercalcemia, eclampsia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, von Hippel Lindau disease and exposure to contrast media.[23] Though the pathophysiology underlying PRES remains debatable, the possible mechanisms are impaired cerebrovascular autoregulation, endothelial damage and vasogenic edema.[23] PRES is a clinicoradiological entity and the reported symptoms in these patients include headache, vomiting, seizures, lethargy, somnolence, stupor, coma, visual disturbances and focal motor deficits.[2]

Endocrine dysfunction-related encephalopathy

Endocrine dysfunction manifests with varied neurological manifestations that ranges from headache, myopathy to encephalopathy and coma. Diabetic ketoacidosis, hyperglycemic hyperosmoloar coma, adrenal crisis, hypothyroid coma, hyperthyroid storm and Hashimoto's encephalopathy are the common causes of endocrine dysfunction-related encephalopathies.[24]

a) Hyperglycemic encephalopathy occurs in children and adolescents with diabetes mellitus due to diabetic ketoacidosis (DKA) or nonketotic hyperosmolar hyperglycemia. DKA occurs more commonly in type-1 diabetes mellitus, often precipitated by starvation, exercise

and infection. In the absence of insulin, triglycerides in the liver are broken down to fatty acids and glycerol and the glycerol is again converted in to glucose. However, the glucose thus formed cannot be utilized by the peripheral tissues due the lack of insulin leading on to a rise in the production of ketone bodies. Hyperglycemia, glucosuria, high anion gap metabolic acidosis, hypokalemia and ketosis are the biochemical markers of DKA. Clinical manifestations in children with DKA are lethargy, abdominal pain, vomiting, polyuria, polydipsia, dehydration, tachypnea and altered sensorium.[25]

b) Hyperosmolar hyperglycemic syndrome (HHS) occurs more commonly in type-2 diabetes mellitus, often precipitated by infection. In HHS, despite hyperglycemia, the peripheral tissues are unable to utilize the glucose and hence, counter regulatory hormones are released that raises the blood sugar level and serum osmolarity. Since the insulin levels are not decreased in type-2 diabetes, lipolysis and ketogenesis are inhibited. Children with HHS manifest with fever, lethargy, tachypnea, tachycardia, dehydration, focal neurological deficits and altered sensorium.[26]

c) Hypothyroid coma is extremely rare in children. These children usually manifest with lethargy, bradycardia, hypothermia, dyspnea and seizures. In children with hypothyroidism, factors that attribute to clinical symptomatology are hyponatremia, hypothermia, hypoventilation and hypoxia. Hashimoto's encephalopathy refers to an immune-mediated neurological disorder with varied clinical symptoms such as seizures, movement disorders, psychiatric symptoms and coma. Though the exact pathophysiology is not clear, it is believed to result from an underlying immune-mediated pathogenic process. Anti-thyroglobulin and anti-microsomal antibodies are detected in these patients despite the euthyroid state.[27] The treatment modalities include high dose steroids, plasmapheresis and intravenous immunoglobulins.[27,28]

d) Patients with hyperthyroidism rarely manifest with thyroid storm following surgery, trauma or infection. These patients exhibit tremors, seizures, involuntary movements and coma.

e) Adrenal crisis is usually precipitated by dehydration, infection, trauma in children with pre-existing adrenal insufficiency and also following abrupt withdrawal of steroid. These patients manifest with lethargy, vomiting, hypotension, shock, confusion and coma.[29,30]

Clinical spectrum

Though the signs of global cerebral dysfunction predominate in metabolic encephalopathies, a careful clinical examination to look for neuropsychological signs

Table III. Neuroimaging findings in metabolic encephalopathies of different etiologies

Etiology	MRI findings
Osmotic demyelination syndrome	Central pontine myelinolysis- trident-shaped hyperintensity in central pons Extrapontine myelinolysis-T2 hyperintensity involving caudate, putamen and other sites of involvement are cerebral white matter and cerebellum
Wernicke encephalopathy	Symmetric signal changes in bilateral thalami, mammillary bodies, hypothalamus, tectal plate, cranial nerve nuclei, dentate nuclei, periaqueductal grey matter and cerebellar vermis
Posterior reversible encephalopathy syndrome	Vasogenic edema in the subcortical white matter of parietal and occipital lobes and rarely cortex. Other sites are subcortical white matter in frontal region, basal ganglia, thalamus and cerebellum
Uremic encephalopathy	Lentiform fork sign involving basal ganglia on MRI
Hepatic encephalopathy	T1 hyperintensity involving bilateral globus pallidi MRS show increased glutamine/glutamate peak and decreased myoinositol and choline peaks
Reye syndrome	Signal changes in bilateral thalami, brainstem, cerebellar white matter, subcortical white matter and cerebral cortex

Table IV. Neuroimaging findings in children with inherited metabolic disorders

Imaging findings	Metabolic disorder
Intracranial calcification on CT brain	Dihydropteridine reductase deficiency MELAS Kearns Sayre syndrome Congenital lactic acidosis Respiratory chain disorders
White matter signal changes on T2Weighted images	Glutaric aciduria type I L-2-hydroxyglutaric aciduria Menkes disease Sulfite oxidase deficiency Molybdenum cofactor deficiency PKU MSUD Peroxisomal disorders Mitochondrial complex deficiency
Basal ganglia or brainstem signal changes	Biotin thiamine responsive basal ganglia disease Leigh syndrome L-2-hydroxyglutaric aciduria Methylmalonic aciduria Mitochondrial complex deficiency Wernicke encephalopathy Osmotic demyelination syndrome
Dentate nuclei hyperintensity	L-2-hydroxyglutaric aciduria Mitochondrial encephalopathy Succinate semialdehyde dehydrogenase deficiency
MRS findings	Prominent NAA peak- Canavan disease Prominent lactate peak- mitochondrial cytopathies Absent creatine peak- cerebral creatine deficiency syndromes

MELAS- Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes, NAA - N acetylaspartate

and focal neurological deficits is mandatory. The spectrum of neuropsychological changes in metabolic encephalopathies include disturbances of consciousness such as hypersomnolence, decreased arousal, stupor and coma, memory disturbances, thought and perception problems and increased or decreased psychomotor activity. Autonomic disturbances may also occur in these patients. Global brainstem signs such as orofacial automatisms, pathological reflexes, asterixis, myoclonus, tremor, decerebrate and decorticate posturing can be seen. Focal cerebral and brainstem signs that may occur in patients with metabolic encephalopathies are aphasia, hemiparesis, vision disturbances, dysarthria, nystagmus, gaze deviation, pupillary abnormalities, hemisensory loss, changes in tone and deep tendon reflexes and ataxia.[31]

Laboratory diagnosis

In children with suspected metabolic encephalopathies, the etiology could be established by meticulous history taking, clinical examination, arterial blood gas analysis, blood biochemistry tests, neuroimaging and electroencephalography (EEG).[32] A high anion gap metabolic acidosis will be detected in children with diabetic ketoacidosis and lactic acidosis. In those children with documented ketoacidosis, estimate the blood sugar, blood ammonia and lactate to identify an underlying IEM. Respiratory acidosis will be detected in children with pulmonary encephalopathy due to hypercarbia. Neuroimaging forms an important diagnostic tool in establishing the etiology of metabolic encephalopathies in

children. The summary of neuroimaging findings in children with metabolic encephalopathies of varied etiology and suspected inborn errors of metabolism are summarized in Table III and IV.[10,11,33-38]

Freshly voided urine samples must be collected in infants and children with suspected metabolic encephalopathies. Urine samples have to be collected before treatment and while on treatment. These samples have to be stored at -20° C and urinary samples are to be analyzed for odour, P^H, sulfite excretion, electrolytes, ketones, amino acid and ketoacids.[9] Urinary organic acids are analyzed by gas chromatography-mass spectrometry (GCMS). Plasma, dried blood spot on filter paper and whole blood are collected and stored in appropriate vials.

Neuroimaging plays a vital role in identifying the etiology of metabolic encephalopathies. Other laboratory tests that needs to be considered in children with metabolic encephalopathies are shown in Table V.[9, 39-41]

Treatment

The management of metabolic encephalopathies can be categorized as general and specific measures.

1. General measures in children presenting with metabolic encephalopathies involve the management of airway, breathing and circulation. Maintain euglycemia, correct dyselectrolytemia if identified and supplement thiamine or other vitamin cofactors in cases with Wernicke encephalopathy or other inborn errors of metabolism. Antiepileptic medications must be chosen appropriately to achieve seizure freedom. Raised intracranial pressure if identified must be managed appropriately using standard protocols. Strict control of hypertension and elimination of precipitating factors are recommended in management of children with PRES.

2. Specific measures and organ support

a) The management of hepatic encephalopathy involves maintenance of fluid and electrolyte balance and euglycemia. Other measures that target to decrease the blood ammonia levels in children with hepatic encephalopathy are protein restricted diet; use of antibiotics such as ampicillin and metronidazole to reduce gut bacterial colonization and use of sodium benzoate and phenyl acetate.[12]

Table V. Laboratory evaluation of children with metabolic encephalopathies

Biological samples	Biochemical tests
Blood	Basic tests: Complete blood count, ESR and CRP fasting blood sugar, sodium, potassium, calcium, phosphorus, magnesium, arterial blood gas, lipid profile, uric acid, liver function test, prothrombin time, creatine kinase, Nutrition and metabolic tests: ammonia, lactate, amino acids, acyl carnitine profile, homocysteine, vitamin B12, prolactin, VLCFA, isoelectric focusing for transferrins, tandem mass spectrometry, free fatty acids, urine porphobilinogen, urine delta-aminolevulinic acid, Molecular studies Endocrine tests: Thyroid function tests and thyroid antibodies, serum cortisol Toxin assay: From gastric aspirate, blood and urine
CSF	Cell count, glucose, protein, lactate, amino acid, neurotransmitters, bacterial culture, PCR for viruses
Ultrasound abdomen, ECG, Echocardiography	To look for hepatic and cardiac involvement
EEG	To identify background activity, focal slowing, epileptiform discharges, triphasic waves, PLEDS and burst suppression pattern Triphasic waves in hepatic encephalopathy FIRDA inhyperglycemia, hypoglycemia and hyponatremia

ESR- erythrocyte sedimentation rate, CRP- C-reactive protein, VLCFA- Very long chain fatty acid, CSF- Cerebrospinal fluid, PCR- Polymerase Chain Reaction, ECG- Electrocardiography, EEG- Electroencephalography, PLEDS- Periodic Lateralized Epileptiform Discharges, FIRDA- Frontal intermittent rhythmic delta activity

b) Hemodialysis or peritoneal dialysis may be useful in selected cases. Dialysis must be considered in children with uremic encephalopathy and these patients also require an emergent management of associated dyselectrolytemia.

c) Therapies in children with Reye syndrome are focused to maintain the cerebral perfusion pressure and also includes supportive measures such 10% dextrose infusion, raised ICP management and correction of hyperammonemia to minimize the neurological sequelae.[42]

d) Adrenal crisis is managed by volume expansion with intravenous fluids and correction of hyponatremia and hypoglycemia. Stress dose of hydrocortisone (100 mg/m^2/day) must be administered as infusion or bolus in the first 24 hours and may be gradually tapered to oral maintenance doses. Treatment of infection is also crucial in patients with adrenal crisis.[30]

e) Children with diabetic ketoacidosis are managed with appropriate intravenous fluids, insulin infusion and correction of dyselectrolytemia. In contrast to DKA, fluid replacement is the key step in management of hyperosmolar hyperglycemic syndrome while insulin infusion is not crucial.[43]

Points to Remember

- ***Metabolic encephalopathy should be suspected in any child with altered consciousness after excluding CNS infection, structural disorders, toxin ingestion and trauma.***
- ***Organ or system failure like hepatic encephalopathy, hypoxia, dyselectrolytemia and endocrine dysfunction are responsible for metabolic encephalopathy.***
- ***Underlying etiologies are diverse which can be narrowed down by recognizing the clinical clues.***
- ***Management includes acute stabilization and specific measures based on etiology including organ support.***

References

1. Perugula ML, Lippmann S. Encephalopathy or Psychosis? Innov Clin Neurosci 2016: 13; 41-42.
2. Angel MJ, Young GB. Metabolic encephalopathies. Neurol Clin 2011; 29:837-882.
3. Parke, JT. Acute encephalopathies. In: McMillan JA, Feigin RD, De Angelis C, Jones MD (eds), Oski's Pediatrics. Principles and Practice, 4th edn. Philadelphia: Lippincott, Williams & Wilkins 2006; p2258.
4. Chiriboga CA. Acute toxic-metabolic encephalopathy in children. Available from:https.//www.uptodate.com/contents/acute-toxic-metabolic-encephalopathy-in-children/.Accessed on 7th January, 2020.
5. Butterworth RF. Metabolic Encephalopathies. In: Siegel GJ, Albers RW, Brady ST, Price DL (eds), Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 7th edn Boston: Elsevier 2006; pp593-594.
6. King JD, Rosner MH. Osmotic demyelination syndrome. Am J Med Sci 2010; 339:561-567.
7. Zunga PM, Farooq O, Dar MI, Dar IH, Rashid S, Rather AQ, et al. Extra pontine osmotic demyelination syndrome. Ann Neurosci 2015; 22:51-53.
8. Gandhi K. Approach to hypoglycemia in infants and children. Translational Pediatrics 2017; 6:408.
9. Saudubray JM, Nassogne MC, de Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: an over-view. Semin Neonatol 2002; 7:3-15.
10. Saudubray JM, Cazrola AG. Clinical approach to inborn errors of metabolism in Pediatrics. In: Saudubray JM, Baumgartner MR, Walter J editors. Inborn metabolic diseases diagnosis and treatment. 6th edn. Heidelberg: Springer Berlin 2016; pp33-57.
11. Lallas M, Desai J. Wernicke encephalopathy in children and adolescents. World J Pediatr 2014; 10:293-298.
12. Arya R, Gulati S, Deopujari S. Management of hepatic encephalopathy in children. Postgrad Med J 2010; 86: 34-41.
13. Ryan JM, Shawcross DL. "Hepatic encephalopathy". Medicine 2011; 39:617-620.
14. Dara N, Sayyari AA, Imanzadeh F. Hepatic encephalopathy: early diagnosis in pediatric patients with cirrhosis. Iran J Child Neurol 2014; 8:1-11.
15. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT, et al. Hepatic encephalopathy-definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35:716-721.
16. Bajaj JS, Cordoba J, Mullen KD, Amodio P, Shawcross DL, Butterworth RF, et al. International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN). Review article: the design of clinical trials in hepatic encephalopathy-an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. Aliment Pharmacol Ther 2011; 33:739-747.
17. Chapman J, Arnold JK. Reye Syndrome. [Updated 2019 Jan 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526101/. Accessed on 1st January, 2020.

18. Centers for Disease Control and Prevention. Reye syndrome: 1990 clinical case definition. 1990. Available at http://www.cdc.gov. Accessed on 1st January, 2020.
19. Hurwitz ES, Nelson DB, Davis C, Morens D, Schonberger LB. National surveillance for Reye syndrome: a five-year review. Pediatrics 1982; 70:895-900.
20. Zemaitis MR, Foris LA, Chandra S, Bashir K. Uremia. [Updated 2019 Jul 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441859. Accessed on 2nd January, 2020.
21. Arnold R, Issar T, Krishnan AV, Pussell BA. Neurological complications in chronic kidney disease. JRSM cardiovascular disease. 2016;5:2048004016677687.
22. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996; 334:494-500.
23. Lamy C, Oppenheim C, Meder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. J Neuroimaging 2004; 14:89-96.
24. Yu J. Endocrine disorders and the neurologic manifestations. Ann Pediatr Endocrinol Metab 2014; 19:184-190.
25. EL-Mohandes N, Huecker MR. Pediatric Diabetic Ketoacidosis. [Updated 2019 Apr 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan Available from: https://www.ncbi.nlm.nih.gov/books/NBK470282/.Accessed on 3rd January, 2020.
26. Adeyinka A, Kondamudi NP. Hyperosmolar Hyperglycemic Nonketotic Coma (HHNC, Hyperosmolar Hyperglycemic Nonketotic Syndrome) [Updated 2019 Jun 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482142/. Accessed on 3rd January, 2020.
27. Schiess N, Pardo CA. Hashimoto's encephalopathy. Ann N Y Acad Sci 2008; 1142:254-265.
28. Lee J, Yu HJ, Lee J. Hashimoto encephalopathy in pediatric patients: Homogeneity in clinical presentation and heterogeneity in antibody titers. Brain Dev. 2018; 40: 42-48.
29. Tucci V, Sokari T. The clinical manifestations, diagnosis, and treatment of adrenal emergencies. Emerg Med Clin North Am 2014; 32:465-484.
30. Bowden SA, Henry R. Pediatric adrenal insufficiency: diagnosis, management, and new therapies. International Journal of Pediatrics. 2018;2018.
31. Kunze K. Metabolic encephalopathies. J Neurol 2002; 249:1150-1159.
32. Berisavac II, Jovanoviæ DR, Padjen VV, Ercegovac MD, Stanarèeviæ PD, Budimkiæ-Stefanoviæ MS, et al. How to recognize and treat metabolic encephalopathy in Neurology intensive care unit. Neurol India 2017; 65:123-128.
33. Babanrao SA, Prahladan A, Kalidos K, Ramachandran K. Osmotic myelinolysis: Does extrapontinemyelinolysis precede central pontine myelinolysis? Report of two cases and review of literature. Indian J Radiol Imaging 2015; 25:177-183.
34. Zuccoli G, Santa Cruz D, Bertolini M, Rovira A, Gallucci M, Carollo C, Pipitone N. MR imaging findings in 56 patients with Wernicke encephalopathy: nonalcoholics may differ from alcoholics. AJNR Am J Neuroradiol 2009; 30:171-176.
35. Emeksiz S, Kutlu NO, Çaksen H, Alkan G, Yýkmaz HÞ, Tokgöz H. Posterior reversible encephalopathy syndrome in children: a case series. Turk Pediatri Ars 2016; 51:217-220.
36. Kim DM, Lee IH, Song CJ. Uremic Encephalopathy: MR Imaging Findings and Clinical Correlation. AJNR Am J Neuroradiol 2016; 37:1604-1609.
37. Rovira A, Alonso J, Córdoba J. MR imaging findings in hepatic encephalopathy. AJNR Am J Neuroradiol 2008; 29:1612-1621.
38. Singh P, Goraya JS, Gupta K, Saggar K, Ahluwalia A. Magnetic resonance imaging findings in Reye syndrome: case report and review of the literature. J Child Neurol. 2011; 26:1009-1014.
39. Lin CC. [EEG manifestations in metabolic encephalopathy]. Acta Neurol Taiwan 2005; 14:151-161.
40. Kaplan PW. The EEG in metabolic encephalopathy and coma. J Clin Neurophysiol 2004; 21:307-318.
41. Faigle R, Sutter R, Kaplan PW. The electroencephalography of encephalopathy in patients with endocrine and metabolic disorders. J Clin Neurophysiol 2013; 30:505-516.
42. Crocker JF, Bagnell PC. Reye's syndrome: a clinical review. Can Med Assoc J 1981; 124:375-382, 425.
43. Price A, Losek J, Jackson B. Hyperglycaemic hyperosmolar syndrome in children: Patient characteristics, diagnostic delays and associated complications. J Paediatr Child Health 2016; 52:80-84.