Supplementary table 1. Biochemical/metabolic disorders in ICEE; clinical features and relevant diagnostic tests:

Disorder group	Disorder	Sub disorder	Age of onset	Presentation </> 1 year of age	Other features	Treatable?	Test
Vitamin B6	PNPO		< 3 months	<1y	Often infants born prem, sometimes family history of infertility & recurrent miscarriage.	Yes	CSF pyridoxal phosphate (UOA)
	Pyridoxine responsive epilepsy		< 3 months	<1y	Metabolic acidosis, electrolyte disturbance, abdominal distension, and feed intolerance, resulting in misdiagnosis as hypoxic–ischaemic encephalopathy or sepsis.	Yes	CSF pipecolate (pre-treatment); (urine AASA where available)
Congenital disorders of glycosylation.	Many subtypes		</> 3 months	</> 1y	Failure to thrive & multisystem disease in early infancy; hypotonia and seizures can be part of the clinical picture.	most not	Transferrin glycoforms
Organic acidurias	Methylmalonic acidurias		</> 3 months	</> 1y	Acute metabolic decompensations.	Yes	UOA / acylcarnitines
	Propionic acidaemia		</> 3 months	</> 1y	Acute metabolic decompensations.	Yes	UOA / acylcarnitines
	D-2-hydroxyglutaric aciduria		</> 3 months	</> 1y	Developmental delay, hypotonia, dysmorphic features, often with cardiomyopathy.	No	UOA
	L-2-hydroxyglutaric aciduria		> 3 months	</> 1y	Cerebellar dysfunction.	Yes	UOA
	Combined L and D 2OH-glutaric aciduria		< 3 months	<1y	Severe muscle weakness, respiratory distress syndrome, lack of psychomotor development.	No	UOA

Supplementary table 1. Biochemical/metabolic disorders in ICEE; clinical features and relevant diagnostic tests:

	3-methylglutaconic aciduria	type Ix	< 3 months	<1y	Hypotonia or spasticity, delayed psychomotor development, intellectual disability.	No	UOA
		MEGDEL	</> 3 months	</> 1y	Deafness, encephalopathy and Leigh-like syndrome.	No	UOA
	3-methylcrotonyl-CoA carboxylate deficiency	(Types 1 & 2)	> 3 months	> 1y (majority)	Metabolic decompensation.	Partially	UOA / acylcarnitines
	Aminoacylase 1 deficiency		</> 3 months	</> 1y	Wide phenotypic heterogeneity.	No	UOA
	EMA encephalopathy		</> 3 months	<1y	Developmental delay and neuro-regression, prominent pyramidal and extra-pyramidal signs, orthostatic acrocyanosis, petechiae, severe diarrhoea.	Yes	UOA
	4-hydroxybutyric aciduria		> 3 months	>1y	Developmental delay, hypotonia, mental retardation, ataxia, hyperkinetic behaviour, aggression, sleep disturbances.	No	UOA
	Fumarase deficiency		</> 3 months	</> 1y	Hypotonia, profound psychomotor retardation, and brain abnormalities, such as agenesis of the corpus callosum, gyral defects, and ventriculomegaly. Many patients show neonatal distress, metabolic acidosis, and/or encephalopathy. Older children less likely to have epilepsy & brain malformations.	No	UOA
	Glutaric aciduria type 1		> 3 months	</> 1y	Gliosis and neuronal loss in the basal ganglia, progressive	Yes	UOA / acylcarnitines / New-born screening.

Supplementary table 1. Biochemical/metabolic disorders in ICEE; clinical features and relevant diagnostic tests:

					movement disorder / Macrocephaly / acute metabolic decompensations.		
	D-glyceric aciduria		</> 3 months	<1y	Severe mental retardation, microcephaly.	Yes	UOA
	Multiple acyl-CoA dehydrogenase deficiency		< 3 months	<1y	Acute metabolic decompensations, +/- congenital anomalies.	Yes	UOA / acylcarnitines
	Multiple carboxylase / biotinidase deficiency		</> 3 months	</> 1y	Ataxia, hypotonia, encephalopathy, and skin manifestations including alopecia and a generalized or perioral eczematous rash.	Yes	Biotinidase & UOA
Lysosomal	GM1 gangliosidosis		> 3 months	</> 1y	Coarsening facial features, and usually hepato(spleno)megaly. Cherry-red spot & dysostosis. Seizures are a major part of the progressive neurological dysfunction.	No	Leucocyte beta-galactosidase
	Krabbe		</> 3 months	late infantile >1y	Extreme irritability, spasticity, developmental delay.	No	Leucocyte galactocerebrosidase activity
Amino acids	Phenylalanine	BH4-deficient hyperphenylalaninaemia		<1y	SGA, extrapyramidal signs (truncal hypotonia, dystonia, chorea), swallowing difficulties.		
		Phenylketonuria	> 3 months	<1y	Intellectual disability, “mousy” odor, light pigmentation, eczema.	Yes	Plasma amino acids
	Proline	Hyperprolinaemia type 2	> 3 months	>1y	seizures that are usually precipitated by infection and fever	Possibly	Plasma amino acids

Supplementary table 1. Biochemical/metabolic disorders in ICEE; clinical features and relevant diagnostic tests:

	Glycine	glycine encephalopathy - (aka non-ketotic hyperglycinaemia)	< 3 months	atypical forms later	lethargy, encephalopathy, profound hypotonia, and hiccoughs.	No	CSF glycine (+ paired plasma AA)
	Methionine	Adenosine kinase deficiency	<3 months	<1y	global developmental delay, early-onset seizures, mild dysmorphic features	No	Plasma AA (Raised methionine)
	Serine	phosphoglycerate dehydrogenase deficiency	<3 months	<1y	Congenital or acquired microcephaly. hypertonia & severe developmental delay	Possibly	CSF serine (+ plasma AA)
	Branched chain AA	Maple syrup urine disease	</> 3 months	</>1y	Acute metabolic decompensations	Yes	Plasma AA (UOA) / new-born screening.
	Urea cycle	CPS deficiency, NAGS deficiency	< 3 months (usually)	</>1y	Encephalopathy, cerebral oedema-associated respiratory changes, hepatomegaly	Sometimes	NH3 and plasma AA
		OTC deficiency	</> 3 months	</>1y		Yes	NH3 and plasma AA, urine orotate
		argininosuccinic aciduria	</> 3 months	</>1y		Yes	NH3 and plasma AA
		citrullinaemia	</> 3 months	</>1y		Yes	NH3 and plasma AA
		HHH	</> 3 months	</>1y	Loss of milestones, spasticity, DD and growth	Yes	NH3 and plasma & urine AA
		Arginase deficiency	</> 3 months	</>1y	Spastic quadriplegia	Yes	NH3 and plasma AA
		Carbonic anhydrase deficiency	</> 3 months	</>1y	life-threatening metabolic crisis, with hyperammonaemia, hyperlactataemia, and ketonuria	Yes	NH3 / plasma AA /UOA
		Congenital glutamine deficiency	< 3 months	<1y	Very rare: encephalopathy, lack of normal development, seizures, and hypotonia	No	Plasma AA

Supplementary table 1. Biochemical/metabolic disorders in ICEE; clinical features and relevant diagnostic tests:

					associated with variable brain abnormalities		
Battens	Multiple subtypes		> 3 months	</>1y	developmental regression／dementia, and pigmentary retinopathy.	CLN2 only	White cell PPT, TPP1 detects CLN1 & 2 only
Purines	Adenylosuccinase deficiency		</> 3 months	</>1y	Hypotonia, sometimes IUGR & microcephaly	No	Urine purines/pyrimidines
	dihydropyrimidine dehydrogenase deficiency		> 3 months	</>1y	Phenotypically heterogeneous	No	(UOA) & purines/pyrimidines
Peroxisomal	Zellweger syndrome / peroxisome biogenesis defects		</> 3 months	</>1y	dysmorphic features, ERG frequently markedly reduced /absent. Punctate calcification of cartilage, small renal cysts may be apparent on ultrasound, and LFTs may be abnormal, sometimes with clinical jaundice.		VLCFA
	Adrenoleukodystrophy		> 3 months	>1y	Small no of boys Px with seizures first	Possible	VLCFA
Fatty acid oxidation	2,4-dienoyl-CoA reductase deficiency		<3 months	<1y	n = 2	No	Plasma amino acids, acylcarnitines, lactate
Folate	Neurodegeneration due to cerebral folate deficincy		> 3 months	>1y	irritability & WM abnormalities on brain MRI	Yes - reversible	CSF MTHF
	dihydrofolate reductase deficiency		> 3 months	>1y	megaloblastic anaemia or pancytopenia	Yes - reversible	CSF MTHF
	FOLR mutations		> 3 months	>1y	progressive ataxia	Yes - reversible	CSF MTHF
Creatine	GAMT deficiency		> 3 months	>1y	Typically, of multiple seizure types. Movement disorder in adolescence	Yes	Plasma and urine guanidinoacetate and creatine

Supplementary table 1. Biochemical/metabolic disorders in ICEE; clinical features and relevant diagnostic tests:

	Creatine transporter defect		</> 3 months	</>1y	mental retardation, severe speech delay, behavioural abnormalities, and seizures	Yes	Urine creatine
Glucose transport	GLUT-1		</> 3 months	</>1y	cyanotic attacks or of eye movement seizures which may be mistaken for opsoclonus–myoclonus	Yes	CSF/plasma glucose ratio
	Molybdenum cofactor / Sulfite oxidase deficiency		< 3 months	<1y	dystonia and developmental delay	Possibly	Urine sulphocysteine (urine purines)
Mitochondrial disease	Numerous	Pyruvate dehydrogenase deficiency	</> 3 months	</>1y	Leigh syndrome (girls with West syndrome)	Yes, sometimes	plasma and CSF lactate, fibroblast PDH activity