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Wisdom of the Land

Epileptic Encephalopathy

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Scope of Talk

- Overview of Epileptic Encephalopathy
- Issues in epileptic encephalopathy
- Frequently seen epileptic encephalopathy
- Application to daily practice in reality
- Q & A

What is Epileptic Encephalopathy?

Epileptic Encephalopathy

- 1840: First described by West WJ from the letter to *The Lancet* describing **"West syndrome"**
- 1955: Illingworth RS reported 12 cases of **"sudden mental deterioration with convulsion in infancy"**
- 1966: Gastaut H "EE related to the concept that the underlying epileptic activity may contribute to the neurodevelopmental compromise noted in children with early onset, severe epilepsy and abundant spike and wave activities"

Epileptic Encephalopathy

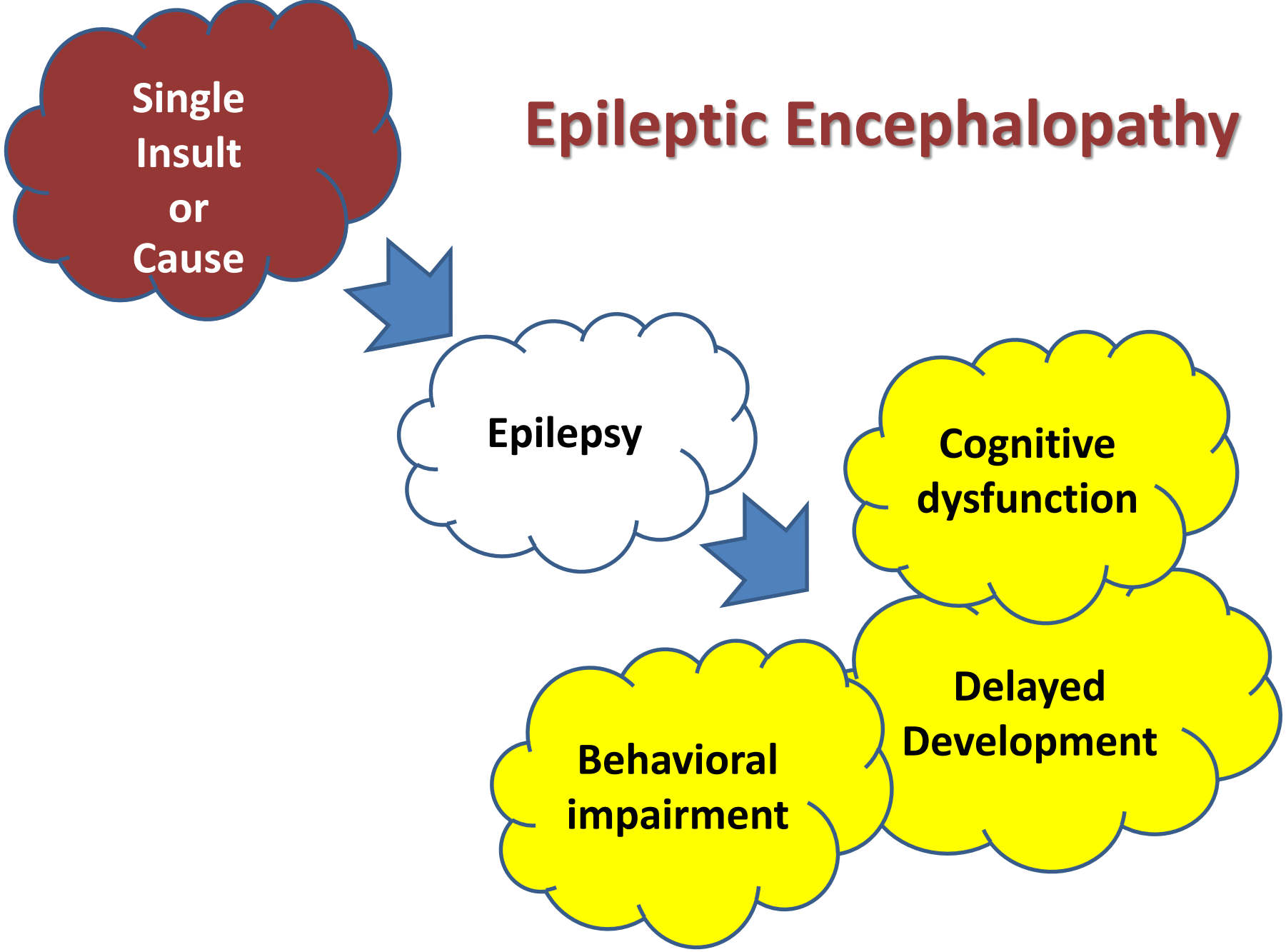
- 1841 West syndrome
- 1957 Landau-Kleffner syndrome
- 1960 Lennox-Gastaut syndrome
- 1987 Myoclonic-atonic (-astatic) epilepsy
- 1971 Electrical Status Epilepticus during sleep (ESES) & Continuous Spikes and Waves during Sleep (CSWS)
- 1976 Early Infantile Epileptic Encephalopathy (EIEE)
- 1978 Severe Myoclonic Epilepsy in Infancy (SMEI) or Dravet syndrome
- ……..

Epileptic Encephalopathy

ILAE 2001:

"A condition where the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance of cerebral function"

Epileptic Encephalopathy



Epileptic Encephalopathy

ILAE Task Force Report 2010

“ Epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairment above and beyond what may be expected from the underlying pathology alone, and that these can be worsen over time”

Epileptic Encephalopathy

Epileptic encephalopathy

is a terminology traditionally given to a group of epilepsies

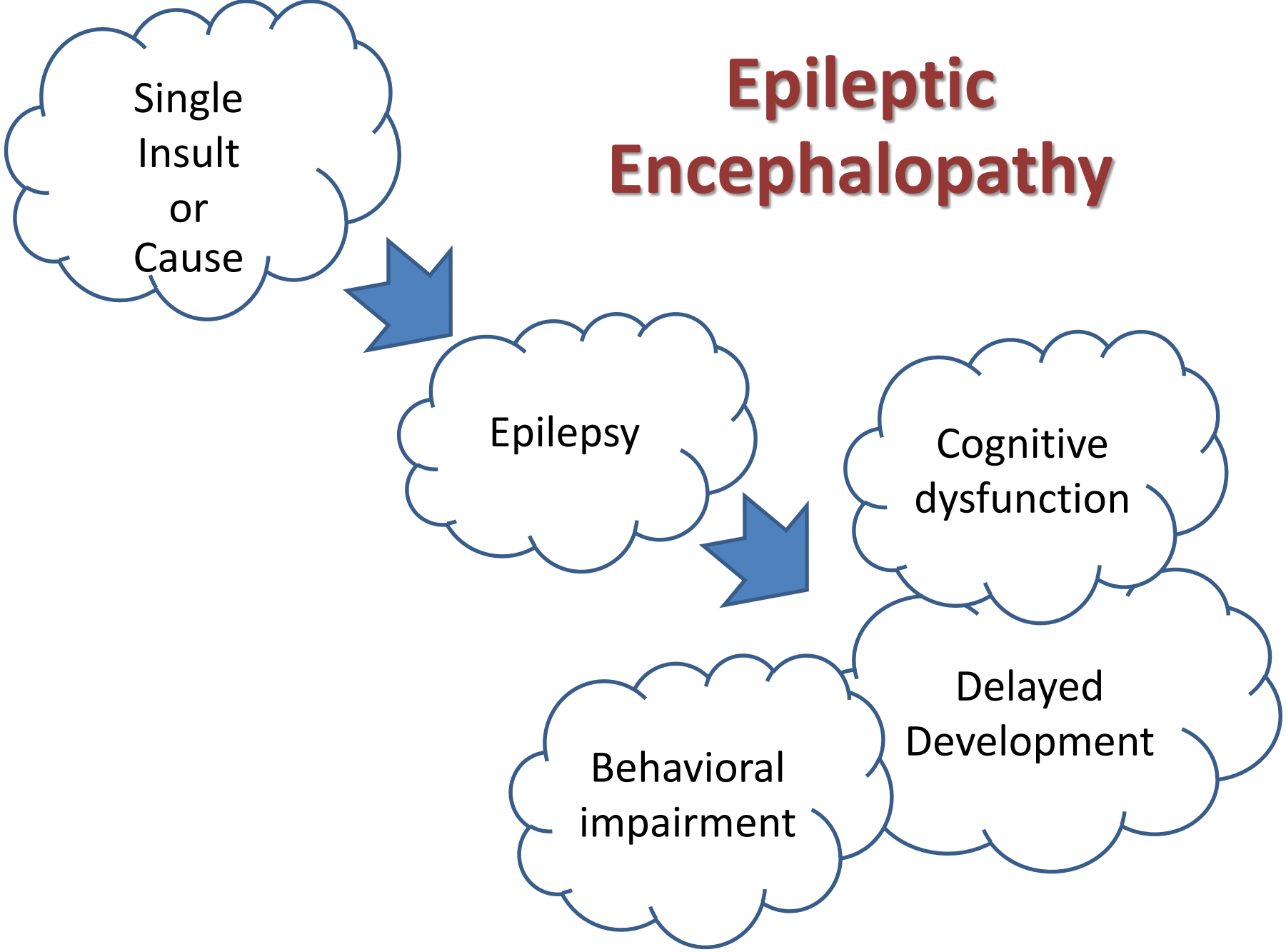
with onset early in childhood,

and poor prognosis for seizure and developmental

outcome,

presumed to be related to the ongoing epileptic activity

Epileptic Encephalopathy



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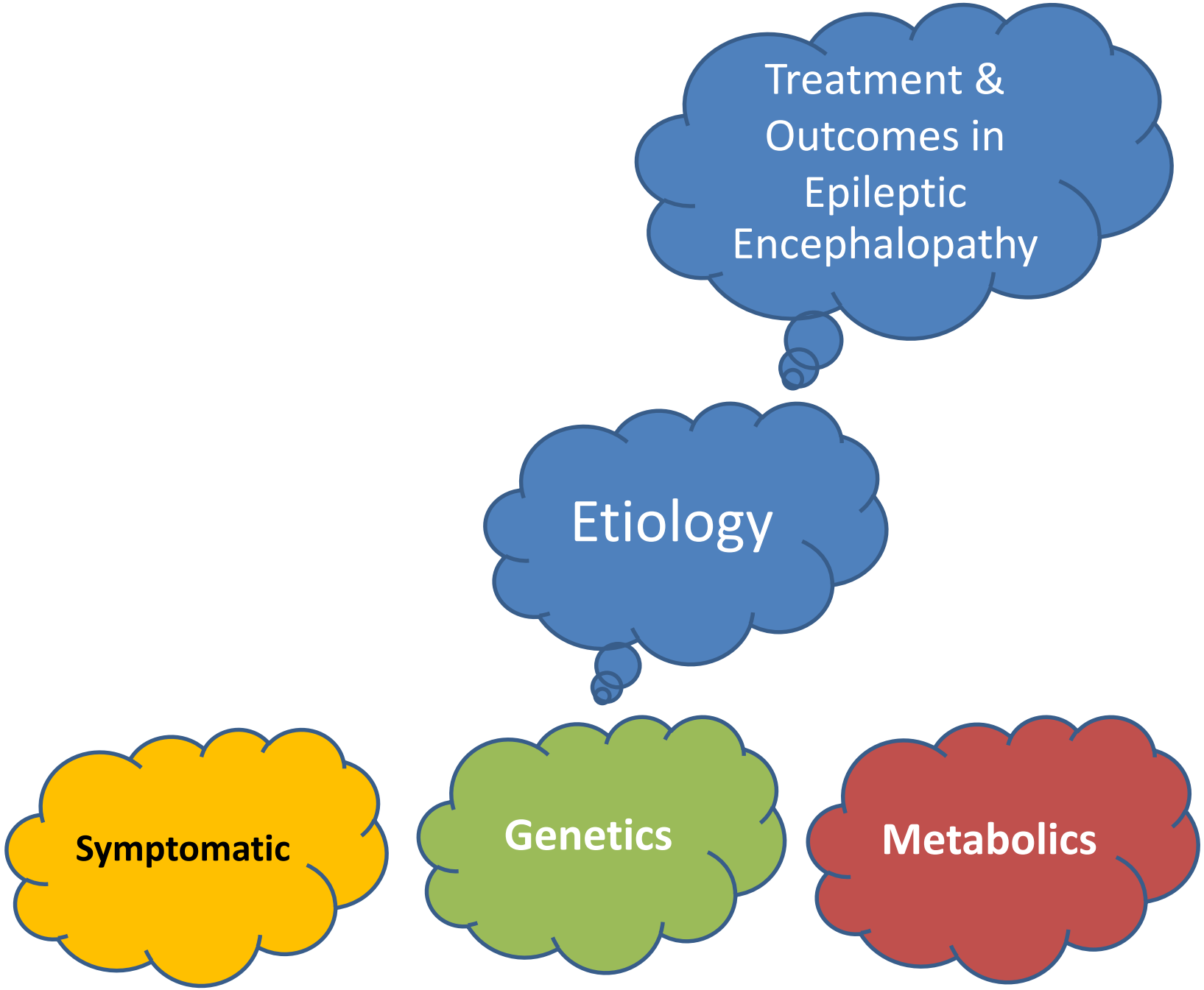
Treatment & Outcomes in Epileptic Encephalopathy
Etiology
Symptomatic
Genetics
Metabolics

Metabolic Causes of Epileptic Encephalopathy:

Amino acidemias & Organic acidopathies

Yuezhou J, Pearl PL. Epilepsy Res Treat 2013;ID124934

Disorder	Defective enzyme	Diagnostic metabolites
Propionic acidemia (PA)	Propionyl CoA carboxylase	Propionylcarnitine (C3; P)* Methylcitrate (U)* 3-Hydroxypropionic acid (U)
Methylmalonic acidemia (MMA)	Methylmalonic mutase Cobalamin A Cobalamin B	Methylmalonic acid (P, U) Propionylcarnitine (C3; P) Methylcitrate (U) 3-Hydroxypropionic acid
Methylmalonic acidemia with homocysteinuria, cobalamin C/D	Cobalamin C Cobalamin D	Methylmalonic acid (P, U) Propionylcarnitine (C3; P) Methylcitrate (U) Total homocysteine (P) 3-Hydroxypropionic acid (U)
Isovaleric acidemia (IVA)	Isovaleryl dehydrogenase	Isovaleric acid (U) Isovalerylcarnitine (C5; P)
3-Methylcrotonylglycinuria (3MCC)	3-Methylcrontonyl CoA carboxylase	3-Hydroxyisovaleric acid (U) 3-Methylcrotonylglycine (U) Hydroxyisovalerylcarnitine (C5OH; P)
3-Hydroxy-3-methylglutaryl CoA lyase deficiency	3-Hydroxy-3-methyl-glutaryl CoA Lyase	Hydroxyisovalerylcarnitine (C5OH; P) 3-Hydroxy-3-methylglutaric acid (U) 3-Methylglutaconic acid (U)
Malonic aciduria	Malonyl CoA decarboxylase	Malonate (U)
2-Methyl-3-hydroxybutyrl CoA dehydrogenase deficiency	2-Methyl-3-hydroxybutyryl CoA dehydrogenase	2-Methyl-3-hydroxybutyrate (U) Tiglylglycine (U)

Amino acidemias & Organic acidopathies

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Disorder	Defective enzyme	Diagnostic metabolites
Ethylmalonic encephalopathy	Branched chain Keto-dehydrogenase	Ethylmalonic acid (U) Methylsuccinic acid C4–C6 acylglycines (P)
Beta-ketothiolase deficiency	3-Methyl acetoacetate thiolase	C5:1 (P) 2-Methyl-3-hydroxybutyrate (U) Tiglylglycine (U) 2-Methyacetoacetate (U)
Biotinidase deficiency and Holocarboxylase synthetase deficiency	Biotinidase Holocarboxylase synthetase	Propionylcarnitine (C3; P) Hydroxyisovalerylcarnitine (C5OH; P) Biotinidase enzyme deficiency (P) Lactate (P, U) 3-Methylcrotonylglycine (U) Methylcitrate (U) 3-Hydroxypropionic acid (U)
2-Methyl butyryl CoA dehydrogenase	2-Methyl butyryl CoA dehydrogenase	2-Methylglycience (U) Isovalerylcarnitine (C5; P)
Glutaric acidemia I	Glutaryl CoA dehydrogenase	Glutaric acid (U) 3-Hydroxyglutaric acid (U) Glutaryl carnitine (C5-DC; P)
3-Methylglutaconic acidurias	3-Methylglutaconyl CoA hydratase (Type I) Barth (Type II) Costeff (Type III) Type IV Type V	3-Methylglutaconic acid (U) Hydroxy-isovalerylcarnitine (P)
Canavan disease	Aspartoacylase	N-Acetylaspartic Acid (U)

Amino acidemias & Organic acidopathies

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Disorder	Defective enzyme	Diagnostic metabolites
D-2-Hydroxyglutaric aciduria	D-2-Hydroxyglutarate dehydrogenase Hydroxy-oxoacid transhydrogenase	D-2-Hydroxyglutaric acid (U)
4-Hydroxybutyric Aciduria	Succinate semialdehyde dehydrogenase	Gamma-hydroxybutric acid (U)
Fumaric aciduria	Fumarate hydratase	Fumarate (U)
Maple syrup urine disease (MSUD)	Branched chain Keto-dehydrogenase	Leucine (P) Alloisoleucine (P) Dicarboxylic acids (U)
Dihydrolipoamide dehydrogenase	MSUD III	Leucine (P) Alloisoleucine (P) Dicarboxylic acids (U) Lactic acid (P, U)
Phenylketonuria (PKU)	Phenylalanine hydratase (PAH)	Phenylalanine (P) Low tyrosine (P)

Metabolic Causes of Epileptic Encephalopathy: Fatty Acid Oxidation Disorders & Biochemical Characteristics

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Disorder	Biochemical characteristics
Carnitine uptake defect (CUD) (Primary/systemic carnitine deficiency, carnitine transporter OCTN2 deficiency)	↓↓↓ Carnitine (P)
Carnitine palmitoyltransferase I deficiency (CPT 1A)	↑ Ammonia (P) ↑ Liver enzymes (ALT, AST)
Carnitine palmitoyltransferase II deficiency (CPT II) (i) lethal neonatal (ii) infantile (iii) myopathic	↑ C12–C18 acylcarnitines (P)
Carnitine-acylcarnitine translocase deficiency (CACT)	↑ Ammonia (P) ↑ Liver enzymes (ALT, AST) ↑ Creatine kinase (P) ↑ Long chain acylcarnitines (P) ↓ Free carnitine (P)
Mitochondrial trifunction protein deficiency (TFP) (i) Isolated long chain Acyl-CoA Dehydrogenase deficiency (LCHAD)	Hypoketotic hypoglycemia
Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)	Hypoglycemia (ketotic or nonketotic)
Medium chain acyl-CoA dehydrogenase deficiency (MCAD)	Hypoketotic hypoglycemia
Medium chain 3-ketoacyl-CoA thiolase deficiency (MCKAT)	Ketotic lactic aciduria C6–C12 dicarboxylic aciduria
Short chain acyl-CoA dehydrogenase deficiency (SCAD)	↑ Ethylmalonic acid (U)
Medium/short chain acyl-CoA dehydrogenase deficiency (M/SCHAD)	Hyperinsulinemic hypoglycemia ↑ 3-Hydroxybutylcarnitine ↑ 3-Hydroxy butyric acid (U) ↑ 3-Hydroxy glutaric acid (U)

Metabolic Causes of Epileptic Encephalopathy: Mitochondrial Disorders & Epilepsy

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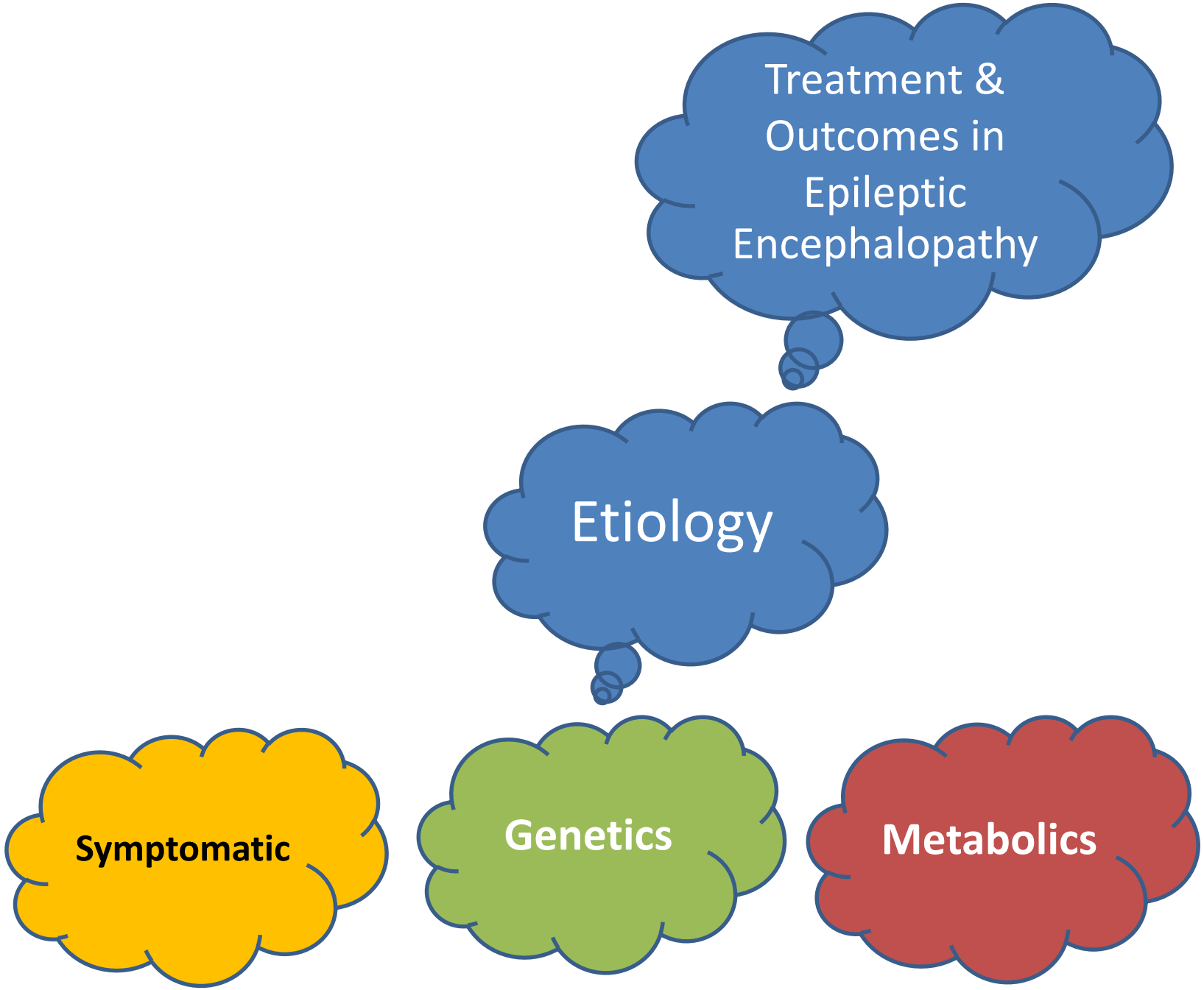
Category of disorder	Syndrome
Mitochondrial complex deficiencies	(i) Complex I deficiency (ii) Complex II deficiency (iii) Complex III deficiency (iv) Complex IV deficiency (v) Complex V deficiency
Mitochondrial DNA disorders	(i) mtDNA depletion syndromes (a) POLG1 disease (1) Alpers-Huttenlocher disease (2) Childhood onset epilepsia partialis continua (EPC) (3) Myoclonic epilepsy myopathy sensory ataxia (MEMSA) (ii) mtDNA deletion syndromes (a) Kearns-Sayre syndrome (KSS) (b) Chronic progressive external ophthalmoplegia (CPEO) (iii) Myoclonic epilepsy with ragged-red fibers (MERRF) (iv) Myoclonic epilepsy, lactic acidosis, and stroke (MELAS)
Other associated syndromes	Leigh syndrome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Genetic Causes of Epileptic Encephalopathy

Gene	Locus	Protein Function	Epileptic Encephalopathy	Clinical Features	Available Gene Test*
Aristaless-related homeobox gene (*ARX*, OMIM number 300382)	Xp22.13	Transcriptional repressor and activator	X-linked infantile spasms/ West syndrome or early infantile epileptic encephalopathy 1 (OMIM number 308350)	Infantile spasms Mental retardation Hypsarrhythmia	Sequence analysis of the entire coding region Targeted mutation analysis Deletion/duplication analysis
			X-linked myoclonic seizures, spasticity, and intellectual disability syndrome (OMIM number 308350)	Generalized spasticity Myoclonic epilepsy Intellectual impairment	Mutation scanning of select exons Prenatal diagnosis Carrier testing
			Idiopathic infantile epileptic-dyskinetic encephalopathy (OMIM number 308350)	Infantile spasms Mental retardation Dyskinetic movements Generalized dystonia	
			Ohtahara syndrome (OMIM number 308350)	Tonic spasms and other seizures Neurocognitive impairment Suppression burst on EEG	
Cyclin-dependent kinase-like 5 (*CDKL5*, OMIM number 300203)	Xp22	Serine-threonine kinase	Early infantile epileptic encephalopathy 2 (OMIM number 300672)	Infantile spasms Mental retardation and severe motor impairment Hypotonia Poor eye contact Rett-like phenotype (secondary deceleration of head growth, sleep disturbances, hand apraxia, and stereotypies)	Sequence analysis of the entire coding region FISH-metaphase Deletion/duplication analysis Prenatal diagnosis Carrier testing

Mastrangelo M, Leuzzi V. Pediatr Neurol 2012;46:24-31.

Genetic Causes of Epileptic Encephalopathy

Gene	Locus	Protein Function	Epileptic Encephalopathy	Clinical Features	Available Gene Test*
Solute carrier family 25, member 22 (*SLC25A22*, OMIM number 609302)	11p15.5	Mithocondrial glutamate/ H^+ symporter	Ohtahara syndrome (OMIM number 308350) Early infantile epileptic encephalopathy 3 (OMIM number 609304)	Myoclonic seizures Hypotonia Microcephaly Suppression burst pattern on EEG Abnormal electroretinogram	Sequence analysis of the entire coding region Deletion/duplication analysis Prenatal diagnosis Carrier testing
Syntaxin binding protein 1 (*STXBP1*, OMIM number 602926)	9q341	Modulator of synaptic vesicle release	Ohtahara syndrome (OMIM number 308350) Early infantile epileptic encephalopathy 4 (OMIM number 612164)	Tonic spasms or tonic-clonic seizures Mental retardation Hypotonia Suppression-burst on EEG	Sequence analysis of the entire coding region Deletion/duplication analysis Prenatal diagnosis
Nonerythrocytic α-spectrin-1 (*SPTAN1*, OMIM number 182810)	9q33-q34	Cytoskeletal protein	Early infantile epileptic encephalopathy 5 (OMIM number 613477)	Infantile spasms with hypsarrhythmia Generalized seizures Mental retardation Spastic quadriplegia Progressive microcephaly Hypomyelination and diffuse brain atrophy on MRI	Sequence analysis of the entire coding region Prenatal diagnosis
Phospholipase Cβ1 (*PLCβ1*, OMIM number 607120)	20p12.3	Enzyme involved in cellular signalling	Ohtahara syndrome (OMIM number 308350) West syndrome, or early infantile epileptic encephalopathy 1 (OMIM number 308350)	Tonic seizures Infantile spasms	Sequence analysis of the entire coding region (not commercially available) Deletion/duplication analysis (not commercially available)
Membrane-associated guanylate kinase inverted-2 (*MAGI2*, OMIM number 606382)	7q11.23-q21.1	Synaptic scaffolding protein	West syndrome, or early infantile epileptic encephalopathy 1 (OMIM number 308350)	Infantile spasms Mental retardation	Sequence analysis of the entire coding region (not commercially available) Deletion/duplication analysis (not commercially available)

Genetic Causes of Epileptic Encephalopathy

Gene	Locus	Protein Function	Epileptic Encephalopathy	Clinical Features	Available Gene Test*
Protocadherin 19 (*PCDH19*, OMIM number 300460)	Xq22	Adhesion protein	Epilepsy and mental retardation limited to females (OMIM number 300088) Dravet syndrome (OMIM number 607208)	Febrile and afebrile seizures Rare myoclonic jerks and atypical absences Mental retardation Motor impairment	Sequence analysis of the entire coding region Sequence analysis of select exons Deletion/duplication analysis Prenatal diagnosis Carrier testing
Pyridoxamine 5-prime-phosphate oxidase (*PNPO*, OMIM number 603287)	17q21.32	Enzyme in pyridoxine activation cascade	*PNPO* deficiency (OMIM number 610090)	Parental consanguinity Low Apgar scores Perinatal respiratory distress Pyridoxine-unresponsive seizures Suppression burst pattern on EEG	Sequence analysis of the entire coding region Analyte Prenatal diagnosis Carrier testing

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Epileptic Encephalopathy

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- 1957 Landau-Kleffner syndrome
- 1960 Lennox-Gastaut syndrome
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- 1971 Electrical Status Epilepticus during sleep (ESES) & Continuous Spikes and Waves during Sleep (CSWS)
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- ……..

West Syndrome

- Triad: epileptic spasms, delayed development, typical EEG
- Cumulative incidence: 2.9/10000 live-birth
- EEG:
  - often reveals a hypsarrhythmic pattern (very high-voltage, up to 500 mV, slow waves, irregularly interspersed with spikes and sharp waves randomly occur in all cortical areas, asynchronous over both hemispheres
  - variants
- Seizures manifestation:
  - Clusters of increasing plateau–decreasing intensity brisk (0.5–2.0 s) flexions or extensions of the neck, with abduction/adductionof the upper limbs.
  - Often associated with a lateralized brain lesion
- Developmental delay predates the onset of spasms:70%

Lennox-Gastaut Syndrome

- 2.9% of all childhood epilepsy and characterized by
  - Intractable brief tonic and atonic seizures, atypical absences,
  - Generalized interictal EEG pattern of spike and slow-wave discharges
  - Cognitive impairment
- Refractory to treatment
- Poor prognosis

Landau-Kleffner Syndrome

- A rare, severely disabling disorder
- Insidious, or sudden, loss of language understanding (auditory agnosia), followed by progressive or fluctuating loss of verbal expression
- Age at onset: 3 - 7 years
- Focal seizures represent the initial symptom in 60% of children
- EEG:
  - Spike-waves predominate in the temporoparietal regions, bilaterally, or on either side
- Outcome: varies

CSWS/ESES

- Epilepsy with continuous spike-and-wave discharges during slow sleep (or electrical status epilepticus during slow sleep), continuous sleep-related EEG discharges, persisting for months to years
- Seizure
  - Nocturnal, focal seizures start at 3–5 years, followed by continuous spike and waves during slow-wave sleep
  - Atypical or atonic absences
- Associated with cognitive decline
  - Marked decrease in intelligence quotient scores
  - Attention deficit and hyperactivity,
  - Some with language disturbances & autistic features
- Normal function with seizure remission related to early Rx

Dravet Syndrome

- Prevalence in children with seizure onset in the first year of life: 3 - 8%
- Seizure
  - Initial manifestations start before 1 yr old
    - repeated generalized or unilateral clonic (hemiclonic with alternating side) seizures, typically triggered by fever
    - prolonged, recur in clusters in the same day, and may evolve into status epilepticus
    - Precipitated by fever
  - Ages of 1 and 4 years other seizure types appear,
    - Myoclonic jerks can be massive and involve the whole body, leading to falling, or be mild and barely visible, exhibiting a multifocal distribution
    - Absence seizures are present in 40–90% of patients
    - Focal, tonic seizures
  - NCSE 40%
- Long-term outcome:
  - Developmental delay, behavioral & attention problems, gait dysfunctions
  - Mental retardation in *PCDH19* mutation

Myoclonic-astatic Epilepsy (Doose Syndrome)

- A generalized epilepsy syndrome with multiple seizure types in a previously normal child between the ages of 18 and 60 months, with a peak around 3 years
- Incidence 1–2% of all childhood epilepsies up to age 9 yrs
- Seizure:
  - myoclonic– astatic,
  - absences,
  - tonic–clonic, and eventually tonic seizures
- Outcomes:
  - Cognitive impairment in children with early onset
  - Remission with normal cognitive function up to 75%

Epileptic Encephalopathy

- Issues every physician facing
  - Investigation & specific diagnosis
  - Treatment
  - Co-morbidity
  - Long-term outcome
  - Genetic counseling

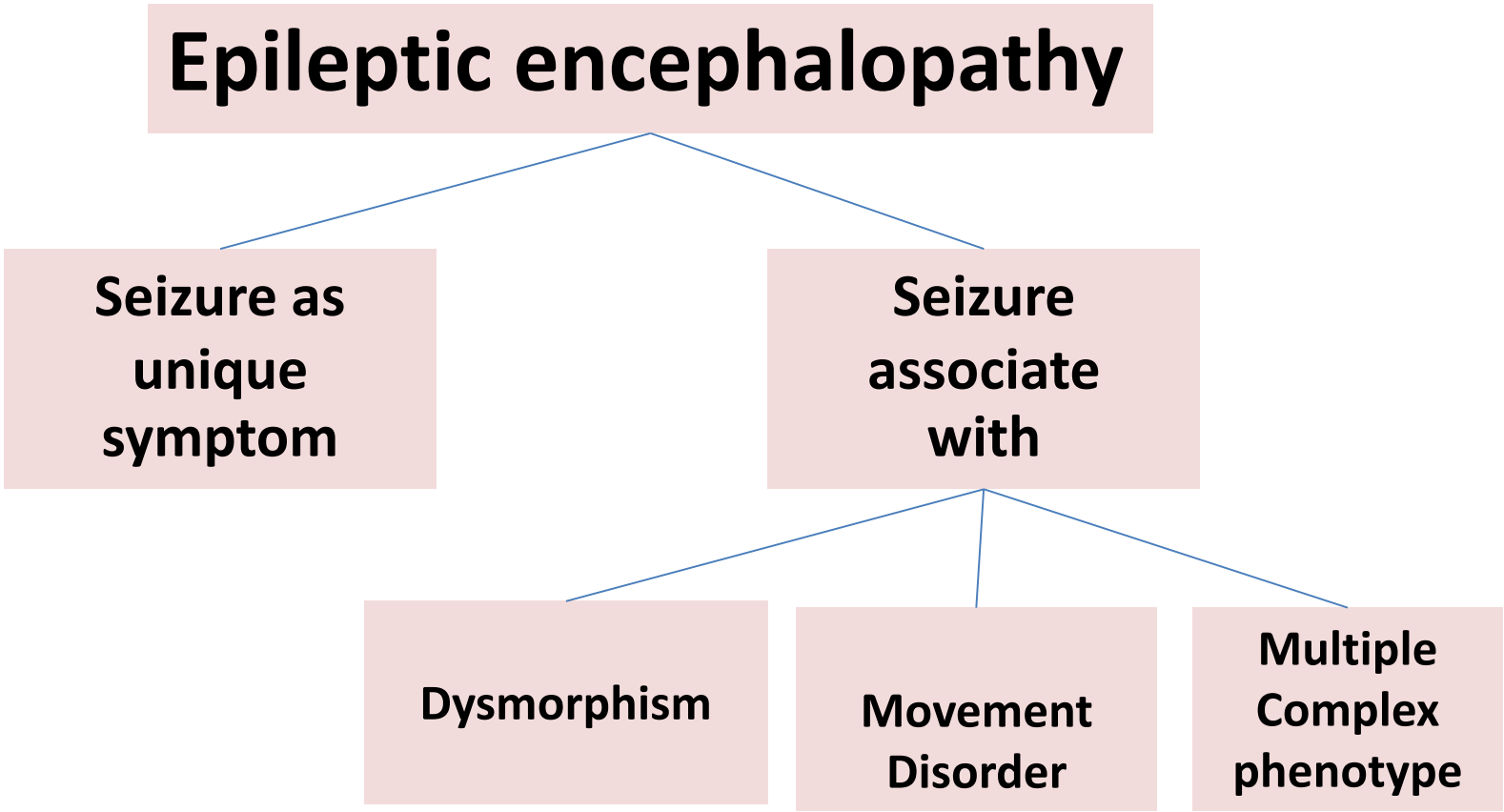
Investigation

- Exclusion of symptomatic causes
- Consider from initial clues
- For those who do not have definitive cause, with a normal MRI or a non-specific MRI, consider genetic etiology
- For those with relatively progressive clinical course: metabolic work-up should be considered

Investigation to Diagnose Genetic-Metabolic Epileptic Encephalopathy

Not that easy/simple

Diagnostic Algorithm for Patients with Infantile Epileptic Encephalopathies



Mastrangelo M, et al. Euro J Paediatr Neurol 2012;16:179-191.

Epileptic Encephalopathy with Seizure as Unique Symptoms

Pyridoxine dependent epilepsy
Folinic acid responsive epilepsy
Pyridoxal-5′-phosphate responsive epilepsy
Dravet and Dravet-like syndrome
Ohtahara syndrome (EIEE)
Early myoclonic encaphalopathy (EME)
Syntaxin binding Protein 1 (STXBP1) deficiency
Glutamate mitochondrial transporters deficiencies (SLC25A22 and SLC25A18)
Phospholipase C beta-1 deficiency
MAGI2 related epileptic encephalopathy
Protocadherin 19 related epileptic encephalopathy
Hyperprolinemia type II
GABA transaminase deficiency

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Epileptic Encephalopathy with Seizure & Dysmorphism

1p36 monosomy
Wolf-Hirschhorn syndrome
18q- syndrome
Angelman syndrome
Ring chromosome 20 syndrome
Down syndrome
Cyclin-dependent kinase-like 5 (CDKL5) deficiency
Rett Syndrome (MeCP2, CDKL5 or FOXG1-related)
Focal cortical dysplasia (TSC1 and TSC2)
Polymicrogyria (SRPX2, KIAA1279, GPR56, PAX6, TBR2, COL18A1, RAB3GAP1, 22q11., FLN1A, ARFGEF2, LRP)
Subcortical band heterotopia (DCX, LIS1, trisomy 9p)
Periventricular nodular heterotopia (unbalanced translocation, t[1; 6][p12; p12.2)]
Lissencephaly (LIS1, DCX, microdeletion in 17p including LIS1 and YwaE, ARX, TUBA1A, RELN)
Schizencephaly (EMX2 involved in sporadic cases)
Early infantile epileptic encephalopathy type I (ARX-related EIEE1)
Miller-Dieker syndrome
Smith-Lemli–Opitz syndrome
Phenylketonuria and hyperphenylalaninemias
Sulfite oxidase deficiency
Molybdenum cofactor deficiency
Menkes disease

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Epileptic Encephalopathy with Seizure & Multiple Organ Involvement

Glutathione synthetase deficiency
Mitochondrial disorders (SUCLA2, SUCLG1)
Biotin metabolism disorders
Congenital glutamine deficiency
Developmental delay, Epilepsy and Neonatal Diabetes (DEND syndrome)
Hyperinsulinism/Hyperammoniemia (HI/HA)
Mitochondrial disorders (Leigh syndrome, multiple deletion syndrome or Alpers disease, pyruvate dehydrogenase deficiency)
Lysosomal disorder (Krabbe disease)
Peroxisomal disorder (neonatal adrenoleukodystrophy, Zellweger syndrome, infantile Refsum disease, punctuate rhyzomelic chondrodysplasia)
Niemann-Pick disease type A and C
Neuronal ceroid lipofuscinosis
MAGI2 deletion syndrome
Serine byosynthesis disorders

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Epileptic Encephalopathy with Seizure & Movement Disorders

- GLUT1 deficiency syndrome
- Creatine deficiency syndrome
  (AGAT, GMAT, X-linked creatine transporter deficiency)
- EIEE1 (ARX-related epileptic encephalopathy)
- 4-hydroxybutyric aciduris (SSADH)

Clues:
Metabolic/Genetic Epileptic Encephalopathy

Symptom or sign	Differential diagnoses
Alopecia and dermatitis	Biotinidase deficiency (present in <50%)
Ambiguous genitalia	*ARX*-related conditions, SLO
Ataxia	Angelman, biotinidase deficiency, congenital disorders of glycosylation, GLUT1 deficiency, mitochondrial disorders, *SCN1A*, *PCDH19*
Blistering skin lesions	Incontinentia pigmenti
Chilblain lesions	Aicardi–Goutieres
Cardiomyopathy	D-2-hydroxyglutaric aciduria, mitochondrial disorders
Dysmorphic features (may not be present at initial presentation)	Angelman, chromosomal microdeletions or duplications, congenital disorders of glycosylation, lysosomal disorders, Menkes, Mowat–Wilson, peroxisomal disorders, sulfite oxidase deficiency and molybdenum cofactor deficiency
Dystonia or movement disorder	Aromatic L-amino acid decarboxylase deficiency, *ARX* mutations, disorders of creatine biosynthesis, *FOXG1* mutations, Glutaric aciduria type 1, GLUT1 deficiency, *MECP2* mutations, mitochondrial disorders, neuronal ceroid lipofuscinoses, *STXBP1* mutations
Hepatomegaly	Fructose 1,6 biphosphatase deficiency, glycogen storage diseases, hyperinsulinism, mitochondrial disorders, VLCADD
Hepatosplenomegaly	Lysosomal, peroxisomal
Hirsutism	*SURF-1* mutations
Macrocephaly	Canavan, glutaric aciduria type 1, Tay–Sachs
Microcephaly	Angelman, *CDKL5* mutations, congenital disorders of glycosylation, *FOXG1* mutations, GLUT1 deficiency, *MECP2* mutations, serine deficiency disorders, Smith–Lemli–Opitz, sulfite oxidase deficiency, molybdenum cofactor deficiency
Oculogyric crisis	Aromatic L-amino acid decarboxylase deficiency
Ophthalmology	
Cataract	Peroxisomal, serine deficiency disorders
Cherry red spot	Sphyngolipidoses
Chorioretinal lacunae	Aicardi
Corneal clouding	Lysosomal
Lens subluxation	Sulfite oxidase deficiency, molybdenum cofactor deficiency (occurs late)
Optic atrophy	Canavan, PEHO syndrome, neuronal ceroid lipofuscinosis
Proteinuria, nephrotic syndrome, renal impairment	Galloway–Mowat
Short limbs	Hypophosphatasia
Sparse or kinky hair	Menkes
2/3 Toe syndactyly	SLO

Kamien BA, et al. J Clin Neurosc 2012;19:934-941.

Investigation in Epileptic Encephalopathy

Cerebrospinal fluid (CSF)	
CSF glucose compared to blood glucose ratio	CSF:blood glucose ratio <0.35 indicates GLUT1 deficiency
CSF lactate	Raised in disorders of energy metabolism
CSF amino acids compared to blood amino acids	Non-ketotic hyperglycinaemia, serine deficiency
CSF folate	Low in MTHFR deficiency
CSF neurotransmitter and pterin profiles	For disorders of neurotransmission and biogenic amine metabolism
Blood	
Copper and ceruloplasmin	Decreased in Menkes disease
7-Dehydrocholesterol	Elevated in SLO
Uric acid	Increased in glycogen storage disorders, disorders of purine metabolism, fatty acid oxidation defects. Reduced in sulfite oxidase deficiency and molybdenum cofactor deficiency
Transferrin isoforms	For congenital disorders of glycosylation
Very long chain fatty acid analysis	For peroxisomal disorders
Total homocysteine levels	MTHFR deficiency and biotinidase deficiency may not be reliably detected during amino and organic acid profiling
Biotinidase activity (dried blood spot)	Disorders of biotin metabolism
Urine	
AASA and P6C	For pyridoxine-dependent seizures
Sulfite	Increased in sulfite oxidase deficiency
Purines and pyrimidines	Disorders of purine and pyrimidine biosynthesis and degradation
Guanadino compounds	Disorders of creatine biosynthesis
Magnetic resonance spectroscopy	Reduced lactate peak – cerebral creatine deficiency Elevated lactate – mitochondrial Elevated glycine – non-ketotic hyperglycinaemia
Electron microscopy of lymphocytes or skin	Neuronal ceroid lipofuscinoses (consider in the presence of microcephaly or cerebral atrophy)

AASA = alpha-aminoadipic semialdehyde, GLUT1 = glucose transporter type 1, MTHFR = methylenetetrahydrofolate reductase, P6C = piperideine-6-carboxylic acid, SLO = Smith–Lemli–Opitz.

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Diagnostic Algorithm for Patients with Infantile Epileptic Encephalopathies

- Ohtahara, West syndrome, or severe early onset (<2 months) unclassifiable seizures:
  - STXBP1 analysis (particularly if there are also frequent non-epileptic movement disorders)
  - Males – ARX polyalanine repeat analysis (particularly in the presence of dystonia);
  - Females – CDKL5 analysis (particularly in the presence of Rett-like features such as acquired microcephaly and stereotypic hand movements)
- Dravet syndrome
  - SCN1A analysis -> if negative and female – PCDH19 analysis

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Diagnostic Algorithm for Patients with Infantile Epileptic Encephalopathies

- **POLG1 analysis**
  - Onset of seizures after 9 months, especially if there is liver involvement, ophthalmoplegia, worsening with sodium valproate, occipital EEG pattern, or MRI findings (hyperintense lesions, white matter abnormality, and atrophy)
- **FOXG1 analysis**
  - If seizures occur after 3 months, particularly if dystonia and acquired microcephaly are present, or the MRI shows frontal gyral simplification with myelination delay and a thin corpus callosum
- **MECP2 analysis**
  - In males if hypotonia, progressive microcephaly, limb rigidity, or movement disorder are present
  - In female with typical Rett syndrome

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Treatment of Epileptic Encephalopathy

- Treatment of the underlying cause, if possible
- Selection of AEDs according to syndrome, if categorizable
- Avoid polytherapy wherever possible. If necessary, limited to rational polytherapy.
- Allow sufficient time for assessment of the effect of treatment
- Consider other options (KD, surgical treatment)

Treatment of Epileptic Encephalopathy

Syndrome	Rx of Choice	Options	Rx to be avoided
Ohtahara	Corticosteroids LEV	KD, ZNS, VGB, PB	N/A
West	Corticosteroids VGB	NTZ, TPM, ZNS, KD	CBZ
Dravet	Valproate TPM	Clobazam,KD	CBZ, GBP, LTG, OXC, PTH, PGB, TGB, VGB
LGS	Valproate LTG	TPM, rufinamide, FBM, Clobazam, LEV, KD, VNS	BZD risk for SE GBP, OXC< CBZ, LTG: for myoclonic seizure
LKS	Corticosteroids	Valproate, clobazam, Sx	N/A
ESES/CSWS	Corticosteriods Clobazam	Valproate, KD	N/A
Doose	Valproate LTG KD	Clobazam, rufinamide, FBM	CBZ, PTH, VGB

Treatment of Epileptic Encephalopathy: AEDs

- VGB: for WS & focal seizure, risk of VAVL (low in infancy)
- VPA: LGS, Doose, CSWS/ESES
- LTG: LGS, Doose
- LEV: CSWS/ESES,
- TPM: WS, LGS, Dravet
- Clobazam: LGS, Dravet, CSWS/ESES
- ZNS: WS, Doose
- PER: LGS
- LCM: LGS
- Rufinamide
- Steripentol

Treatment of Epileptic Encephalopathy: Hormonal Therapy

- WS:
  - No difference between corticosteroids and VGB
  - Possible better developmental outcome in children treated with corticosteroids
  - Less serious adverse effects than VGB
- CSWS/ESES:
  - Well established efficacy
- LGS & Ohtahara syndrome:
  - not well defined efficacy

Treatment of Epileptic Encephalopathy: Ketogenic Diet

- High fat, low-protein, and very low carbohydrate diet as a long standing treatment option for epilepsy > 90 yrs
- Treatment of choice for
  - Glucose-1 transporter defect
  - Pyruvate dehydrogenase deficiency
- Favorable seizure control
  - in refractory epilepsy
    - >90% seizure-reduction 7 - 10%
    - >50% seizure-reduction 38 - 47%
  - Epileptic encephalopathy
    - Doose syndrome (>50% SR in 50% of pts)
    - Dravet syndrome (SF 12%, > 75% SR 60-70%)

Treatment of Epileptic Encephalopathy: Surgical Treatment

- Hemispeherectomy, cortical excision
  - Benefit in epileptic encephalopathy with symptomatic group/migratory defect
- Corpus callosotomy (palliative treatment)
  - Reduction of atonic seizures in LGS, Doose syndrome
- VNS (as adjunctive treatment)
  - LGS, CSWS
- Subpial transection
  - LKS (limited number, not well defined outcome)

Epileptic Encephalopathy

- Issues every physician facing
  - Investigation & specific diagnosis
  - Treatment
  - Co-morbidity
  - Long-term outcome
  - Genetic counseling

Long-term Outcomes

- Varies to etiology, syndrome, and intervention
  - Metabolic & genetic epileptic encephalopathy:
    - Pyridoxine, folinic acid and pyridoal-5’-phosphate dependent epilepsy
    - Urea cycle disorders
    - Glu-1 transportation disorder
  - Unknown etiology: WS, Dravet, Doose, CSWS, etc.

Long-term Outcome of West Syndrome Treated with Vigabatrin

- 100 patients were diagnosed with West syndrome
  - VGB: 81 patients (male 55.6%, female 44.4%)
  - Other AEDs: 19
- Follow-up duration for those who received VGB
  - Ranged from 18 to 200 mo.
  - Mean 94.2 mo.
- Seizure responsiveness at final evaluation
  - 7 (8.6%): seizure-free without AED
    seizure-free duration 6 - 16 yrs (mean 13 yrs.)
  - 14 (17.2 %): seizure-free with daily AED
    Seizure-free duration 3 - 14 yrs (mean 9.7 yrs)
  - 21 (28.4%): had other type of seizures after discontinue VGB and needed other AEDs to control seizure

Lesson-learned

- Application of knowledge
- Looking for treatable cause
- Investigation according feasibility
- Early intervention
- Consider treatment options to deliver good QOL
- Optimum treatment