EST 30th ANNIVERSARY ANNUAL MEETING

Neonatal and Infantile Epilepsy: Early Intervention & Long-term Outcomes

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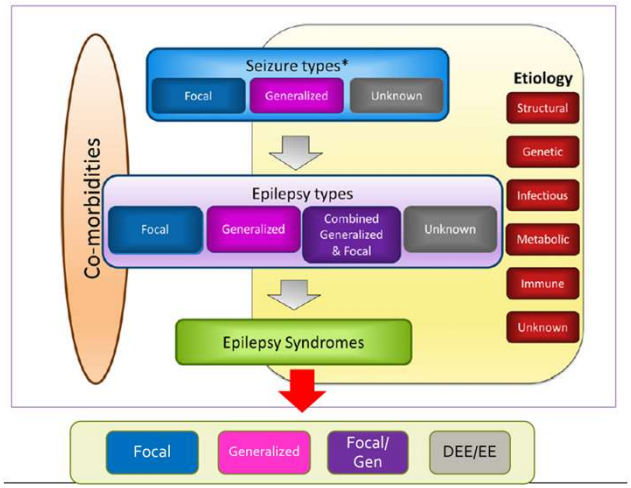
Agenda

Infantile Epilepsy: Early Intervention & Long-term Outcomes

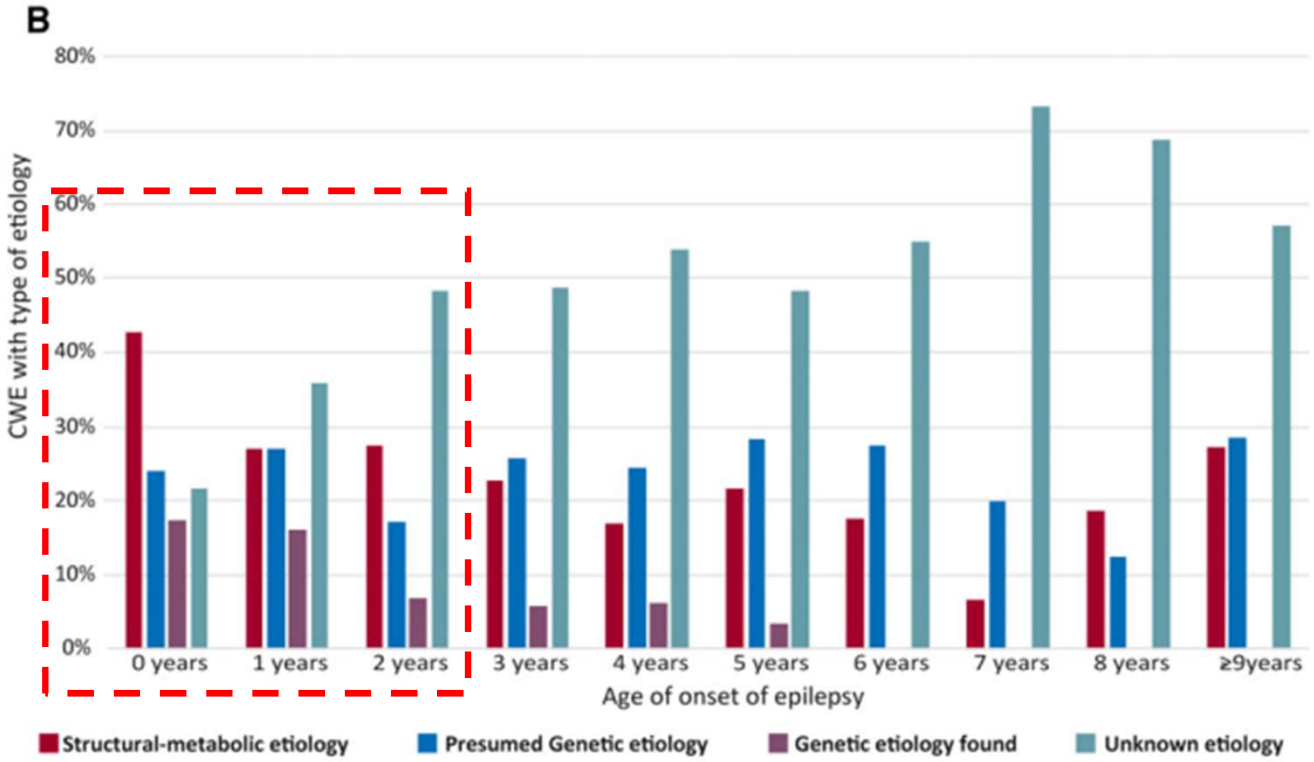
1 month- 24 months of age

Lecture นี้จะขอไม่รวมถึง IESS

Type of etiology by age of epilepsy onset, with ILAE 2017



Epilepsia 2017



Epilepsia 2017

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DOI: 10.1111/epi.17239

Epilepsia

SPECIAL REPORT

ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions

Sameer M. Zuberi[1] | Elaine Wirrell[2] | Elissa Yozawitz[3] | Jo M. Wilmshurst[4] | Nicola Specchio[5] | Kate Riney[6,7] | Ronit Pressler[8,9] | Stephane Auvin[10] | Pauline Samia[11] | Edouard Hirsch[12] | Santiago Galicchio[13] | Chahnez Triki[14] | O. Carter Snead[15] | Samuel Wiebe[16] | J. Helen Cross[17,18] | Paolo Tinuper[19,20] | Ingrid E. Scheffer[21] | Emilio Perucca[22,23] | Solomon L. Moshé[24,25,26] | Rima Nabbout[27]

Received: 11 August 2022 | Accepted: 20 October 2022
DOI: 10.1002/epi4.12665

Epilepsia Open™

CONCEPTS AND HYPOTHESES

3D figure of epilepsy syndromes

Rima Nabbout[1,2] | Mathieu Kuchenbuch[3,4] | Paolo Tinuper[5,6] | J. Helen Cross[7] | Elaine Wirrell[8]

Self-limited epilepsies

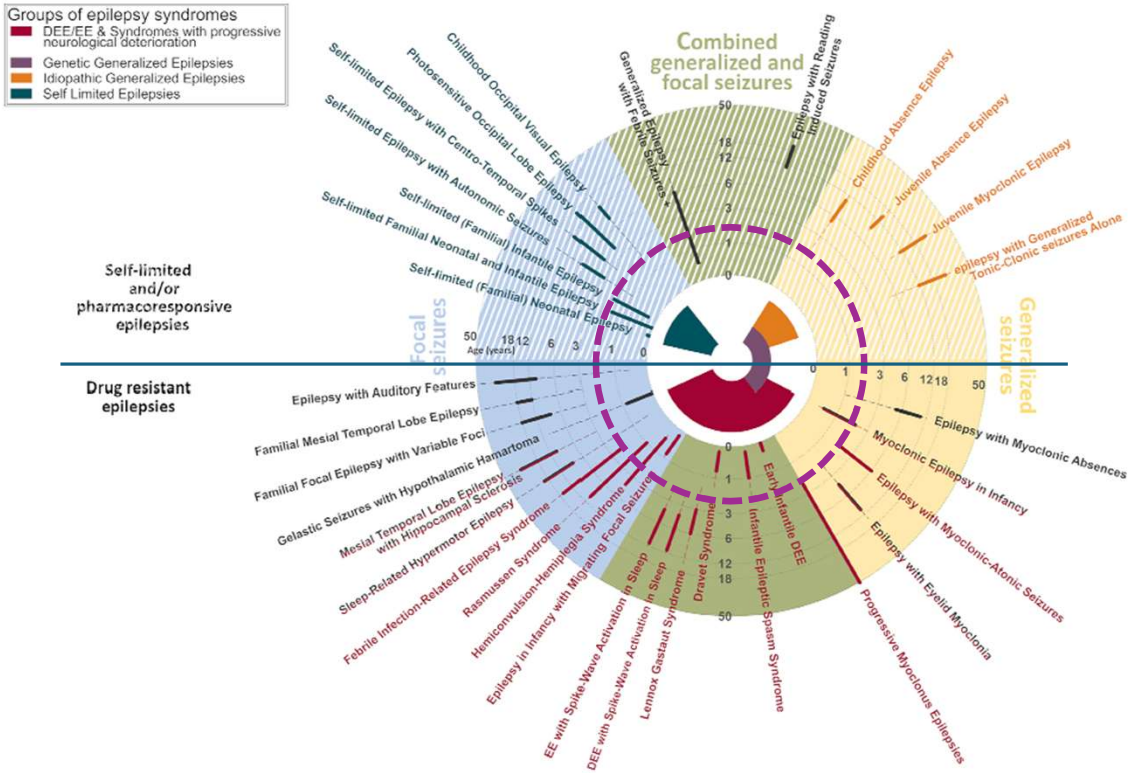
- Self-limited neonatal epilepsy (SeLNE)
- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
- Self-limited infantile epilepsy (SeLIE)
- Genetic epilepsy with febrile seizures plus (GEFS+)
- Myoclonic epilepsy in infancy (MEI)

Developmental and epileptic encephalopathies (DEE)

- Ealy infantile developmental and epileptic encephalopathy (EIDEE)
- Epilepsy in infancy with migrating focal seizures (EIMFS)
- Infantile epileptic spasms syndrome (IESS)
- Dravet syndrome (DS)

Etiology-specific syndromes

- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5′-Phosphate Deficiency (PNPO)-DEE (P5PD-DEE)
- *CDKL5*-DEE
- *PCDH19* clustering epilepsy
- Glucose Transporter 1 Deficiency Syndrome (GLUT1DS)
- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

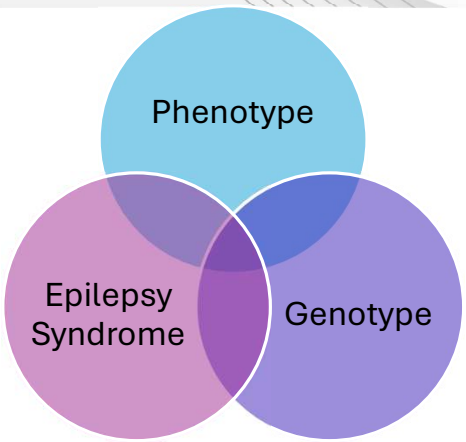


Lecture นี้จะขอไม่รวมถึง IESS

Infantile Epilepsy and Prognosis

Risk Factors of Infantile Epilepsy

- Perinatal injury
- Cortical malformations
- Genetic etiologies



- New onset epilepsy or DRE

- Medical treatment
- Dietary treatment
- Surgical treatment

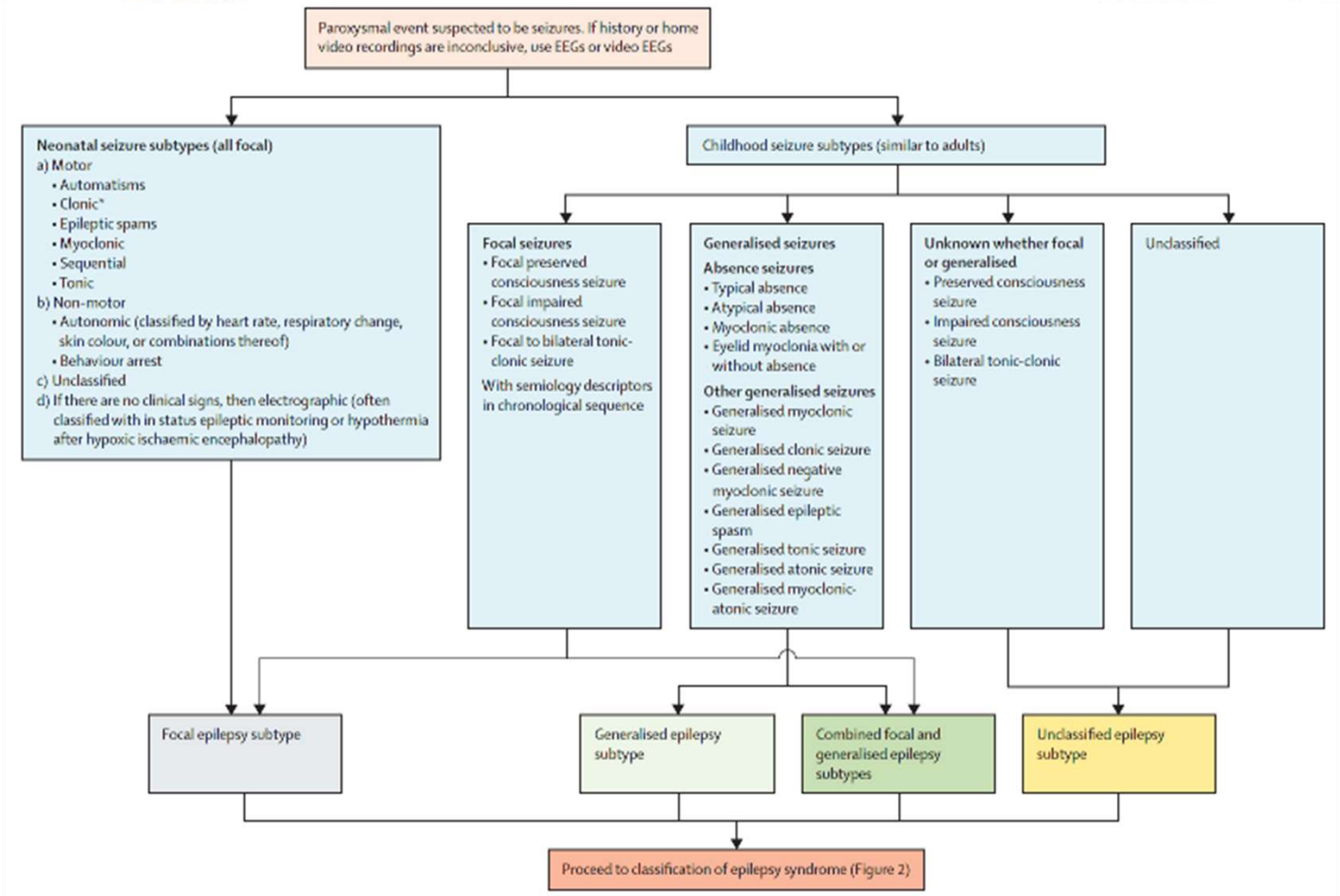
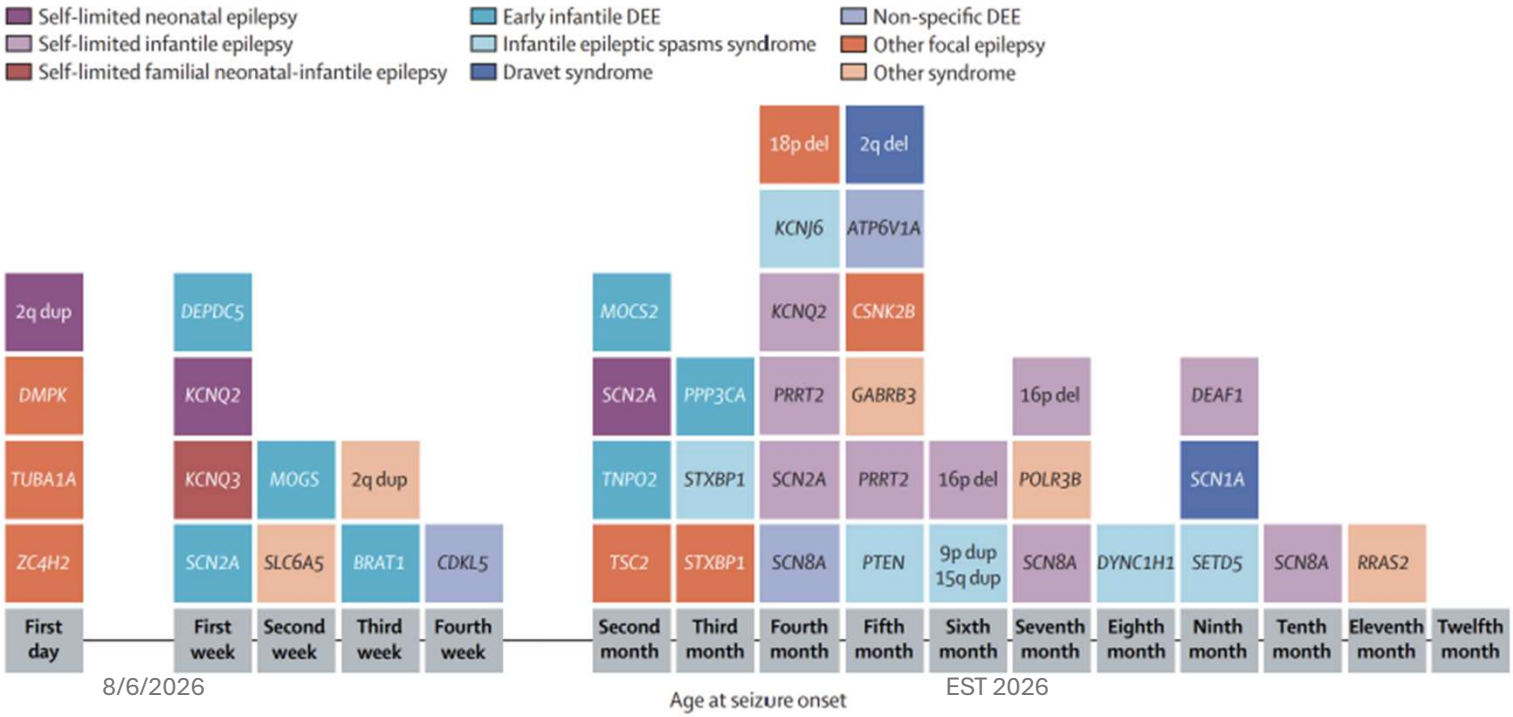


Figure 1: Classification of seizure and epilepsy subtypes in neonates and childhood

Evaluation of the feasibility, diagnostic yield, and clinical utility of rapid genome sequencing in infantile epilepsy (Gene-STEPS): an international, multicentre, pilot cohort study

Alissa M D'Gama, Sarah Mulhern, Beth R Sheidley, Fadil Boodhoo, Sarah Buts, Natalie J Chandler, Joanna Cobb, Meredith Curtis, Edward J Higginbotham, Jonathon Holland, Tayyaba Khan, Julia Koh, Nicole S Y Liang, Lyndsey McRae, Sarah E Nesbitt, Brandon T Oby, Ben Paternoster, Alistair Patton, Graham Rose, Elizabeth Scotchman, Rozalia Valentine, Kimberly N Wiltrout, Gene-STEPS Study Group*, IPCHiP Executive Committee*, Robin Z Hayeems, Puneet Jain, Sebastian Lunke, Christian R Marshall, Shira Rockowitz, Neil J Sebire, Zornitza Stark, Susan M White, Lyn S Chitty, J Helen Cross, Ingrid E Scheffer, Vann Chau†, Gregory Costain†, Annapurna Poduri†, Katherine B Howell†, Amy McTague†

Lancet Neurol 2023; 22: 812–25



Yield of genetic testing and recommended testing strategy

Diagnosis	Proportion of individuals with detectable pathogenic variant (s)	Genetic test(s) indicated
Focal epilepsies		
Familial self-limited neonatal / neonatal-infantile epilepsy (SeLNE, SeLNIE) Previously benign familial neonatal/neonatal-infantile epilepsy BFNE/BFNIE	> 90% of familial cases	ES/GS*
Self limited familial infantile epilepsy (SeLIE) Previously benign familial infantile epilepsy [BFIE]	> 90% of familial cases	ES/GS*
Autosomal dominant sleep related hypermotor epilepsy (ADSHE) Previously autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	~ 30% of familial cases	ES/GS*
Autosomal dominant epilepsy with auditory features (ADEAF)	~ 50% of familial cases	ES/GS*
Familial focal epilepsy with variable foci	~ 80% of familial cases	ES/GS*
Isolated FE	Rarely due to identified monogenic causes	ES/GS* only to be considered in case of: - positive family history - additional symptoms (*e.g.* ID, autism, dysmorphology, *etc.*) - pharmacoresistance
Generalized epilepsies		
Genetic epilepsy with febrile seizures plus (GEFS+)	~ 30% of familial cases	ES/GS*
Familial adult myoclonic epilepsy (FAME)	Up to 90%: repeat expansion	RP-PCR
Idiopathic generalized epilepsy (IGE) Childhood absence epilepsy (CAE) Juvenile absence epilepsy (JAE) Juvenile myoclonic epilepsy (JME) Generalised tonic-clonic seizures alone (GTCA)	Rarely due to identified monogenic causes	ES/GS* only to be considered in case of: - positive family history - additional symptoms (*e.g.* ID, autism, dysmorphology, *etc.*) - pharmacoresistance
Isolated GE	Rarely due to identified monogenic causes	ES/GS* only to be considered in case of: - positive family history - additional symptoms (*e.g.* ID, autism, dysmorphology, *etc.*) - pharmacoresistance
Developmental and epileptic encephalopathies (DEE)		
Unspecified DEE and related phenotypes (*e.g.* PME, complex MCD, Fragile X, *etc.*)	~ 50%	ES/GS* and/or fragment length analysis
Neonatal Early-infantile DEE	~ 60%	ES/GS*

Epileptic Disord 2022; 24 (5): 765-786

Mutated genes associated with early infantile onset DEE

Specific classification of early-infantile-onset DEEs	Associated gene
Dravet syndrome	*SCN1A, PCDH19*
Ohtahara syndrome	*KCNQ2, STXBP1*
West syndrome	*SCN3A, SCN2A, SCN8A, CACNA1H, DEPDC5, MECP2, DYNC1H1, CDKL5, ALG11, CCDC88C, GABAA1, IL1RAPL1, RNASEH2B, SLC19A3, STXBP1, QARS, COL4A2*
Early myoclonic epileptic encephalopathy	*TBC1D24*
GLUT1 deficiency syndrome	*SLC2A1*
Malignant migrating focal seizures of infancy	*KCNT1*
Early-infantile-onset DEE-BS	*KCNQ2, STXBP1, SCN2A, PIGA*
Early-infantile-onset DEEs with dyskinesia	*STXBP1, CDKL5, SLC2A1*
Early-infantile-onset DEEs limited to females with cluster seizures	*SMC1A*
Early-infantile-onset DEEs starting with febrile seizure	*SCN1A, PCDH19, HNRNPU*

DEE: developmental and epileptic encephalopathy; DEEs: developmental and epileptic encephalopathies; DEE-BS: developmental and epileptic encephalopathy with burst suppression; GLUT1: glucose transporter type 1.

Epileptic Disord 2022; 24 (2): 343-352

Phenotypic & Genotypic and ASMs Treatment

Table 1. Summary of the phenotypic and genotypic information of epilepsy related to sodium channels.

Gene	Syndrome	Functional Analysis	Type of Seizures	Treatment Used	Recommended Treatment	Reference
SCN1A	GEFS+	GoF	febrile	STRP, VPA, CLB, TPM, CBD, STCL, FEN	STRP + VPA + CLB	[9–15]
	DEE	LoF	Tonic–clonic, myoclonic			
SCN2A	BFNIS	GoF	partial, secondary generalized	PHT, CBZ, LEV, BDA, VPA	high-dose PHT	[20–22,31]
	DEE	GoF	nd			
	Episodic ataxia	GoF	nd			
	Autism spectrum disorder	LoF	nd			
	Intellectual disability, DEE	LoF	nd			
SCN8A	BFNIE, DEE	GoF	tonic	PHT, CBZ, TPM, LEV, VAL, PB	high-dose PHT	[27–31]
	EIEE13	GoF	myoclonic			
	Autism spectrum disorder	LoF	myoclonic			
	Intellectual disability	LoF	tonic, clonic, autonomic			

Table 2. Summary of the phenotypic and genotypic information of epilepsy related to potassium channels.

Gene	Variant	Functional Analysis	Type of Seizures	Treatment Used	Recommended Treatment	References
KCNA1	c.781G>A	nd	Focal	VPA	CBZ	[47]
	c.888G>T	GoF	Tonic, focal	4-AP, LEV, OXC, VPA, LCM, PHT, CLB, VGB, KD		[64]
	p.Val368Leu	LoF	Tonic–clonic	OXC, PB	OXC	[65]
	c.1213 C>T	nd	Clonic	PB, CLB, CBZ, ZNS, VPA		[66]
	c.1214C> T	nd	Generalized convulsive	PB; CBZ, LEV, PHT, LTG, VPA	AZA	
KCNA2	c.1214C>T	LoF	Focal, myoclonic seizures, FDS, focal motor seizures, secondary generalized tonic–clonic	TPM, OXC, VPA, LEV	AZA	[20]
	c.788T>C	LoF	Myoclonic, myoclonic-atonic	PB, VPA, OXC, LEV, CBZ, CLB, LTG	CLB, LTG	
	c.1214C>T	LoF	Focal, focal dyscognitive, focal motor seizures,	VPA, LEV	VPA, CLB, TPM	
	c.1214C>T	LoF	febrile, focal motor seizures, secondary generalized tonic–clonic	OXC, VPA, CLB, STM, LEV, PRED	LEV	
	c.894G>T	GoF	Generalized tonic–clonic, myoclonic	PB, PHT, VPA, CBZ, LTG, CLB, TPM, OXC, LCM, LEV	Nd	
	c.890G>A	GoF	Generalized tonic–clonic, absences	PMD, VPA, LTG	LTG	
KCNQ2	c.1678C>T	nd	Myoclonic seizures	PB, VGB	TPM	[22]
	c.917C>T	nd	Tonic	PB, CLB, LEV	VGB, ZNS, KD	
	c.997C>T	nd	Tonic	PB	TPM	
	c.601C>T	nd	Myoclonic	PB, CLB, LEV, PHT, TPM, VGB	PHT, OXC	
	c.338C>T	nd	Tonic, clonic, autonomic	PB	OXC, high-dose steroids, KD	
	c.773A>T	nd	Tonic, clonic, autonomic	CBD	LEV, KD	
	c.638G>A	nd	Tonic, autonomic	LEV, PB	PGB, LEV, VPA, KD	
	c.629G>A	nd	Tonic, clonic	PB, PHT, VPA, LEV	PHT, OXC	
	c.637C>T	nd	Tonic	VPA, VGB, TPM	LTG	
	c.794C>T	nd	Tonic	CBZ, CLB, LCM	LTG	
	c.1118 + 1G>T	nd	Tonic, clonic	VPA, OXC	VPA, OXC	
KCNQ1	c.817C>T	nd	Subsequent tonic–clonic		CBZ	[80]
KCNT1	c.1283G>A	nd	FIAM, generalized tonic, generalized tonic–clonic	KD, QUIN, CBD	CLB, LRZ, PB	[69]
	c.2849G>A	nd	Generalized tonic, generalized tonic–clonic, FIANM	KD, CBD	LEV, PB	

Table 2. *Cont.*

Gene	Variant	Functional Analysis	Type of Seizures	Treatment Used	Recommended Treatment	References
KCNT2	c.991T>A	nd	Epileptic spasm	PB, TPM	nd	[81]
	c.592C>G	nd	Focal, migrating	VPA, TPM, LTG, NZP	nd	
	c.1690A>T	LoF	focal	VPA, LTG, LEV	nd	[77]
	c.720T>A	nd	Focal seizures, myoclonus, epileptic spasm, tonic, atypical absence	TPM, NZP, LEV, LTG, VBG, ETX, LCM, KD	nd	[75]
	c.569G>A, p.	GoF	Epileptic spasm, nocturnal tonic, and bilateral tonic–clonic	VPA, VBG, RUF, PRED, KD, STM	nd	

Treatments: AZA, acetazolamide; CBD, cannabidiol; CBZ, carbamazepine, CLB, clobazam; ETX, ethosuximide; KD, ketogenic diet; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; NZP, nitrazepam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PMD, primidone; PRED, prednisolone; QUIN, quinidine; RUF, rufinamide; STM, sulthiame; TPM, topiramate, VGB, Vigabatrine; VPA, valproate; 4-AP, 4-aminopyridine; ZNS, zonisamide. Others: FIANM, focal impaired awareness non-motor onset; GoF, gain-of-function mutation; LoF, loss-of-function mutation; nd, not detected.

Int. J. Mol. Sci. 2023, 24, 16280

No comprehensive treatment guideline for infants with

- Undifferentiated syndromic
- Non-syndromic epilepsy

EST 30th ANNIVERSARY ANNUAL MEETING

Check for updates

EPILEPSY CURRENTS

Clinical Practice Guideline

Epilepsy Currents
2026, Vol. 26(3) 174–202

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Sage

American Epilepsy Society Clinical Practice Guideline: Infantile Epilepsy

Daniel Freedman, DO[1], Ifeoluwa Babatunde, PharmD, MS[2], Rebecca L. Morgan, PhD, MPH[2], Renad Abu-Sawwa, PharmD, BCPPS[3], Dara Albert, DO, MEd, FAES[4], Mandana Behbahani, MD[5], Kevin Chapman, MD, FAES[6], Erin Fecske, DNP, APRN, CPNP-PC, CNRN, FAES[7], William Davis Gaillard, MD, FAES[8], Monika Jones, JD[9], Mary Anne Meskis[10], Leah Schust Myers[11], Kim Nye[12], Chima Oluigbo, MD, FAES[8], Heidi H. Pfeifer, RD, LDN, FAND[13], Reneé A. Shellhaas, MD, MS, FAES[14], Lindsey Thompson, PhD, RD, LD[15], Howard L. Weiner, MD, FAES[16], Courtney J. Wusthoff, MD, MS, FAES[17], and Elissa Yozawitz, MD, FAES[18]

INFANTILE EPILEPSY CLINICAL DECISION TOOL

Antiseizure Medications

Disclaimer: medications are ordered alphabetically, not in order of efficacy

FIRST-LINE TREATMENT

Generalized/Unknown Epilepsy
Levetiracetam *(Recs I-A-1; I-A-4)*
Lacosamide *(Recs I-A-6)*
Topiramate *(Recs I-A-5)*

Focal Epilepsy
Carbamazepine *(Rec I-A-5)*
Lacosamide *(Recs I-A-6)*
Levetiracetam *(Recs I-A-1; I-A-4)*
Oxcarbazepine *(Rec I-A-3)*
Topiramate *(Rec I-A-5)*

Persistent Seizures

*With certain genetic etiologies, targeted therapies may be available

REFERRAL to Pediatric Epilepsy Center

SECOND-LINE TREATMENT

Generalized/Unknown Epilepsy
Lacosamide
Lamotrigine
Levetiracetam
Topiramate

Focal Epilepsy
Carbamazepine
Lacosamide
Lamotrigine
Levetiracetam
Oxcarbazepine
Topiramate

Persistent Seizures

*With certain genetic etiologies, targeted therapies may be available

Meets criteria for Drug-Resistant Epilepsy

DRUG-RESISTANT EPILEPSY ANTISEIZURE MEDICATION TREATMENT

Generalized/Unknown Epilepsy
Brivaracetam *(Rec I-B-3)*
Lamotrigine *(Rec I-B-5)*
Lacosamide
Levetiracetam
Rufinamide *(Rec I-B-4)*
Topiramate *(Rec I-B-2)*
Valproate* *(Rec I-B-1)*

Focal Epilepsy
Brivaracetam
Carbamazepine
Lacosamide
Lamotrigine *(Rec I-B-3)*
Levetiracetam
Oxcarbazepine
Topiramate *(Recs I-B-2)*

- Evidence analyses for priority Clinical Questions selected for the AHRQ systematic review and followed for the AES Infantile Epilepsy Guideline were the basis for all Recommendations referenced above except where noted for clobazam, Epidiolex, and zonisamide. Recommendations were developed using GRADE methodology.
- All Recommendations referred to in this visual are Conditional with Very Low Certainty of Evidence (CoE), except
  - Recommendations are I-A-4 and I-B-2 is Conditional with Low CoE

Special epilepsy syndromes

Lennox-Gastaut syndrome: Consider clobazam, rufinamide, valproate, Epidiolex

Dravet syndrome: Consider clobazam, valproate*, stiripentol, Epidiolex (follow published protocol)

**Valproate: Use with caution with unknown etiology or in the absence of other treatment.*

Commonly used medications that were not evaluated by this Guideline:
clobazam, pharmaceutical grade cannabidiol, zonisamide, phenobarbital, phenytoin, fenfluramine
Felbamate and gabapentin not used often
*note that zonisamide does not have FDA approval in this age range

Non-syndromic epileptic Treatment

Non-syndromic epileptic Treatment

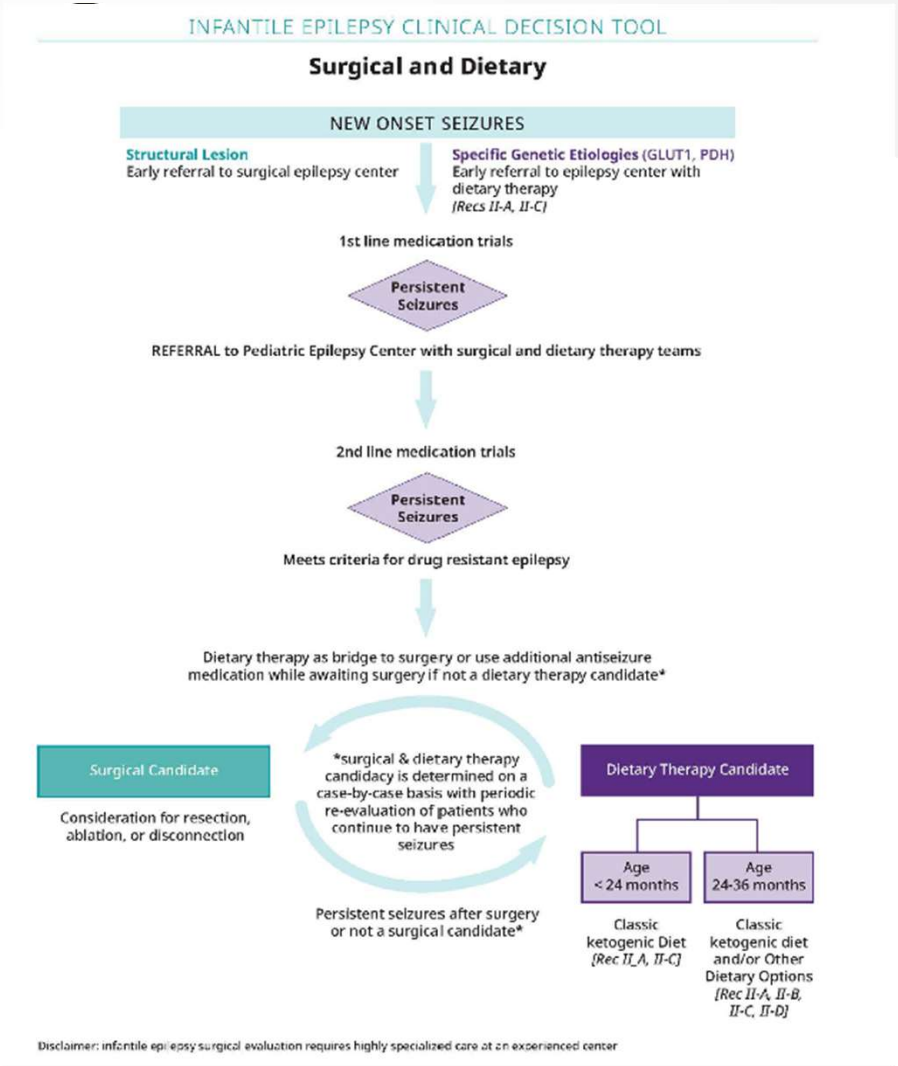


Table 3. Summary of Recommendations Related to Surgical Treatments for Infants (1 Month to <36 Months) Diagnosed With Specific Types of Drug-Resistant Epilepsy.

Treatment Intervention and Comparator	Recommendation (Please see Summary of Evidence for Detailed Evidence Review of Each Intervention)
III-A. Hemispherectomy/hemispherotomy compared with **no hemispherectomy/hemispherotomy**	For infants and children 1 month to <36 months of age diagnosed with **drug-resistant epilepsy**, the AES guideline panel made a **strong recommendation** for hemispherectomy/hemispherotomy surgery for candidates who have been diagnosed with holohemispheric drug-resistant epilepsy secondary to select structural pathologies, including but not limited to hemimegaloencephaly, Rasmussen's encephalitis, Sturge-Weber syndrome, perinatal stroke, and hemispheric cortical dysplasia. *Remarks:* *- Strong recommendation because of (1) the life-threatening nature of DRE secondary to select pathologies, (2) the high risk of morbidity and mortality in children when left untreated, and (3) the greater potential for postoperative seizure-freedom compared with additional antiseizure medications.* (**Strong** recommendation, **Low** certainty of evidence)
III-B. Intralobar, multilobar, or focal resection, posterior disconnections compared with **no resections**	For infants and children 1 month to <36 months of age diagnosed with **drug-resistant focal or lesional epilepsy**, the AES guideline panel **recommends** intralobar, multilobar, or focal resections or posterior disconnections rather than no intralobar, multilobar, or focal resections or posterior disconnections. *Remarks:* *- Strong recommendation driven by the life-threatening nature of drug-resistant focal or lesional epilepsy and the high risk of mortality in children when left untreated.* (**Strong** recommendation, **Very Low** certainty of evidence)
III-C. Supratentorial brain tumor resection compared with **no resection**	For infants and children 1 month to <36 months of age diagnosed with **tumor-related epilepsy**, the AES guideline panel **suggests** supratentorial brain tumor resection rather than no supratentorial tumor resection. *Remarks:* *- The biological character or grade of the tumor influences the decision calculus regarding undergoing surgery and tolerance for surgical complications.* (**Conditional** Recommendation, **Very Low** Certainty of Evidence)

Abbreviations: AES, American Epilepsy Society; DRE, drug-resistant epilepsy.

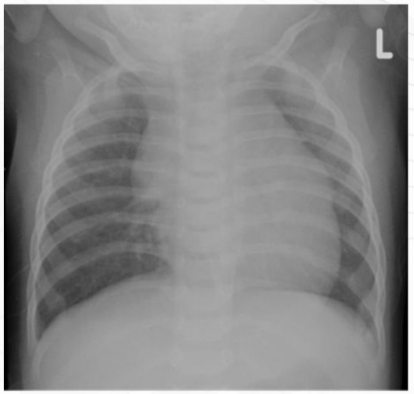
Epilepsy Currents 2026, Vol. 26(3) 174–202

Recommendations for Surgery

1. hemispherectomy/hemispherotomy surgery for infants and children < 36 months of age with DRE secondary to select underlying lesional pathologies.
2. Infralobar, multilobar or focal resections or posterior disconnections for DRE or lesional epilepsy

Case Vignette 1: Twin A: TCN

- 5 months old girl, twin A
- Development: normal for 5 months then…
- Sz type 1: generalized tonic +/- eye rolling/staring
- Sz type 2 (later): epileptic spasms
- Sz type 3 (later): myoclonic seizure
- **DRE**: *PHT*, VGB, PB, LEV, TPM



	26/8/62	
Glucose	91	
BUN	7	mg/dl
Cr	0.19	mg/dl
Na	135	mmol/L
K	5	mmol/L
Cl	105	mmol/L
Total CO_2	15	mmol/L
Anion gap	15	
Ca	10.4	mg/dl
P	5.3	mg/dl
Mg	1.96	mEq/L

	26/8/62	
Total protein	6.2	g/dl
Albumin	4.4	g/dl
Globulin	1.8	g/dl
ALP	259	U/L
Cholesterol	148	mg
AST	56	U/L
ALT	45	U/L
TB	0.43	mg/dl
DB	0.23	mg/dl

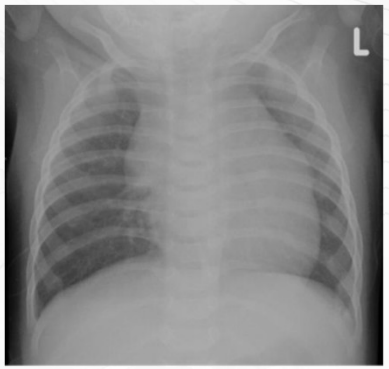
	26/8/62	
Blood lactate	4.39 mmol/L	(0.5-2.2)
Blood ammonia	73.5 mcg/dl	(18.7-86.9)

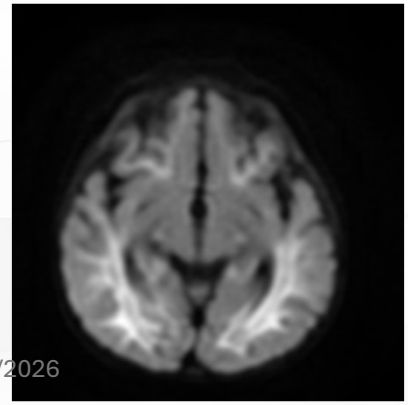
Serum Glycine 678.27 nmole/ml (103-386)

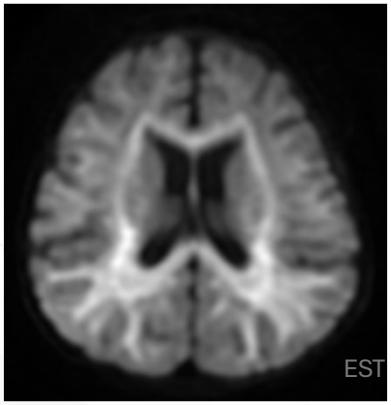
Case Vignette 1: Twin A: TCN

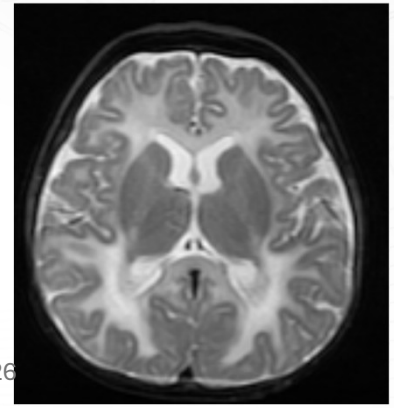
WES: Homozygous VUS of BOLA3

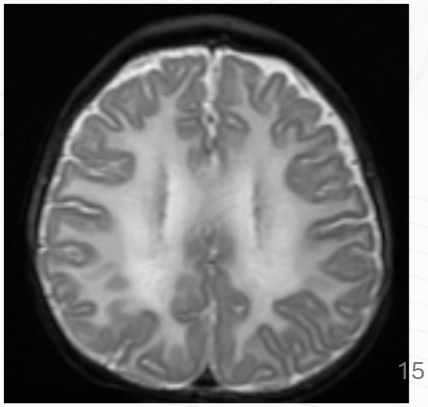
- 5 months old girl, twin A
- Development: normal for 5 months then…
- Sz type 1: generalized tonic +/- eye rolling/staring
- Sz type 2 (later): epileptic spasms
- Sz type 3 (later): myoclonic seizure
- **DRE**: *PHT*, VGB, PB, LEV, TPM











Case Vignette 2: Twin B: TWR (same-sex dizygotic twin)

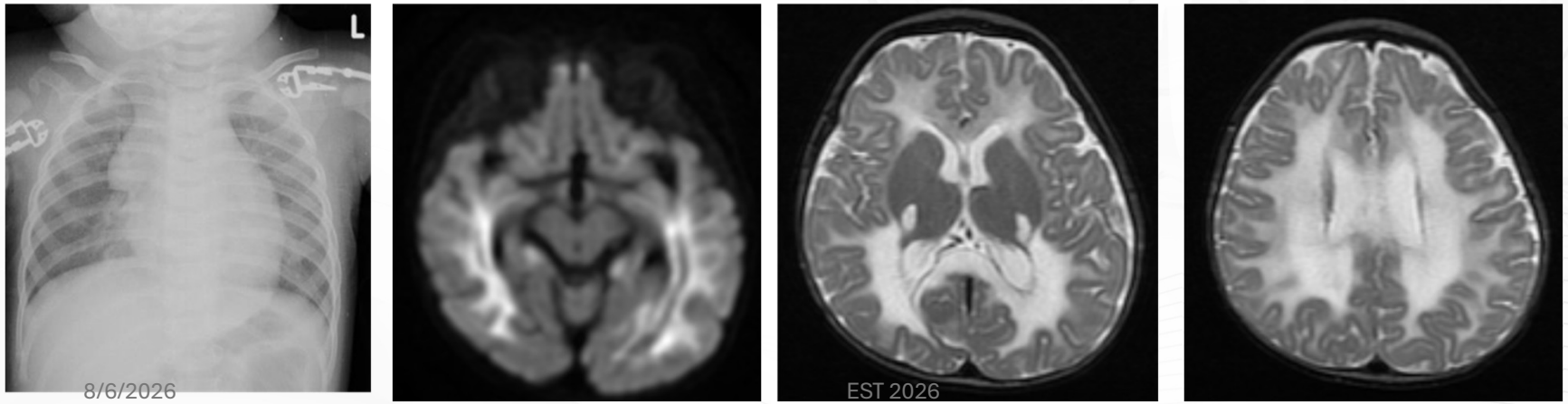
Twin A: death at 6 months

WES: Homozygous VUS of BOLA3

- Presented at 9 months old
- Delayed development from 6 months of age, followed by regression
- IPD: focal seizure, IS
- Ix:
- ASMs: LEV, VGB, vitamin cocktails

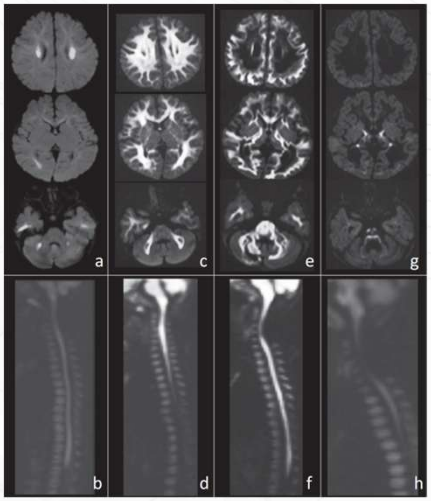
Serum Glycine 747.397 nmole/ml (103-386)
CSF glycine 43.64 nmole/ml (≤ 12)

Twin B: death at 14 months



BOLA3 Gene Mutations

- Multiple Mitochondrial Dysfunction syndrome 2 (MMDS2) and
- BOLA3-related variant NKH (disorder of glycine metabolism)



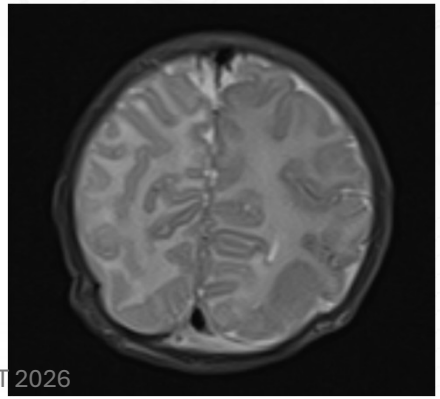
- Clinical feature
  - Severe neurodegeneration after a period of normal development
  - Leukodystrophy
  - Cardiomyopathy
  - Optic atrophy
  - Epileptic encephalopathy (seizure, often cluster of myoclonic seizure)
- MRI: deep WM lesion , and/or spinal cord involvement, optic nerve involvement
- ↑glycine in serum and CSF, ↑lactate, deficient glycine cleavage enzyme activity, ↓ pyruvate dehydrogenase activity
- Prognosis: early onset, rapid progression, often fatal in infancy

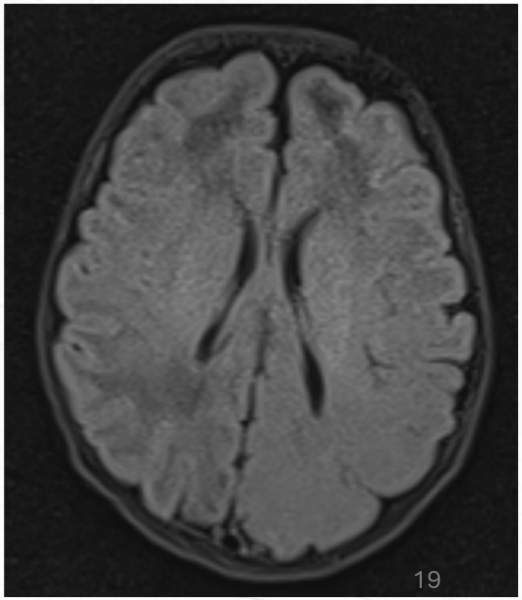
Feature	MMDS2 (BOLA3)	Variant NKH (BOLA3)
Genetic Cause	BOLA3 mutations	BOLA3, LIAS, GLRX5 mutations
Biochemical Findings	Hyperglycinemia, lactic acidosis	Hyperglycinemia, low GCS activity
Clinical Features	Developmental regression, seizures, optic atrophy, cardiomyopathy, leukodystrophy, early fatality	Same as MMDS2 (when BOLA3 is the cause)
Imaging	White matter lesions, necrosis, optic nerve/spinal cord involvement	Same as MMDS2 (when BOLA3 is the cause)
Terminology	MMDS2 = BOLA3-related variant NKH	Variant NKH (BOLA3) = MMDS2

Case Vignette 3: NP

Referral case

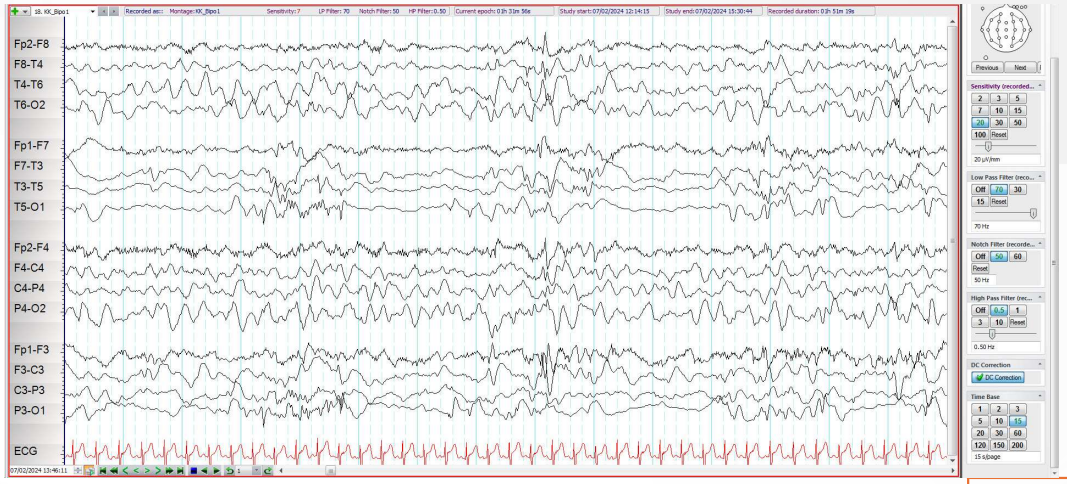
- 2-month-old male infant
- Sz type 1: right focal seizure since age 14 days
- *Sz type 2 (later): focal with bilateral involvement , IS*
- Ix: R/O CNS infection (CSF/serum glucose 48/110 mg/dl)
- ABO + acyclovir Rx
- ASMs: PB, LEV, Vt B6, *PHT*, TPM
- MRI, age 24 days





Case Vignette 3: NP

Referral case



WES: heterozygous missense variant in COL4A1

- ASMs: PB, LEV, Vt B6, *PHT*, TPM
- **1st Surgical TPO disconnection**: at age 3 months
- ASMs: LEV, PER, PHT, LCM, clobazam
- Plan 2nd Surgery FP disconnection at 5.5 months: family postpone
- Death at 1 yr 9 months: SUDEP?

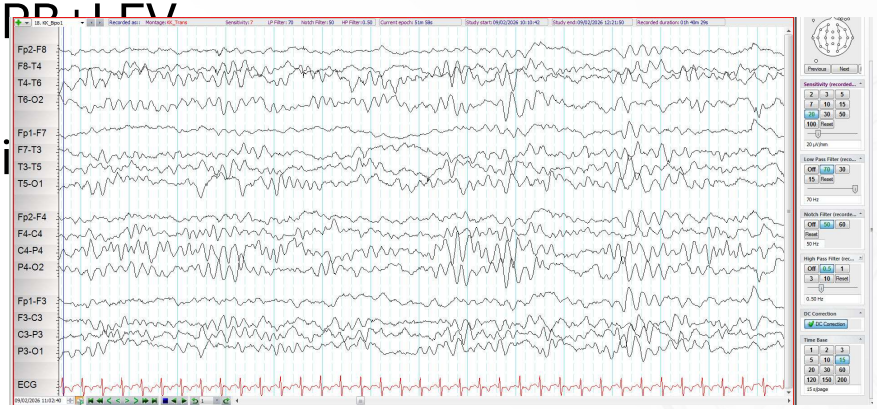
Variant / Gene Change	Reported Phenotype	Evidence Strength	Notes
COL4A1 (general mutations)	Porencephaly, schizencephaly, polymicrogyria, cortical dysplasia, leukoencephalopathy	Strong	Multiple case series and reviews confirm association
COL4A1 c.4334G>T	Brain malformation (possible)	Unreported / uncertain	Not specifically documented in literature; pathogenicity plausible given gene function
Other COL4A1 variants (missense/nonsense)	Infantile hemolytic anemia, ocular anomalies, small-vessel disease	Moderate–strong	Expanded phenotype beyond CNS malformations

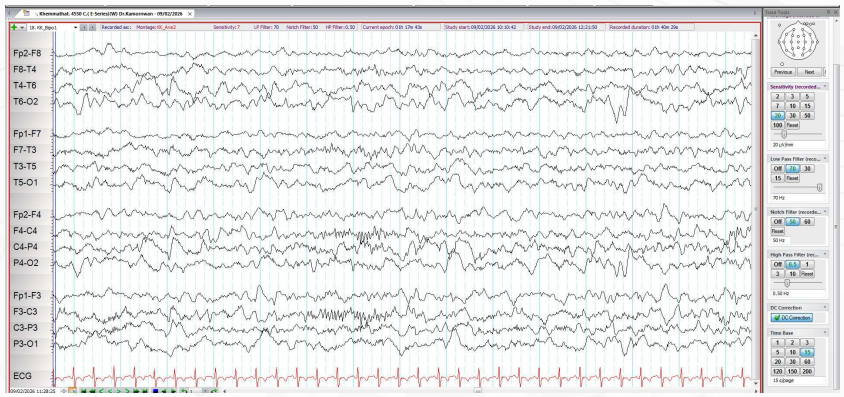
Case Vignette 4: K-

- 8-month-old male infant
- Sz onset: 8 months
  - associated with fever (atypical pneumonia)
  - 2 seizures: 5 minutes and 2 minutes
  - Normal development
  - DDx: CNS infection, complex febrile seizure, genetic epilepsy, etc.
  - ASMs: PB

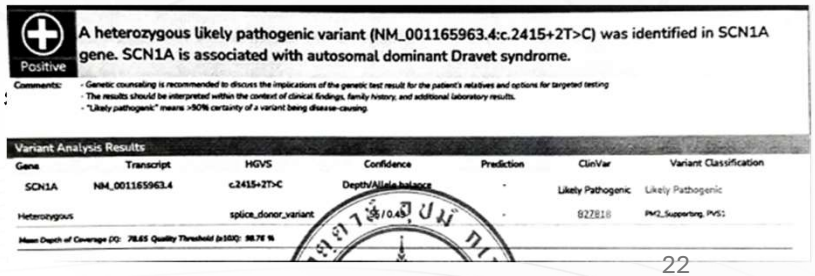
Case Vignette 4: K-

- Recurrent seizure at 9, 10 months old:
  - ASMs PB+LEV
  - EEG
  - Geneti





- Recurrent seizure at 14 months old:
  - fever 38.5^{0}C
  - Asym GTC seizure with eye deviate toward left
  - 4 seizures at ER
  - PB+LEV



Case Vignette 4: K-

THERAPY

AVOID Na⁺ channel blockers*

PHARMACOLOGICAL

1st line
valproate
↓
2nd line
stiripentol + valproate + clobazam
topiramate
ketogenic diet
from 2y onwards:
cannabidiol**
fenfluramine**
↓
3rd line
clonazepam
levetiracetam
zonisamide
ethosuximide
phenobarbital
OR consider vagus nerve stimulation

NONPHARMACOLOGICAL

Management of cognition & behaviour (e.g., inattention & hyperactivity)
Physiotherapy
Speech & language therapy
Occupational therapy

*Na⁺ channel blockers should also be avoided in adults. However, further studies are needed to ensure that these drugs produce, as the disease evolves, the same negative effects as in childhood. If already introduced with no apparent negative effect, Na⁺ channel blockers may be considered as 2nd line therapy in adults.

**To now, there is limited evidence on the use of CBD and FFA in adults.

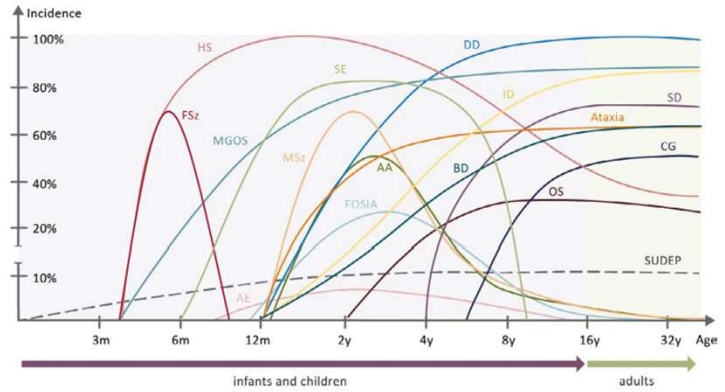


FIGURE 1 Clinical manifestations of DS and their relative incidence according to age. Schematic representation of clinical manifestations of DS and their relative incidence according to age, adapted from Gataullina & Dulac, 2017[129] with updated information gathered in this review. AA, atypical absences; AE, acute encephalopathy; BD, behavioural disturbances; CG, crouching gait; DD, developmental delay; ID, intellectual disability; FOSIA: Focal onset seizure with impaired awareness; FSz, complex febrile seizures; HS, hyperthermia sensitivity; MGOS, Motor generalized onset seizures; MSz, myoclonic seizures; OS, obtundation status; SD, sleep disturbances; SE, convulsive status epilepticus; SUDEP, sudden unexpected death in epilepsy.

Epilepsia Open 2022:7:11-26

Case Vignette 5: NL

Twin A; different sex

- At age 2 years: motor dev delay, maintains eye contact, but sometimes twitches head when making eye contact
- LEV then VPA was given due to head twitching
- Language: able to say A-Z and 1-10, but not “mum-dad”
- PT/OT but not genetic test (economic)
- Not regular F/U
- Age 11 years: sways while walking, es
  : LP: WBC 100 mm^3, RBC 100 m
  protein 37 mg/dl, glucose 3

Data Analysis: HP:0001250 | Seizure
HP:0001257 | Spasticity
HP:0001263 | Global developmental delay

Capture Kit: **SureSelect V6+UTR-post** Type of Sequencer: **Illumina platform**

RESULT Summary

Gene	Variant	Associated disorder	Zygosity	Classification
SLC2A1	c.558G>A	Epilepsy, idiopathic generalized, susceptibility to, 12 (AD)/ GLUT1 deficiency syndrome 1, infantile onset, severe (AD, AR)/GLUT1 deficiency syndrome 2, childhood onset (AD)	Heterozygous	Pathogenic
SLC7A6OS	c.559C>T	Epilepsy, progressive myoclonic, 12 (AR)	Heterozygous	Not reported
KDM6B	c.2830C>T	Neurodevelopmental disorder with coarse facies and mild distal skeletal abnormalities (AD)	Heterozygous	Not reported

Common manifestation	Uncommon manifestation
Microcephaly Cognitive impairment Continuous movement disorder Epilepsy: early infancy (absence, GT → focal/myoclonic, astatic seizure) Paroxysmal exertion-induced dyskinesia (PED)	Paroxysmal kinesigenic and nonkinesigenic dyskinesia (PKD/PNKD) Fatigue Oculogyric crises

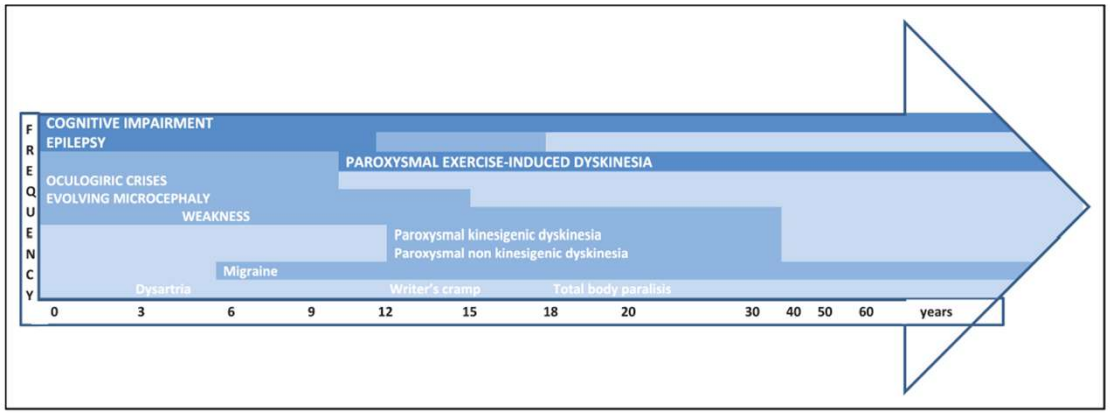


Figure 1. Evolution of GLUT1 deficiency syndrome symptoms and its frequency according to age. Symptoms shaded in dark to lighter color corresponds to the frequency of occurrence of symptoms and were placed from top to bottom.

Table 2. Clinical Description of the Ocular Phenomenology in Our GLUT1 Deficiency Syndrome Patients.

Patient no.	Birth date	Mutation	CSF ratio	Onset (mo)	Episode duration	Frequency	Disappearance (mo)	Clinical description	Other symptoms
5	March 29, 1987	Q283X; exon 6; nonsense	0.33	3	Few seconds	Daily	12	Brief upward deviation of eyes	MR, EOE, PED, A, C, DS
6	September 28, 1986	R126C; exon 4; missense	0.38	4	Few seconds	Weekly	6	Eyeball revulsion	MR, EOE, PED, A, DS
7	March 22, 2012	R249Afs131X; exon 6; nonsense	0.37	2	5-6 s	Sporadic	10	Sustained upward deviation of eyes	MR, EOE
8	June 16, 2005	R153C; exon 4; missense	0.51	67	Few seconds	Weekly	73	Episodes of tonic deviation of gaze upward and/or sideways	EOE, PED
9	September 4, 1999	R400H; exon 9; missense	0.44	11	Few seconds	Monthly	180[a]	Uncoordinated horizontal left and right slow eye movements	MR, PED
10	November 9, 2002	R400C; exon 3; missense	0.38	2	Few seconds	Daily	9	Right eye convergence and fixed gaze	MR, E
11	March 7, 2007	L124Wfs12X; exon 1; nonsense	0.36	13	60-120 s	Weekly	72[a]	Darting conjugate rolling eye movements, upward and laterally tonic deviation	MR, E, PED
12	December 24, 2013	NA	0.39	5	12-180 s	Monthly	10	Mono/bilateral convergent paroxysmal squint, rolling eye movements	MR, EOE

Abbreviations: A, ataxia; C, choreoathetosis; CSF, cerebrospinal fluid; DS, dysarthria; E, epilepsy; EOE, early-onset epilepsy; MR, mental retardation; PED, paroxysmal exercise-induced dyskinesia.
[a]After introduction of ketogenic diet.

Journal of Child Neurology 2016, Vol. 31(9) 1174-1180

Consensus Diagnostic Approach

Definite Glut1DS: Characteristic clinical features **plus** hypoglycorrhachia **plus** pathogenic SLC2A1 variant

Probable Glut1DS: 2 from 3 criteria above (clinical, LP, genetic)
Possible Glut1DS: Suggestive features but incomplete criteria; consider further evaluation

EEG Findings (Glut1DS)

Often normal between seizures (interictal EEG)

Infants: May show focal slowing and epileptiform d/c
Children (2+ years): 2.5–4 Hz GSW pattern can be seen
Unique clue: EEG abnormalities may improve after feeding (pre-prandial worsening)

Key point: EEG can be normal, so a normal result does not rule out Glut1DS

Lumbar Puncture (LP)

Hallmark: Low CSF glucose with normal blood glucose

CSF glucose: < 40 mg/dL, but can be up to 52 mg/dL in milder cases
CSF/blood glucose ratio: Usually <0.5
CSF lactate: Low-normal or low (helps distinguish from mitochondrial diseases)
Best practice: Perform after 4–6 hour fast; check blood glucose just before LP

Genetic Testing

Main test: SLC2A1 gene sequencing
Findings: Pathogenic SLC2A1 variant in 81–89% of cases
Deletion/duplication analysis: Confirms 11–14%
Negative result: Does not fully exclude Glut1DS if clinical and LP findings are typical
Genotype-phenotype: Missense = milder, nonsense/splice site/deletions = more severe

Other tests: Erythrocyte glucose uptake, METAglut1TM blood test (emerging)

Case Vignette 6&7 : Twin A and Twin B

10 years old

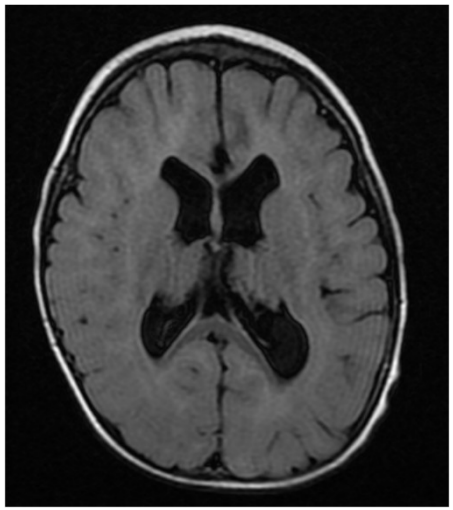
Twin A, preterm 34 weeks, BW 1,680

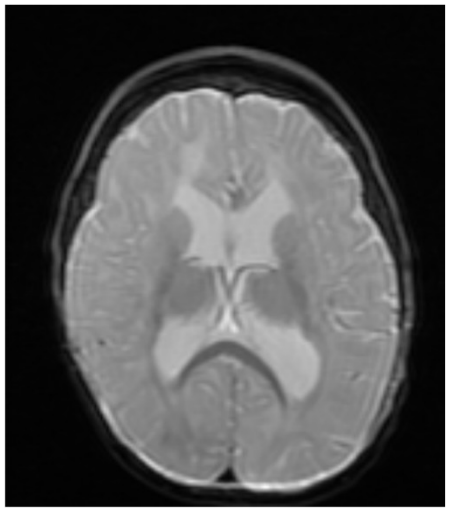
Twin B, preterm 34 weeks, BW 1,700

Case Vignette 6&7 : Twin A and Twin B

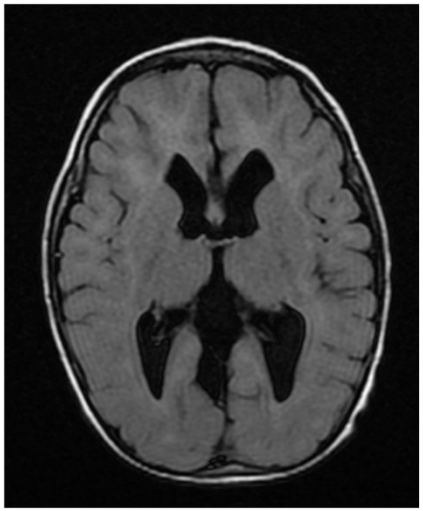
10 years old

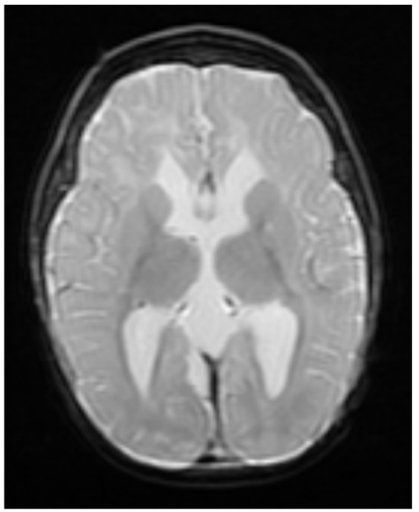
Twin A, preterm 34 weeks, BW 1,680





Twin B, preterm 34 weeks, BW 1,700





MRI at 20 months

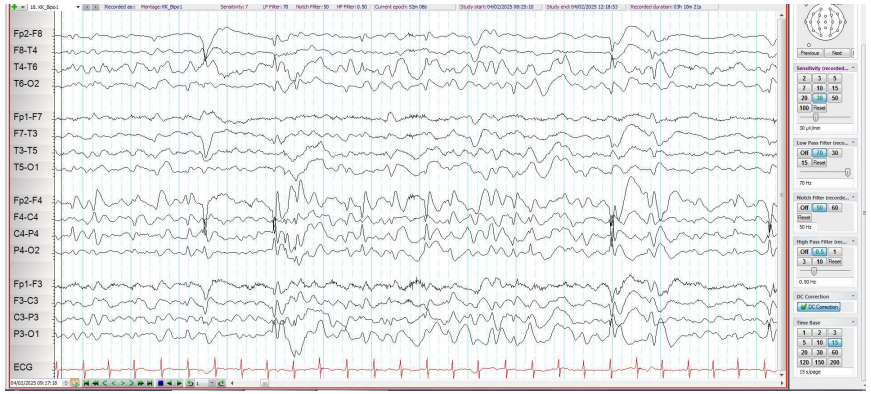
Case Vignette 6&7 : Twin A and Twin B

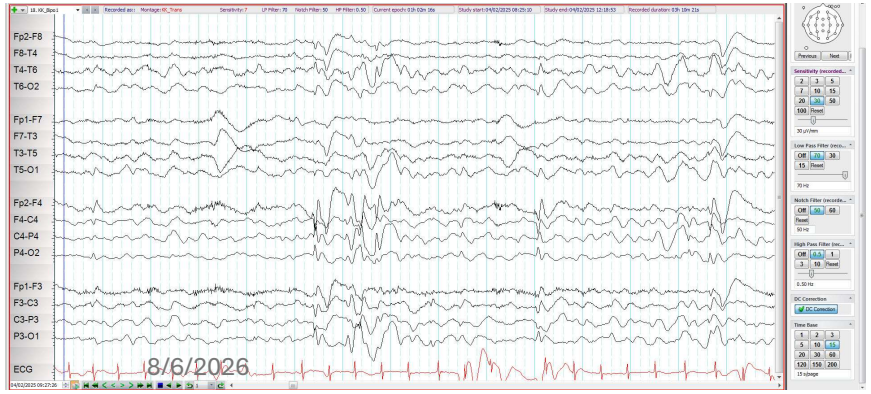
Last EEG at age 8 years old

10 years old

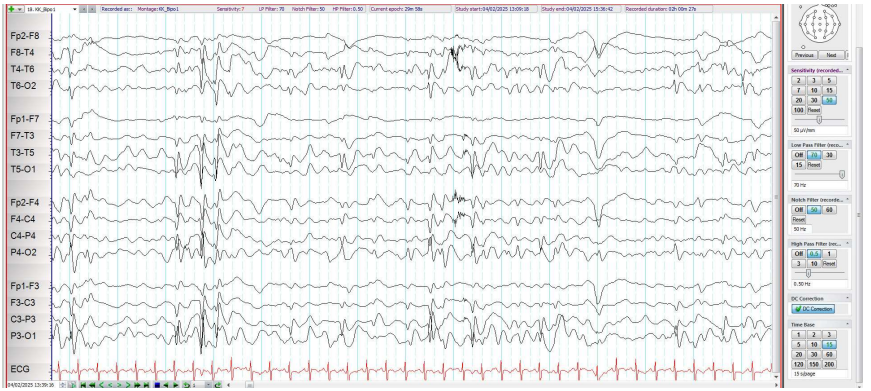
Inframe-deletion KMT2B mutation

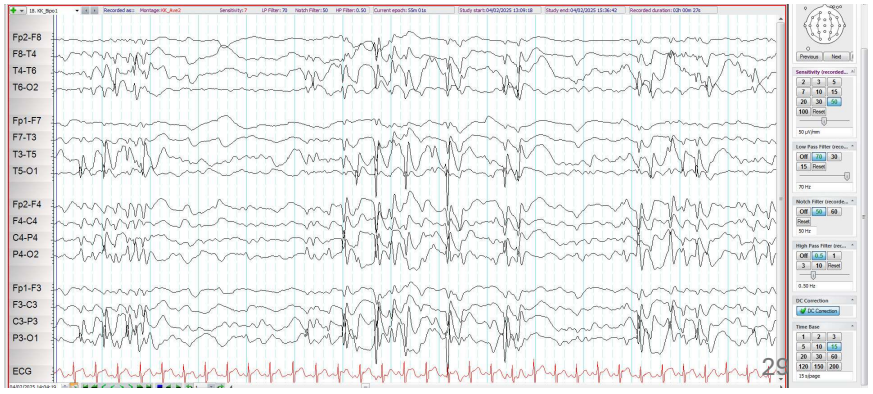
Twin A, preterm 34 weeks, BW 1,680



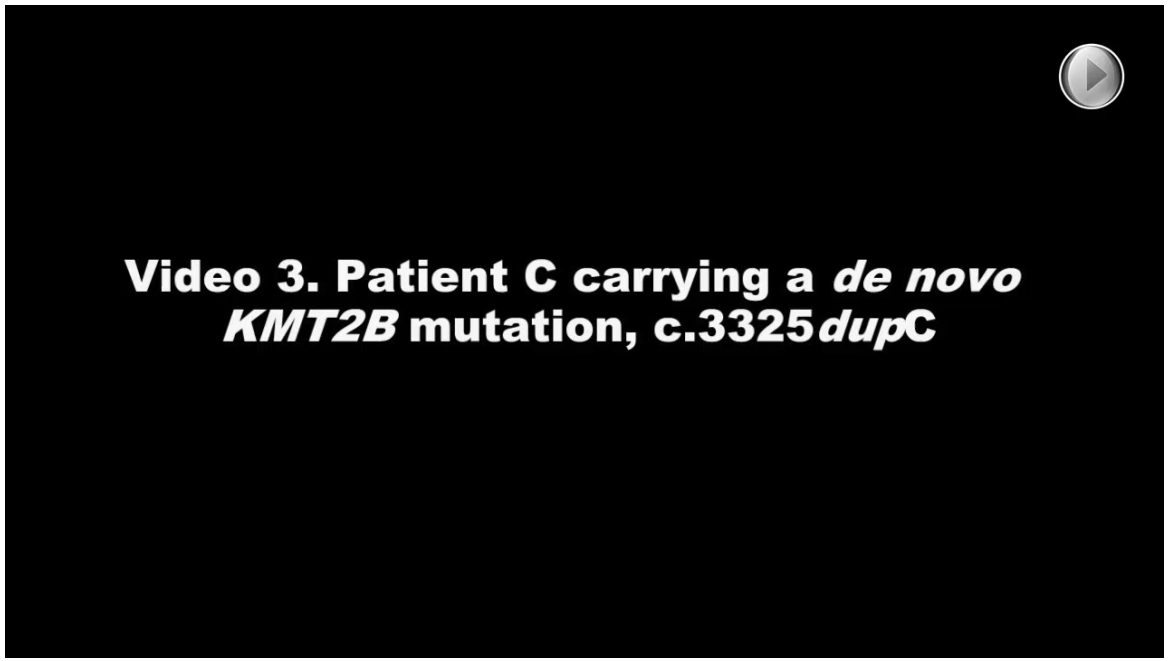


Twin B, preterm 34 weeks, BW 1,700





VDO of patient with KMT2 gene



Parkinsonism and Related Disorders 52 (2018) 55-61

Outcome of Infantile Epilepsy

Condition	Interventions	Treatment
Genetic Epileptic Encephalopathy	Early genetic testing	Precision therapy Other supportive: KD, CBD, targeted drugs for channelopathies
Structural/Metabolic causes	Brain imaging Genetic with biochemical /metabolic assays	ASMs KD
Self-limited epilepsies Idiopathic epilepsies	EEG, phenotypes	ASM Etc.

Outcome of Infantile Epilepsy

Condition/Prognosis	Seizure frequency	Development
Genetic Epileptic Encephalopathy	Ongoing of seizures	Regression
Structural/Metabolic causes	Prognosis varies with reversibility	Prognosis varies with reversibility
Idiopathic epilepsies	Resolved/good controlled	Often better development

Advance Innovative Gene-Based Therapies

Therapy	Mechanism	Best Suited For	Examples / Target Genes	Current Status	Key Challenges
Antisense oligonucleotides (ASOs)	Modify RNA splicing or increase/decrease protein production	Loss-of-function or selected gain-of-function disorders	**SCN1A**, **KCNT1**, **SCN2A**, **UBE3A**	Most advanced; several Phase 1–3 trials	Repeated intrathecal dosing, long-term durability
Gene replacement therapy (AAV)	Delivers a normal copy of the gene	Loss-of-function disorders	**CDKL5**, **PCDH19**, **SLC13A5**, selected DEEs	Early clinical trials	AAV size limitation, immune response, redosing difficult
CRISPR/Cas9 gene editing	Corrects the DNA mutation permanently	Selected pathogenic variants	**SCN1A**, **STXBP1**, **KCNQ2**, **SCN2A**	Mostly preclinical	Off-target editing, safety, ethical concerns
Base editing / Prime editing	Precise DNA correction without double-strand breaks	Single nucleotide variants	**SCN1A**, **SCN2A**, **KCNQ2**	Preclinical	Efficient brain delivery, long-term safety
CRISPR activation (CRISPRa)	Increases expression of the normal gene without cutting DNA	Haploinsufficiency	**SCN1A** (Dravet syndrome)	Preclinical	Delivery to neurons, sustained expression
RNA interference (RNAi)	Silences toxic mutant transcripts	Gain-of-function disorder	**KCNT1**, **SCN8A**	Early development	Specificity, repeated administration

Take Home Messages

- Genetic diagnosis as the gateway to prognosis and therapy
- Shift from symptomatic antiseizure medication to mechanism-driven interventions
- Guideline in epilepsy treatment base on international and country resources
- Future therapies (ASOs, CRISPR, AAV, neuromodulation) as paradigm-changing

EST 30th ANNIVERSARY ANNUAL MEETING

Thank You for Your Attention