Beyond-seizure benefits of early diagnosis and treatment in rare, childhood-onset developmental and epileptic encephalopathies (DEEs)

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Disclosures

- SA has received funding from GW Pharmaceuticals, Norvartis, PTC Therapeutics, Boston Scientific, Nutricia, UCB, BioMarin, LivaNova, Medtronic, Desitin, Ipsen, Orion, CDKL5 UK, TSA and the National Institute for Health Research

Developmental and epileptic encephalopathy

- History
  - Dr William James West[1]
  - Epileptic spasms, hypsarrhythmia and developmental plateauing or regression[2]

Volume 35, Issue 911, P724–725, 13 February 1841

ON A PECULIAR FORM OF INFANTILE CONVULSIONS[1]

West WJ

The Lancet

1. West WJ, et al. Lancet 1841;35:724–725; 2. BMJ Best Practice. Infantile spasms; summary; definition. Available from: https://bestpractice.bmj.com/topics/en-gb/752 (Accessed 16 December 2021)

Epileptic encephalopathy

- Frequent seizures and/or interictal epileptic discharges
- Significant impact on cognition, behaviour and/or motor function
- The majority begin in infancy and childhood

Nickels KC, Wirrell EC. Semin Pediatr Neurol 2017;24:264–275

Developmental and epileptic encephalopathies

- Ohtahara syndrome or early infantile epileptic encephalopathy
- Early myoclonic encephalopathy
- Epilepsy of infancy with migrating focal seizures or migrating partial seizures of infancy
- West syndrome
- Dravet syndrome
- Epilepsy with myoclonic-atonic seizures or Doose syndrome
- Lennox-Gastaut syndrome
- Landau-Kleffner syndrome

Engel J. Epilepsia 2001;42:796–803

Landau-Kleffner syndrome

- Seizures occur in three out of four children; however, they are infrequent and often resolve with age[1]
- Sleep EEG shows continuous spike-wave[2]
- Developmental regression[2]

EEG, electroencephalogram

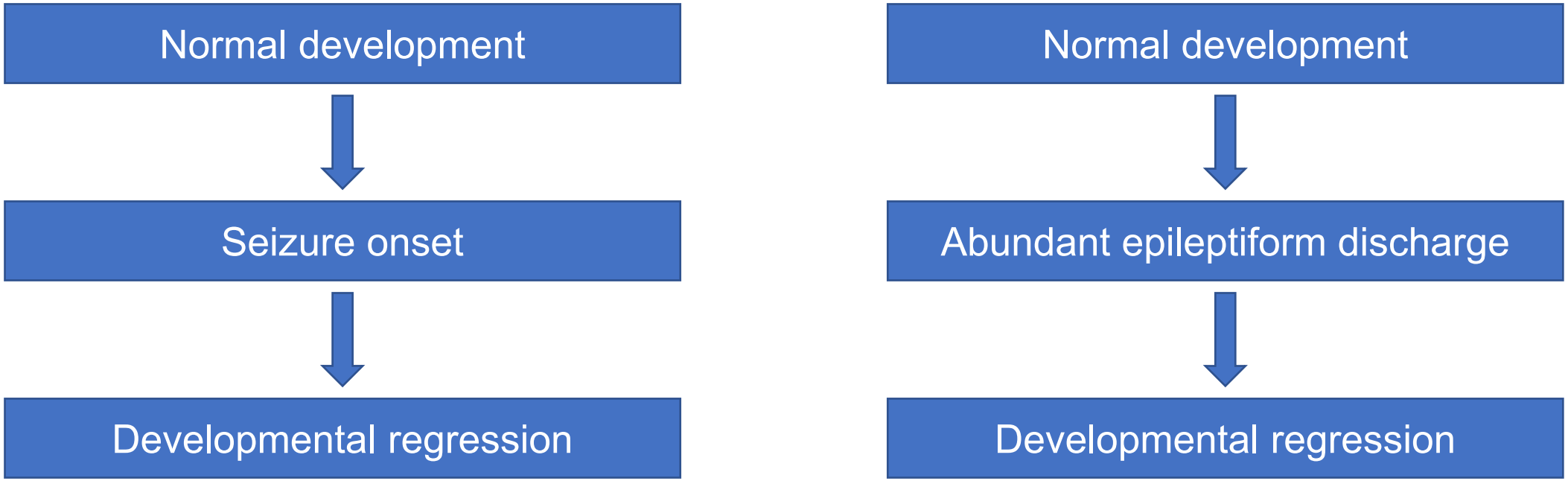
1. Epilepsy Foundation. Landau-Kleffner syndrome. Available from: https://www.epilepsy.com/learn/types-epilepsy-syndromes/landau-kleffner-syndrome (Accessed 16 December 2021); 2. Pearl PL, et al. Epilepsy Curr 2001;1:39–45

The International League Against Epilepsy (ILAE)

- The epileptiform activity itself contributes to severe cognitive and behavioural impairments beyond that expected from the underlying pathology alone (such as a cortical malformation)[1]
- Revised term – developmental and epileptic encephalopathy
  - Genetic variants cause developmental delay[2]

1. Berg AT, et al. Epilepsia 2010;51:676–685; 2. Specchio N, Curatolo P. Brain 2021;144:32–43

Developmental and epileptic encephalopathies



Information reflects the speaker’s own experience and opinions

Reasons for diagnostic delay

- A ≥1-month diagnostic delay was associated with an average 7.4-point drop (P=0.02) in the Vineland Adaptive Behavior Scales motor score
- Diagnostic delay associated with future IQ
- Paediatricians missing or deferring diagnosis
- Parents not recognising events as seizures
- College-educated parents

IQ, intelligence quotient
Berg AT, et al. Epilepsia 2014;55:123–132

Type of seizures

- Patients with focal epilepsy experience considerable diagnostic delays – non-motor semiologies

Pellinen J, et al. Epilepsia 2020;61:2643–2652

Impact of diagnostic delay on seizure outcome

- 176 patients (age range of 15–75 years)
- 77% had more than two seizures before treatment
- 45% had three to ten seizures
- The median number of all seizures before diagnosis was five
- Focal aware seizures and focal impaired awareness seizures were more frequent than focal to bilateral tonic-clonic seizures
- The median diagnostic delay was 12 months
- Increasing number of seizures before diagnosis indicated a worse seizure outcome

Parviainen L, et al. Epilepsia Open 2020;5:605–610

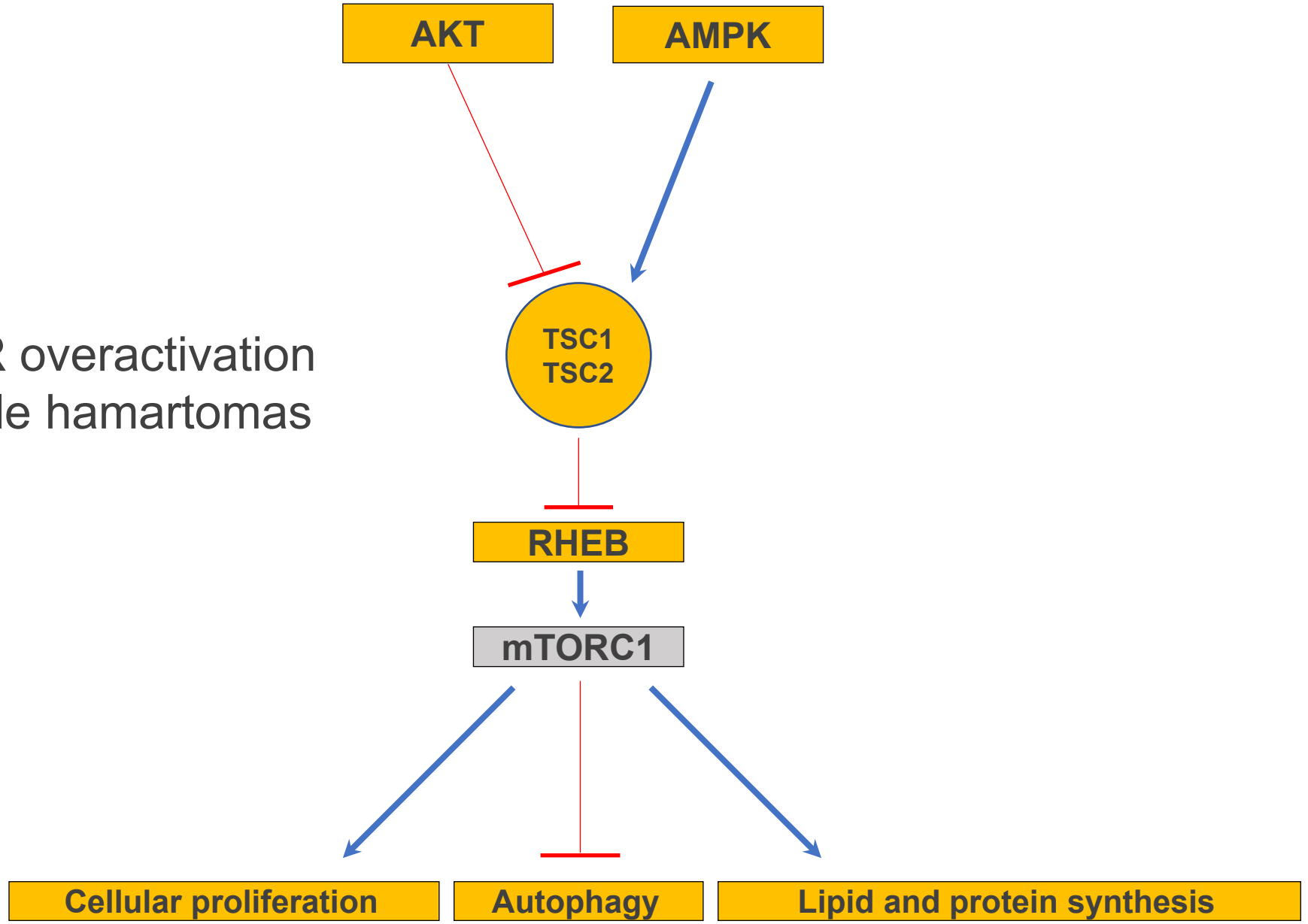
Other reasons for diagnostic delay

- Age of epilepsy onset[1]
- Associated comorbidities[2]
- Aetiology[3]

1. Dulac O. Epilepsia 2001;42(Suppl. 3):23–26; 2. Nickels KC, Wirrell EC. Semin Pediatr Neurol 2017;24:264–275; 3. Berg AT, et al. Pediatrics 2004;114:645–650

TSC

- mTOR overactivation
- Multiple hamartomas



AKT, AKT serine/threonine kinase; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin kinase; mTORC1, mTOR complex 1; RHEB, guanosine triphosphate-binding protein Rheb; TSC, tuberous sclerosis complex; TSC1, TSC complex subunit 1; TSC2, TSC complex subunit 2
Adapted from Palavra F, et al. Oxid Med Cell Longev 2017;2017:9820181

Infantile spasms

- Infantile spasms – neurodevelopmental and cognitive issues[1,2]
- No infantile spasms – learning and cognitive disabilities[1–3]

- Lead time to treatment[3]
  - Spasms → treatment
  - Lead time – developmental outcome at 4 years

1. Goh S, et al. Neurology 2005;65:235–238; 2. Capal JK, et al. Epilepsy Behav 2017;70:245–252;
3. Information reflects the speaker's own experience and opinions

Early treatment

Unadjusted VABS scores at the 4-year assessment in each category of lead time for all infants and by aetiology

	All infants		Proven aetiology		No identified aetiology	
Lead time to treatment	VABS mean (SD)	Number	VABS mean (SD)	Number	VABS mean (SD)	Number
<8 d	76.2 (28.4)	11	55.6 (12.9)	5	93.3 (26.4)	6
8–14 d	62.8 (26.4)	17	49.7 (12.9)	10	84.7 (29.6)	6
15 d to 1 m	65.4 (29.8)	8	51.0 (13.9)	3	74 (34.7)	5
1–2 m	65.3 (25.0)	15	60.3 (26.9)	8	71 (23.3)	7
>2 m	55.5 (24.3)	21	43.8 (9.4)	10	66.2 (28.9)	11
Not known		5		3		2
Total number		77		39		37

d, days; m, months; SD, standard deviation

O'Callaghan FJ, et al. Epilepsia 2011;52:1359–1364

CDKL5 deficiency disorder

- X-linked dominant condition[1]
- DEE[2]
- The incidence is ~1:40000–60000 live births[3]
- During infancy and childhood, individuals with CDD suffer impairments affecting cognitive, motor, visual, sleep, gastrointestinal and other functions[4,5]

CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5

1. Weaving LS, et al. Am J Hum Genet 2004;75:1079–1093; 2. National Organisation for Rare Disorders. CDKL5 deficiency disorder. Available from: https://rarediseases.org/rare-diseases/cdkl5/ (Accessed 16 December 2021); 3. Symonds JD, et al. Brain 2019;142:2303–2318;
4. Fehr S, et al. Eur J Hum Genet 2013;21:266–273; 5. Olson HE, et al. Pediatr Neurol 2019;97:18–25

CDKL5 deficiency disorder (2)

- We investigated the natural history, complications and the effectiveness of current treatment strategies, in conjunction with the CDKL5-UK charity

- 44 patients
- The median age at which the parents noticed there was a problem with their child was 4 weeks
- The median age at which the CDD diagnosis was made was 2 years

Amin S, et al. Hippokratia 2017;21:130–135

Case study

- AB
- 16 years old
- Female
- Developed seizures at 9 weeks old
- Several antiseizure medications
- Diagnosis – CDD confirmed by genomic test 2 years ago

Information reflects the speaker’s own experience and opinions

Epilepsy diagnosis

- Single gene

Epilepsy Gene Panels

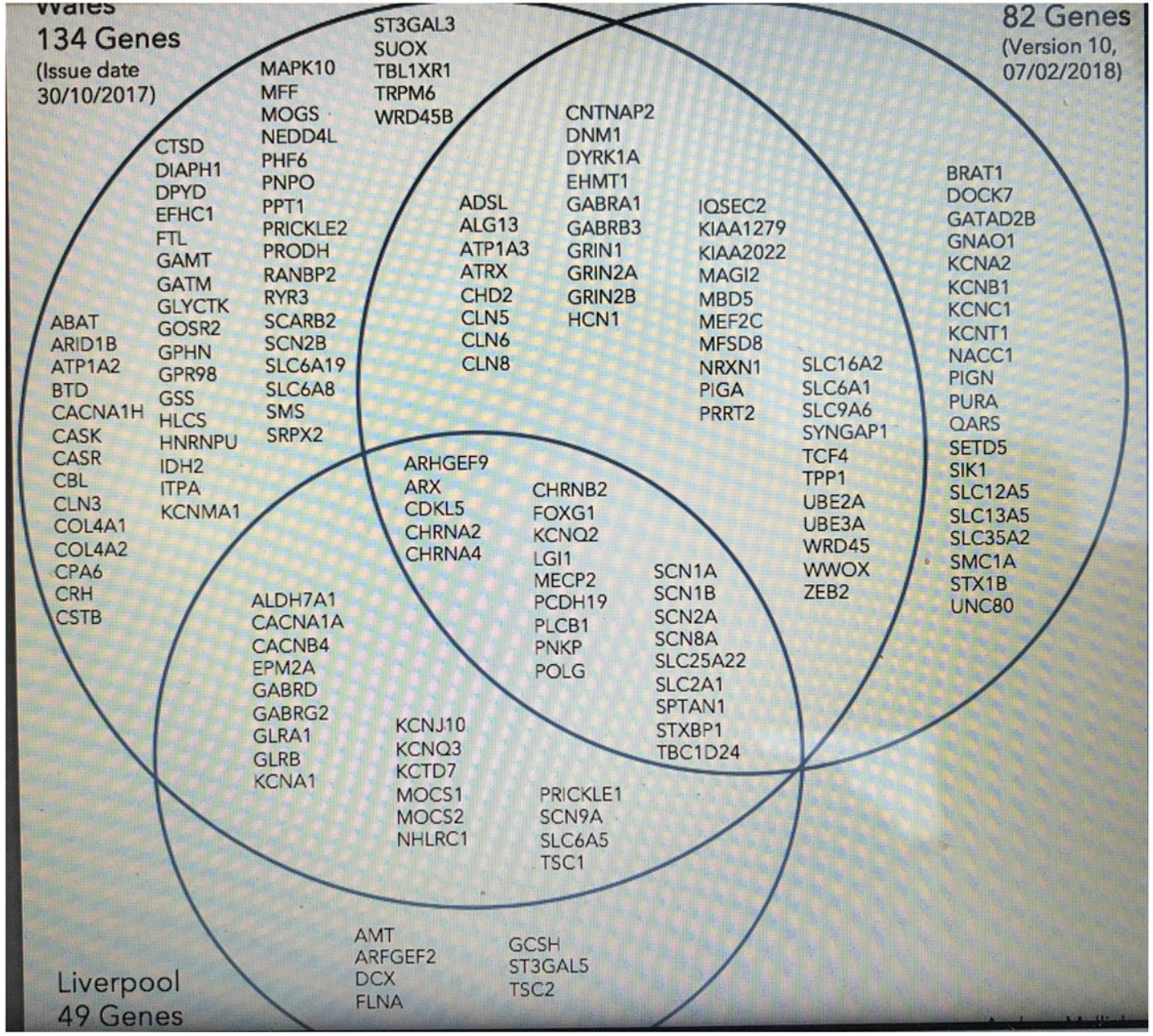


Image provided by Dr Andrew Mallick

National Genomic Test Directory

- R59 – early-onset or syndromic epilepsy

Genomics England. Panels: Genetic epilepsy syndromes. Available from: https://panelapp.genomicsengland.co.uk/panels/402/ (Accessed 16 December 2021)

Testing criteria

- Unexplained epilepsy with clinical suspicion of a monogenic cause including:
  - Onset under 2 years,[1] OR
  - Clinical features suggestive of specific genetic epilepsy, for example, Dravet syndrome,[2] OR
  - Additional clinical features: intellectual disability,[3] autism spectrum disorder,[4] structural abnormality (eg dysmorphism, congenital malformation)[5] and unexplained cognitive/memory decline[6]

1. Information reflects the speaker's own experience and opinions; 2. Fountain-Capal JK, et al. Pediatr Neurol 2011;45:319–323;
3. ILAE classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE Task Force on Nosology and Definitions. Current ILAE draft proposal available from: https://www.ilae.org/files/dmfile/CHILDApril6withfigs.pdf (Accessed 2 December 2021); 4. Young Epilepsy. The psychosocial impact of epilepsy on young children and their families. Available from: https://www.youngepilepsy.org.uk/dmdocuments/SEEN%20Report_2017.pdf (Accessed 2 December 2021); 5. Berg AT, et al. Epilepsia 2010;51:676–685; 6. Reilly C, et al. Eur J Paediatr Neurol 2015;19:308–313

Next steps

- Referral
  - As soon as possible
- Requesting specialities
  - Clinical genetics
  - Metabolic medicine
  - Neurology

Information reflects the speaker’s own experience and opinions

Does a delay in diagnosis matter?

- Worse developmental outcome with diagnostic delays and longer exposure to the epileptic activity[1]
- Uncontrolled seizures impair cognitive function[2]
- Longer delay between onset of spasms and treatment demonstrated in West syndrome – poor developmental outcomes[3]
- Wrong diagnosis and wrong drug – seizure exacerbation[4]

1. Berg AT, et al. Epilepsia 2014;55:123–132; 2. Holmes GL. Semin Pediatr Neurol 2016;23:120–126; 3. Lagae L, et al. Seizure 2010;19:159–164;
4. Epilepsy Foundation. AEDs that can cause seizures. Available from: https://www.epilepsy.com/living-epilepsy/epilepsy-and/professional-health-care-providers/diagnosis-treatment/drugs-their-contribution-seizures/aeds-can-cause-seizures#:~:text=Increased%20seizures%20can%20occur%20for,absence%20or%20juvenile%20myoclonic%20epilepsy (Accessed 16 December 2021)

The beginning of precision medicine?

- CDD – neurosteroids[1]
- TSC – mTOR inhibitors[2]
- Dravet syndrome (*SCN1A*) – STK-001[3]
- *GLUT1* – KD[4]
- *PCDH19* – neurosteroids[5]
- *KCNT1* – quinidine[6]
- *KCNQ2* – carbamazepine[7]

GLUT1, glucose transporter 1; KCNQ2, potassium voltage-gated channel subfamily Q member 2; KCNT1, potassium sodium-activated channel subfamily T member 1; KD, ketogenic diet; PCDH19, protocadherin 19; SCN1A, sodium voltage-gated channel alpha subunit 1

1. Olson HE, et al. J Neuro Disord 2021;13:40; 2. Palavra F, et al. Oxid Med Cell Longev 2017;2017:9820181; 3. UCSF Clinical Trials. An open-label study to investigate the safety of single and multiple ascending doses in children and adolescents with Dravet syndrome. Available from: https://clinicaltrials.ucsf.edu/trial/NCT04442295 (Accessed 16 December 2021) 4. Cappuccio G, et al. PLoS One 2017;12:e0184022; 5. De Nys R, et al. Int J Mol Sci 2021;22:9769; 6. Jia Y, et al. Front Neurol 2019;10:64; 7. Pisano T, et al. Epilepsia 2015;56:685–691

Precision medicine – access to clinical trials

- An open-label study to investigate the safety of single and multiple ascending doses in children and adolescents with Dravet syndrome

Safety and tolerability of single and multiple ascending doses of STK-001 in patients with Dravet syndrome

Change in seizure frequency, overall clinical status and quality of life will be measured as secondary endpoints in this open-label study

STK-001 is an ASO that is intended to increase the level of productive *SCN1A* mRNA and consequently increase the expression of the sodium channel $Na_v1.1$ protein

ASO, antisense oligonucleotide; mRNA, messenger RNA

UCSF Clinical Trials. An open-label study to investigate the safety of single and multiple ascending doses in children and adolescents with Dravet syndrome. Available from: https://clinicaltrials.ucsf.edu/trial/NCT04442295 (Accessed 16 December 2021)

Other gene therapy options

- CDD – ataluren, etc.[1]
- Lentiviral gene therapy for epilepsy[2]

1. Devinsky O, et al. Ann Clin Transl Neurol 2021;8:639–644; 2. Snowball A, et al. J Neurosci 2019;39:3159–3169

Access to registries

- International registry of Dravet syndrome[1]
- International registry of CDD[2]
  - UK registry of CDD[3]
- UK natural history study of TSC[4]

1. Platform Residras. International registry of Dravet syndrome and other syndromes correlated with genes on SCN1A and PCDH19. Available from: http://www.platform-residras.com/index.html (Accessed 16 December 2021); 2. CDKL5 registry. Available from: https://www.cdkl5registry.org/ (Accessed 16 December 2021); 3. CDKL5 UK. Available from: https://curecdkl5.org.uk/ (Accessed 16 December 2021); 4. Kingswood C, et al. Eur J Paediatr Neurol 2016;20:296–308

Prevent complications

- SUDEP
  - Presence and frequency of GTCSs[1]
  - Nocturnal supervision[2]
  - Carbamazepine[3]
  - Underlying genetic cause[4]
    - Genetic syndromes such as *SCN1A* and 15q duplication,[5] presenting with refractory epilepsy

GTCS, generalised tonic-clonic seizure; SUDEP, sudden unexpected death in epilepsy

1. Maguire MJ, et al. Cochrane Database Syst Rev 2016;7:CD011792; 2. van der Lende M, et al. Neurology 2018;91:e1508–e1518;
3. Yu W, et al. Acta Epileptologica 2019;1:7; 4. Coll M, et al. Int J Mol Sci 2019;20:1979; 5. Friedman D, et al. Epilepsy Behavior 2016;61:1–5

Genes and cardiac arrhythmias

- *KCNH2*, *KCNJ2*, *KCNE1*, *KCNE2*, *KCNQ1*, *KCNQ2* and *KCNQ3*
- *SCN1A*, *SCN2A*, *SCN1B* and *SCN5A*
- *CACNA1C*

CACNA1C, calcium voltage-gated channel subunit alpha1 C; KCNE1, potassium voltage-gated channel subfamily E regulatory subunit 1; KCNE2, potassium voltage-gated channel subfamily E regulatory subunit 2; KCNH2, potassium voltage-gated channel subfamily H member 2; KCNJ2, potassium inwardly rectifying channel subfamily J member 2; KCNQ1, potassium voltage-gated channel subfamily Q member 1; KCNQ3, potassium voltage-gated channel subfamily Q member 3; SCN1B, sodium voltage-gated channel beta subunit 1; SCN2A, sodium voltage-gated channel alpha subunit 2; SCN5A, sodium voltage-gated channel alpha subunit 5

Nashef L, et al. Epilepsia 2007;48:859–871

Financial implications

- Potential direct costs associated with delay in diagnosis include:
  - Recurrent emergency treatment
  - Unnecessary non-emergency medical evaluations
  - Redundant or unnecessary diagnostic testing
  - Improper medications due to misdiagnoses

Information reflects the speaker’s own experience and opinions

Families

- Parents able to start the ‘grieving’ process at an earlier stage
- Earlier access to the right supportive therapies and access to social care

Information reflects the speaker’s own experience and opinions

Public awareness and important unmet needs

- Clear disparity between public awareness of epilepsy and that of other public health issues[1]
- Increasing public and healthcare worker awareness of the diversity of symptoms of epilepsy[2]
- Increasing public and healthcare worker knowledge of the morbidity and mortality related to untreated epilepsy[2]

1. Price P, et al. Epilepsy Behav 2015;44:239–244; 2. Information reflects the speaker's own experience and opinions

Service improvement

- First seizure clinics
- Support secondary care epilepsy
- Investment in epilepsy nursing services

NHS England. RightCare: Epilepsy Toolkit. Available from: https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2020/03/rightcare-epilepsy-toolkit-v2.pdf (Accessed 16 December 2021)

Further studies

- Additional studies are needed to elucidate aetiology and pathophysiological mechanisms in DEE and provide targeted treatment

Kalser J, Cross JH. Curr Opin Neurol 2018;31:216–222

Improving seizure recognition

- Investigating potential interventions and developing tools that non-specialists can use to improve seizure recognition

Epilepsy Foundation. Seizure first aid resources. Available from: https://www.epilepsy.com/living-epilepsy/toolbox/seizure-first-aid-resources (Accessed 16 December 2021)