epilepsy action

ISSN 2631-7400

Paediatric Epilepsy

Volume Sixteen | Number One | May 2022

CURRENT AWARENESS SERVICE

Highlights from the International Epilepsy Congress 2021

Last year's International Epilepsy Congress held virtually by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) covered a wealth of topics in the field of epilepsy. These scientific meetings are always enriching experiences. They provide a state-of-the-art picture of important research findings and the focus of future research.

I'm pleased to share a roundup of a few of the excellent presentations at the 2021 congress.

Diagnostic delay

Dr Laura Parviainen, physician in Finland and winner of the *Epilepsia Open* Prize this year, discussed the impact of diagnostic delay on seizure outcome in newly diagnosed focal epilepsy.

She explained that while few studies have looked at this, the research shows around 38-55% of patients may have had undiagnosed seizures before the seizure that led to their diagnosis. Some people may experience years of seizures before their diagnosis. Dr Parviainen said this is more common in focal epilepsy and non-convulsive seizures.

Early diagnosis is important as some data show that a large number of seizures before diagnosis is linked to poorer outcomes, and there is also a higher risk of problems including injuries and accidents.

Dr Parviainen and her team's study aimed to find out the impact of diagnostic delay on seizure outcome. The study used data from previous trials and analysed diagnostic delay and the number of seizures before diagnosis. The team then compared these findings with the response to treatment after the trial period of five years.

The study included 176 patients – eight with only focal aware seizures, 25 with focal impaired awareness seizures, 83 with focal to bilateral tonic-clonic seizures (FBTCS) and 60 with multiple seizure types. The study found that most commonly, people had 3-10 seizures before diagnosis, but around 10% had more than 50 seizures before being diagnosed. The delay was under six months for a third of people and, extraordinarily, over 10 years for 15% of people.

In the study, diagnostic delay showed no clear correlation with how the epilepsy was controlled at five years following diagnosis. The study results showed around 40%

→

EDITORIAL ADVISORY BOARD
Professor Richard Appleton, Liverpool
Dr Frances Gibbon, Cardiff
Professor Rajat Gupta, Birmingham
Dr Daniel Hindley, Bolton
Laura Neeley, Liverpool
Dr William Whitehouse, Nottingham
Sarah Collins, Frimley

CO-EDITORS
Professor Richard Appleton
Kami Kountcheva

PUBLISHER
Epilepsy Action

CONTENTS

of patients remained seizure free, and 40% achieved seizure freedom during the follow-up period, after changes in ASMs. Of the rest, 14% had refractory epilepsy and 6% were lost during the follow-up.

Although the study showed no statistically significant association between diagnostic delay and treatment response, there did seem to be a trend. This was that poorer outcomes were seen in people who had many seizures before being diagnosed.

Dr Parviainen discussed that diagnostic delay could be explained by a lack of awareness of seizures and not recognising subtle events or symptoms with no motor components as seizures. She added that denial of symptoms due to stigma, difficulty accessing medical care and a lack of eye witnesses could also contribute to some of the delay in diagnosis.

Dr Parviainen concluded that it is important to increase public and healthcare professional awareness of the diversity of the manifestations and symptoms of epilepsy. This includes in developed countries which have good access to doctors with an understanding of, and expertise in, epilepsy. The full study is available online at ***bit.ly/3y1hvrn***.

Mental health

One of the congress' sessions focused on epilepsy and mental health and suicidality. The first to speak was Dr Milena Gandy, a clinical psychologist in Australia who discussed findings from research carried out by the ILAE's Psychology Task Force.

The Task Force surveyed over 400 healthcare professionals – the majority neurologists or epileptologists – from 67 countries. The research revealed some of the barriers that exist in the epilepsy care setting which prevents optimal mental health support for people with epilepsy. These barriers included a lack of screening resources, a lack of clarity about whose responsibility mental health screening and treatment is, and a lack of standardised procedures and policies. The research also found there was a lack of referrals, compounded by a lack of mental health professionals and particularly those who specialised in epilepsy.

The Task Force is responding to these findings by working to put together updated protocols, helping support integrated care models and increasing the number of trained mental health professionals in epilepsy settings.

Next, Dr Marco Mula shared some practical advice about how to talk about suicide with adult patients in a busy epilepsy clinic. He started off reminding the audience that suicide is the 10th most common cause of death in all age groups. Dr Mula highlighted the different challenges in screening and tackling suicidality in adult services, echoing much of the work that had been presented by Dr Gandy.

Dr Mula stressed that "suicide prevention should be everyone's job" and shared some tips for managing risk when you identify a positive suicide screening in a patient. He championed 'caring' (listening and attending to a person's distress), 'collaborating' (identifying existing coping strategies) and 'connecting' (having in place a clear clinical pathway) to provide effective support.

The final talk in the session came from paediatric psychologist Dr Avani Modi and associate professor Dr Janelle Wagner, both from the US. They presented research on working with patients and families to recognise suicidal ideation in children with epilepsy. They began by saying that suicide is the second leading cause of death in young people. They added that evidence suggests that 14-27% of young people aged 7-17 years old with epilepsy had suicidal ideation, and that risk of suicidal ideation or attempts (parasuicide) is 1.5 times higher in those with, than those without epilepsy.

They explained that adolescence is a vulnerable period, and that depression looks and may present differently in children. It might present as behavioural problems, irritability or talking about death and dying, for example. They added that risk factors of suicide attempts include comorbidities including attention deficit hyperactivity disorder (ADHD) or anxiety, as well as substance abuse, previous suicide attempts or self-harming events and previous psychiatric hospitalisations.

Dr Modi and Dr Wagner stressed that we need to adapt the language we use to be clear and easy to understand and also better understand and engage those with learning and intellectual disabilities and social and communication disorders.

The speakers suggested that yearly screening for mental health problems in all children with epilepsy is important. Those with risk factors, specifically adolescents, patients with a mental health comorbidity, and patients with a chronic epilepsy that had lasted many years, with or without good seizure control, should be screened more often. Those patients with a previous history of suicidal ideation or suicide attempts, or those with depression, should be considered very high risk patients. They said that protocols will depend on the particular healthcare setting.

It is important to use robust and standardised screening tools, to identify the person responsible for using these tools and establish a clear pathway for onward referral should this be required.

Surgery plateau

Maria Eriksson from University College, London in the UK discussed paediatric epilepsy surgery from 2000-18,

in which she asked the question: 'Have we reached a plateau in seizure freedom rates?'

Ms Eriksson explained that since 2012, when the Children's Epilepsy Surgery Service (CESS) was launched in England, there has been a significant increase in the number of surgical procedures performed each year. There has also been an increase in the number of reviewed but rejected cases.

The range of surgical procedures has also broadened over the years, Ms Eriksson said. There has been a significant increase in the proportion of disconnections and a significant decrease in the proportion of lesionectomies. First-time surgeries and reoperations are most commonly performed involving the frontal and temporal lobes, and multi-lobar surgery most commonly done as reoperation. Although frontal lobe and multi-lobar surgeries have seen a significant increase, their proportion compared to other epilepsy surgeries has remained the same.

Low grade epilepsy associated tumours (LEAT), focal cortical dysplasia type II and mesio-temporal sclerosis were the most commonly identified pathologies. Non-specific epilepsy related changes (NSC) and 'no abnormal pathology' are also common. She added that patients are also undergoing surgery earlier now than they were before the establishment of CESS. This is clearly important for a number of reasons, as has been discussed in a recent issue of PECAS (March 2021).

Over time, despite advances in pre-surgical assessment tools and technologies, seizure freedom rates have remained between 60-70%, Ms Eriksson noted. She said there are a few possible explanations for this finding. One is that more children are weaned off their ASMs at one year follow-up. She said studies have shown that seizure freedom rates increased when children still took ASMs and plateaued with increasing numbers of children being weaned off ASMs. Another reason could be the fact that more complex cases are being considered for surgery and are then undergoing more complex procedures. Children with aetiologies that are less likely to result in seizure freedom, but in seizure reduction after surgery are being accepted for this treatment. Consequently, there is less chance of seizure freedom in this group which will then reduce the overall seizure freedom rate in all children undergoing epilepsy surgery. Ms Eriksson said that it could also be a ceiling effect, and there may be a limit to the seizure freedom rates that can be achieved with the currently-available surgical techniques and tools.

It is possible that improved rates of seizure freedom might be achieved with novel surgical procedures. What was not mentioned was the long-term follow-up of children that had become seizure free following surgery in the CESS programme. Long-term studies in adults have shown that even after 15 or 20 years, some patients may lose seizure freedom even if they are still taking ASMs.

Telemedicine and health disparities

Michael Kaufman, Data Scientist at the Children's Hospital of Philadelphia in the US, presented on telemedicine, health disparities and seizure control in children with epilepsy during the COVID-19 pandemic in the US.

The pandemic disrupted healthcare around the world, and created what Mr Kaufman called an "unprecedented shift" in the way we deliver healthcare, including neurological care. Care was entirely in-person and face-to-face before, and had to shift rapidly to telehealth as soon as the pandemic hit.

Mr Kaufman and his team wanted to investigate the long-term impact of telemedicine in child neurology during and following the pandemic restrictions.

Their research showed that there was no difference in children's seizures whether they were seen in-person or using telehealth. However, when they looked more closely, they found that there were disparities within different groups. The researchers found that the percentage of patients who were seen 'virtually' and who had their follow-up within the recommended window of time – the 'care window' – dropped during the pandemic from around 70% to around 50%. Mr Kaufman said it has stayed around the 50% mark since then.

The data showed that reaching people in socially vulnerable and deprived groups was the biggest challenge. People in this group had the lowest follow-ups within the recommended time. Within the different groups, people in the Hispanic or Latino community reported worse seizure severity and control compared to other groups. Mr Kaufman said that it is important to investigate potential language barriers and improve care for this group. Mr Kaufman concluded that the pandemic is likely to have disadvantaged these groups of patients and led to gaps in their care. Attempts must be made to prevent this becoming a long-term problem and the gaps must be closed.

A number of sessions at the IEC raised some important points about improvements needed in epilepsy care, how best to support mental healthcare in patients with epilepsy and where the focus of future research should be. The 14th European Epilepsy Congress is due to be held 9-13 July 2022 in Geneva, Switzerland.

Kami Kountcheva
Co-editor

epilepsy action

epilepsy.org.uk/yourchild

Your child and epilepsy

Grow your confidence managing epilepsy in your family

Your child and epilepsy is a new online course for parents and carers of children with epilepsy. It's been developed with parents, epilepsy nurses and psychologists.

This course is a helping hand to support families on their epilepsy journey. It's full of advice and stories from parents. It aims to give parents and carers the confidence, skills and knowledge to support their child to manage their epilepsy.

There are eight parts that cover:

- Understanding epilepsy
- Supporting your child with their epilepsy
- Keeping your child safe
- The impact of epilepsy on family life
- Your child's wellbeing
- Learning and behaviour
- Growing up and independence
- Sources of help and support

Free course

The course is free and flexible. It can be accessed at any time on a computer, tablet or smartphone with internet access.

Leaflets about the course to give to families can be requested by emailing **nurseorders@epilepsy.org.uk**

To view the course go to: **epilepsy.org.uk/yourchild**
Get in touch **learning@epilepsy.org.uk**

Epilepsy Action
Information you can trust

Find out more
epilepsy.org.uk/trust

Registered charity in England and Wales (No. 234343) © Copyright Epilepsy Action 2020

Genetic testing in the epilepsies in 2022: who, what and why?

Dr Amy McTague, principal research fellow and honorary consultant paediatric neurologist, Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health, Department of Paediatric Neurology, Great Ormond Street Hospital

Introduction

The genomic revolution of the past 20 years has transformed our understanding of health and disease in humans. With the recent completion of the last 8% of the human reference genome, further discoveries in human genetic variation are certain [Nurk et al, 2022]. From the identification of mutations (now referred to as 'pathogenic variants') in *SCN1A* in 2001 [Claes et al, 2001], the advent of next generation sequencing has led to an explosion in the discovery of variants associated with epilepsy. It is now estimated there are >140 genes associated with epilepsy as a primary clinical feature [Ellis, Petrovski, and Berkovic 2020]. In addition, epilepsy is often one feature of a multi-system disorder including other neurodevelopmental conditions such as developmental delay or autistic spectrum disorder. Our clinical approach to genetic testing in patients with epilepsy has necessarily evolved from sequential single gene testing to a more unbiased approach, testing a large number of genes which could potentially explain the patient's difficulties. As we move into an era of yet more genomic complexity, it is essential that practising paediatric neurologists and paediatricians with an interest in epilepsy develop the genetic literacy to understand these results. In this article, I will discuss the changing landscape of genomic testing in epilepsy patients and how it is likely to have an impact on everyday clinical practice including patient care.

Who should have genetic testing in the epilepsy clinic?

In the pre-genomic era, genetic testing would be based on specific phenotypic features prompting testing for a single gene or a small number of genes. Although there are multi-system conditions with dysmorphic features which may prompt clinical suspicion of a genetic disorder, there is significant genetic and phenotypic heterogeneity in the epilepsies [McTague et al, 2016]. That is to say, a specific clinical presentation may have multiple genetic causes and variants in a gene may result in different clinical presentations, sometimes even within the same family. For example, Dravet syndrome is caused in the vast majority of patients by truncating or missense variants or deletions affecting the gene *SCN1A*, but other genetic causes are recognised [Li, Schneider, and Scheffer 2021]. Dravet syndrome is the prototypic developmental and epileptic encephalopathy (DEE), characterised by frequent seizures of multiple types, EEG abnormalities and, in general, poor developmental and cognitive outcome. The DEEs are a heterogeneous group of severe epilepsies encompassing a number of age-related severe electroclinical syndromes and have been extremely fruitful in the identification of new pathogenic genes. In general, pathogenic, often de novo, genetic variants are thought to cause 30-50% of DEEs, although this varies between different electroclinical syndromes [McTague et al, 2016; Ellis, Petrovski, and Berkovic 2020]. For example, epilepsy of infancy with migrating focal seizures (EIMFS) is caused by a wide range of both dominantly and recessively inherited pathogenic variants, although *KCNT1* and *SCN2A* are the most frequently identified genes in this rare and severe epilepsy. In a large international cohort of EIMFS patients, 70% were identified to have a pathogenic variant [Burgess et al, 2019]. In contrast, two studies showed only 7%-30% of patients with West or infantile spasms syndrome had a genetic abnormality [Chourasia et al, 2022; Muir et al, 2019]. Beyond infancy, other DEEs such as Landau Kleffner syndrome or epilepsies within the broader 'epilepsy-aphasia' spectrum may have strong associations with individual genes such as *GRIN2A*, which encodes an NMDA receptor subunit. However, pathogenic variants in a range of other genes and copy number variants can converge on, or result in, a very similar phenotype [Carvill et al, 2013; Kessi et al, 2018]. The genetic architecture of Lennox Gastaut syndrome, a DEE of later childhood, has emerged to implicate largely de novo variants in genes such as *GABRB*, *SHANK3* and *CHD2* and a range of copy number variants [von Spiczak et al, 2017; Allen et al, 2013; Amrutkar and Riel-Romero 2021]. It should also be noted that the phenotype of many patients with severe, drug-resistant epilepsy may not be classifiable as a specific electro-clinical syndrome and therefore genetic testing should not be limited to only those with clinical and EEG features that strongly suggest one of these syndromes.

Children of any age that present with epilepsies associated with developmental stagnation or regression should also undergo genetic testing early in their diagnostic journey. The progressive myoclonic epilepsies (PME), which present in late childhood or adolescence with action myoclonus, generalised tonic-clonic seizures and progressive neurological dysfunction, can be caused by a number of metabolic conditions and lysosomal disorders. They include the neuronal ceroid lipofuscinoses, Lafora body disease and Unverricht-Lundborg disease [Franceschetti et al, 2014]. In addition, a number of newer genetic causes have been identified, such as variants in the potassium channel genes

KCNC1 and *KCTD7* [Park et al, 2019; Cameron et al, 2019; Farhan et al, 2014]. While confirmatory metabolic tests can be helpful, genetic testing leads to a diagnosis in over 70% of patients with PME [Zhang et al, 2020] and should therefore be considered as a first-line test.

It is therefore clearly established that the severe epilepsies of infancy, childhood and adolescence justify genetic testing. However, recently, the focus has widened to other patient groups where genetic testing would not have been considered a first-line test, such as patients with focal epilepsy referred for pre-surgical evaluation. Investigation of extended families with familial focal epilepsies (some of whom had structural lesions) has implicated the *DEPDC5* and *NPRL2*/*NPRL3* genes which encode the GATOR1 complex, an inhibitor of the mTOR pathway [Dibbens et al, 2013; Weckhuysen et al, 2016]. mTOR is a master regulator of many cellular processes with hyperactivation seen in tuberous sclerosis. Importantly, somatic mutations in mTOR pathway genes have been shown to cause malformations of the brain including focal cortical dysplasia Type II and hemimegalencephaly [Baldassari et al, 2019; Poduri et al, 2012; Lee et al, 2012]. However, patients with pathogenic variants in ion channel or synaptic genes may also present with non-lesional focal epilepsy. Recent research into the role of genetic testing in pre-surgical evaluation has shown that while those patients with variants in the mTOR pathway may still have a good surgical outcome, patients with variants in synaptic or channel genes may not respond as well to surgery, although this is not based on prospective data [Boßelmann et al, 2022]. There are notable exceptions, such as patients with *SCN1A* variants and hippocampal sclerosis following prolonged febrile seizures. A recent retrospective study found that while the presence of an *SCN1A* variant does not preclude surgical success for focal seizures, the presence of Dravet syndrome does [Vezyroglou et al, 2020]. Therefore there is an increasing drive to consider genetic testing as an integral part of pre-surgical evaluation in all patients, as it could influence pre-surgical counselling and discussions on potential outcomes following surgery.

Adult patients with epilepsy and intellectual disability may have missed recent genetic innovations but can still benefit from a specific diagnosis. Several studies have shown high diagnostic yields of gene panel testing of up to 23%, with the highest yield in those adult patients with onset in infancy or early childhood and with co-morbid intellectual disability [Johannesen et al, 2020; McKnight et al, 2022]. Notably, many had a change in treatment with positive effects following a specific genetic diagnosis. Genetic re-evaluation should also be considered in young people around the time of their transition to adult epilepsy services.

What genetic testing should be done for epilepsy patients?

Advances in next-generation sequencing paved the way for the use of multiple gene panels in the 2010s, enabling the testing of several hundred genes at once. Many studies demonstrated significant yields of up to 48% (range 9-48%), but this was highly dependent on the patient population [Symonds and McTague 2020]. The most significant factor for gene panel yield in epilepsy patients is age of onset, with yields of 40% demonstrated with seizure onset <2 months of age [Trump et al, 2016]. However, the inherent disadvantages of gene panels, mainly that they capture a limited number of genes which may not include the most recently identified genetic causes, limits their clinical usefulness. Trio whole exome sequencing (WES), where both parents and the proband are simultaneously sequenced for filtering of the genetic data, captures the majority of coding sequence in the genome and offers the opportunity to interrogate either a limited number of genes (a 'virtual' panel) or to perform an 'agnostic' analysis. Trio WES has been shown to be superior over gene panels for childhood epilepsy, also offering the opportunity for re-analysis of exome data as new genes emerge [Rochtus et al, 2020]. Whole genome sequencing (WGS) affords the ability to also capture non-coding regions of the genome and structural variants such as tandem repeats and improves coverage of coding regions. Small studies have confirmed high yield of WGS in childhood epilepsy; a recent study of 30 patient trios who had prior investigation with WES showed increased yield due to detection of structural variants [Palmer et al, 2021]. A meta-analysis of >150 studies of genetic testing in epilepsy also confirmed superior yield for WGS of 48% versus 24% for WES and 19% for gene panels [Sheidley et al, 2022]. The only factors significantly associated with increased yield were the presence of DEE or neurodevelopmental co-morbidities. The pivotal 100,000 Genomes UK study has now made the case for the use of trio WGS as a first line test in rare disorders including the epilepsies [Smedley et al, 2021]. As a result, patients with epilepsy in England who meet certain criteria as outlined in the National Genomic Test Directory [NHS, 2018] are eligible for trio WGS. The NHS testing offers a large panel-based analysis of the WGS data and does not offer an agnostic analysis, this remaining a research-based test at the current time. The details of the NHS WGS epilepsy panel genes are available at the PanelApp website [PanelApp, 2020]. Clinicians should consider whether the intellectual disability or inborn errors of metabolism panels may also be indicated.

A further consideration is the speed at which genetic results are available. As discussed below, a number of conditions with specific treatments can present with epilepsy. Currently, the turnaround time of NHS WGS testing is in the order of months, although more rapid testing may be available after local discussion within genomic laboratory centres. Rapid trio exome testing (R14) is available through the test directory for unwell children in hospital after discussion with clinical genetics teams, but this does not meet the need of the medically stable infant

Table 1. Examples of current treatments for some of the genetic epilepsies.
ASM: anti-seizure medication; LoF: loss of function; GoF: gain of function; SE: status epilepticus

Gene	ASMs/specific treatments recommended	ASMs to avoid
SCN1A	Stiripentol Sodium valproate Clobazam Cannabidiol Fenfluramine	Carbamazepine Lamotrigine Phenytoin
SCN2A (GoF)	Carbamazepine Phenytoin High-dose intravenous phenytoin for SE	–
SCN2A (LoF)	–	Carbamazepine Phenytoin
SCN8A (GoF)	Carbamazepine Phenytoin	–
KCNQ2	Carbamazepine Phenytoin Retigabine (Phase III trial)	–
POLG	–	Sodium valproate
PRRT2	Carbamazepine	–
KCNT1	Consider trial of quinidine in early onset seizures with cardiology monitoring (seek specialist advice)	–
KCNA2	Trial of 4-aminopyridine for gain of function variants (seek specialist advice)	
TSC1/TSC2	Vigabatrin for infantile spasms Everolimus	
SLC2A1	Ketogenic diet	Phenobarbital
ALDH7A1	Pyridoxine	–
PNPO	Pyridoxal phosphate	–
GAMT/ SLC6A8	Oral creatine supplements	–
FOLR1	Folinic acid	–
CAD	Uridine	–
SLC35A2	Galactose supplements (seek specialist advice)	–

with frequent seizures and a potentially treatable epilepsy.

Although microarray alone had a yield of only 9% in the meta-analysis discussed above [Sheidley et al, 2022], it remains an important test to undertake in patients with epilepsy for several reasons. First, recurrent copy number variants (CNVs), such as 15q13.3 deletions, are associated with epilepsy in up to 3% of patients [Niestroj et al, 2020]. Second, a small CNV may be important when a heterozygous variant is identified by WES or WGS in a recessive gene. As WGS CNV analysis improves, the use of CGH microarrays may be superseded but this is not currently available in standard NHS testing. Third and last, it is important to remember that in patients with focal epilepsies particularly with frontal lobe features, behavioural and cognitive impairment or non-convulsive status epilepticus, Ring 20 syndrome should be considered [Peron et al, 2020]. Currently, this still requires an old-fashioned karyotype as the diagnosis may be missed by standard micro-array.

Why is genetic testing useful?

It is clear that genetic testing in the epilepsies, particularly in the severe or early onset epilepsies, has high diagnostic yield. But what are the benefits of a genetic diagnosis for a patient with epilepsy? Firstly, there are an increasing number of aetiology-directed treatments based on a molecular diagnosis (*Table 1*). Metabolic disorders may be identified by genetic testing. These include replacement of vitamins or co-factors, such as in the Vitamin B6-responsive epilepsies or the recently identified uridine-responsive epileptic encephalopathy, or provision of alternate

substrate as in *SLC2A1*-associated glucose transporter deficiency [Myers and Scheffer 2022; Koch et al, 2017].

Understanding the impact of pathogenic variants on ion channel genes has led to a number of tailored or precision therapies. Sodium channel blockers can lead to seizure freedom in gain of function *SCN2A* and *SCN8A* related epilepsies [Wolff et al, 2017; Johannesen et al, 2021] and are also useful in *KCNQ2* and *PRRT2* related epilepsies [Zimmern, Minassian, and Korff 2022], but should be avoided in *SCN1A*-Dravet syndrome. Retigabine is a selective potassium channel opener which may represent a precision therapy for loss of function *KCNQ2* variants [Millichap et al, 2016]. Retigabine was previously withdrawn from use due to side effects including skin discolouration but further analogues are being developed and a trial of retigabine for *KCNQ2*-related epilepsies is ongoing. Gabapentin is also a potent potassium channel opener and has been reported to be associated with significant clinical and EEG improvement in a single patient with *KCNQ2*-related epilepsy [Soldovieri et al, 2020]. For gain of function variants in the potassium channel encoded by *KCNA2*, 4-aminopyridine has been used to treat a small number of patients [Hedrich et al, 2021]. Beyond the channelopathies, pathway-directed therapies include the mTOR inhibitor Everolimus which is licensed for the treatment of tuberous sclerosis related focal seizures [French et al, 2016], but could have potentially have a role for other mTOR hyperactivation epilepsies such as *DEPD5* and *NPRL2* and *NPRL3*.

Gene-specific therapies are emerging for the epilepsies [Turner et al, 2021], with the hope that these may result in improvements for not only seizures but developmental outcomes and co-morbidities. These include RNA-targeting therapies such as antisense oligonucleotide therapies and AAV-delivered gene therapies. The ongoing Admiral study in Dravet syndrome uses an antisense (a short synthetic oligonucleotide) to exclude a 'poison exon' from an *SCN1A* transcript that would not ordinarily lead to functional protein, this increasing the amount of SCN1A protein available [Wengert et al, 2022].

One of the most frequent questions asked by parents is what the future will hold for their child; this often includes their child's epilepsy, learning and behaviour. As we continue to collect valuable natural history data for the genetic epilepsies in ongoing and future studies [Palmer, Howell, and Scheffer 2021], we will be better able to answer this question. However, having a specific genetic diagnosis is a really important first start to the process. But what role does aetiology play in the outcome of children with epilepsy? In a recent population-based study of children that presented with epilepsy under three years of age, multivariate analysis showed that a known aetiology (which was genetic in 30% of patients) was the strongest determinant of both epilepsy and developmental (and learning) outcomes [Symonds et al, 2021].

Receiving a diagnosis of epilepsy is a difficult and stressful time for parents with much uncertainty. One of the benefits of an aetiological diagnosis can be to limit further investigations but also to provide 'closure' and an explanation to parents, who may blame themselves or other factors for their child's symptoms [Jeffrey et al, 2021]. In addition, having a 'label' can allow parents to access networks of support. Diagnoses that include multi-system or later onset features may also require further investigations or disease surveillance. Finally, a definitive diagnosis also allows accurate genetic counselling and pre-conceptual counselling. This highlights the vital importance of close working with colleagues in clinical genetics.

Conclusion

Genetic testing should now be considered a first-line test for patients presenting with epilepsy, particularly in the first three years of life or in association with intellectual disability, or both. This should be undertaken alongside other investigations which include MRI that is of a high enough resolution to detect cortical malformations, and metabolic testing which should focus on the identification of treatable disorders and as early as possible. Broad genetic testing does not replace the need for accurate epilepsy phenotyping; in fact, it is ever more important to add the clinical and EEG features of the epilepsies to better understand and interpret any new genetic variants. As we continue to unravel the complex genetic architecture of the epilepsies, we will need to work closely with clinical genetics, genomic laboratory centres and the wider care team to interpret increasing numbers of genetic variants and to deliver on the promise of precision medicine for our patients.

Acknowledgement: This work is partly funded by the NIHR GOSH BRC. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health

Dr Amy McTague
Principal research fellow and honorary consultant paediatric neurologist
Developmental Neurosciences
UCL Great Ormond Street Institute of Child Health
Department of Paediatric Neurology
Great Ormond Street Hospital

References

Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE et al. De novo mutations in epileptic encephalopathies. *Nature* 2013; **501**: 217-21.

Amrutkar C and Riel-Romero RM. Lennox Gastaut Syndrome. In,

StatPearls (StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC: Treasure Island (FL)).

Baldassari S, Picard F, Verbeek NE, van Kempen M, Brilstra EH, Lesca G, et al. The landscape of epilepsy-related GATOR1 variants. *Genetics in Medicine* 2019; **21** :398-408.

Boßelmann CM, San Antonio-Arce V, Schulze-Bonhage A, Fauser S, P. Zacher, T. Mayer, et al. Genetic testing before epilepsy surgery - an exploratory survey and case collection from German epilepsy centers. *Seizure* 2022; **95**: 4-10.

Burgess R, Wang S, McTague A, Boysen KE, Yang X, Zeng Q, et al. The genetic landscape of epilepsy of infancy with migrating focal seizures. *Annals of Neurology* 2019; **86**: 821-31.

Cameron JM, Maljevic S, Nair U, Aung YH, Cogné B, Bézieau S, et al. Encephalopathies with KCNC1 variants: genotype-phenotype-functional correlations. *Annals of Clinical and Translational Neurology* 2019; **6**: 1263-72.

Carvill GL, Regan BM, Yendle SC, O'Roak BJ, Lozovaya N, Bruneau N, et al. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. *Nature Genetics* 2013; **45**: 1073-6.

Chourasia NC, Yuskaitis CJ, Libenson MH, Bergin AM, Liu S, Zhang B, et al. Infantile spasms: assessing the diagnostic yield of an institutional guideline and the impact of etiology on long-term treatment response. *Epilepsia* 2022 Feb 25. doi: 10.1111/epi.17209.

Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *American Journal of Human Genetics* 2001; **68**: 1327-32.

Dibbens LM, de Vries B, Donatello S, Heron SE, Hodgson BL, Chintawar S, et al. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. *Nature Genetics* 2013; **45**: 546-51.

Ellis CA, Petrovski S, Berkovic SF. Epilepsy genetics: clinical impacts and biological insights. *Lancet Neurology* 2020; **19**: 93-100.

Farhan SM, Murphy LM, Robinson JF, Wang J, Siu VM, Rupar CA, et al. Linkage analysis and exome sequencing identify a novel mutation in KCTD7 in patients with progressive myoclonus epilepsy with ataxia. *Epilepsia* 2014; **55**: e106-11.

Franceschetti S, R. Michelucci L, Canafoglia P, Striano A, Gambardella A, Magaudda P, et al. Progressive myoclonic epilepsies: definitive and still undetermined causes. *Neurology* 2014; **82**: 405-11.

French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet* 2016; **388**: 2153-63.

Hedrich UBS, Lauxmann S, Wolff M, Synofzik M, Bast T, Binelli A, et al. 4-Aminopyridine is a promising treatment option for patients with gain-of-function KCNA2-encephalopathy. *Science Translational Medicine* 2021; 609: eaaz4957. doi: 10.1126/scitranslmed.aaz4957.

Jeffrey JS, Leathem J, King C, Mefford HC, Ross K, Sadleir LG. Developmental and epileptic encephalopathy: Personal utility of a genetic diagnosis for families. *Epilepsia* Open 2021; **6**: 149-59.

Johannesen KM, Liu Y, Koko M, Gjerulfsen CE, Sonnenberg L, Schubert J, et al. Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications. *Brain*. 2021 Aug 25:awab321. doi: 10.1093/brain/awab321.

Johannesen KM, Nikanorova N, Marjanovic D, Pavbro A, Larsen LHG, Rubboli G et al. Utility of genetic testing for therapeutic decision-making in adults with epilepsy. *Epilepsia* 2020; **61**: 1234-39.

Kessi MJ. Peng L, Yang J, Xiong H, Duan N, Pang Yin F. Genetic etiologies of the electrical status epilepticus during slow wave sleep: systematic review. *BMC Genetics* 2018; **19**: 40.

Koch J, Mayr JA, Alhaddad B, Rauscher C, Bierau J, Kovacs-Nagy R, et al. CAD mutations and uridine-responsive epileptic encephalopathy. *Brain* 2017; **140**: 279-86.

Lee JH, Huynh M, Silhavy JL, Kim S, Dixon-Salazar T, et al. De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly. *Nature Genetics* 2012; **44**: 941-5.

Li W, Schneider AL, Scheffer IE. Defining Dravet syndrome: An essential pre-requisite for precision medicine trials. *Epilepsia* 2021; **62**: 2205-17.

McKnight D, Bristow SL, Truty RM, Morales A, Stetler M, Westbrook MJ, et al. Multigene panel testing in a large cohort of adults with epilepsy: diagnostic yield and clinically actionable genetic findings. *Neurology Genetics* 2021; **8**: e650.

McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet Neurology* 2016; **15**: 304-16.

Millichap JJ, Park KL, Tsuchida T, Ben-Zeev B, Carmant L, Flamini L, et al. KCNQ2 encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients. *Neurology Genetics* 2016; **2**: e96.

Muir AM, Myers CT, Nguyen NT, Saykally J, Craiu D, De Jonghe P, EuroEPINOMICS-RES NLES working group, Weckhuysen S, et al. Genetic heterogeneity in infantile spasms. *Epilepsy Research* 2019; **156**: 106181.

Myers KA, Scheffer IE. Precision medicine approaches for infantile-onset developmental and epileptic encephalopathies.

Annual Review of Pharmacology and Toxicology 2022; **62**: 641-62.

NHS England. NHS England» National Genomic Test Directory. [online] England.nhs.uk. 2018. Available at: *https://www.england.nhs.uk/publication/national-genomic-test-directories/*.

Niestroj LM, Perez-Palma E, Howrigan DP, Zhou Y, Cheng F, Saarentaus E, et al. Epilepsy subtype-specific copy number burden observed in a genome-wide study of 17 458 subjects. *Brain* 2020; **143**: 2106-18.

Nurk S, Koren S, Rhie A, Rautiainen M, Bzikadze AV, Mikheenko A, et al. The complete sequence of a human genome. *Science* 2022; **376**: 44-53.

PanelApp. Genetic epilepsy syndromes (Version 2.518). [online] 2020. Available at: *https://panelapp.genomicsengland.co.uk/panels/402/*

Palmer EE, Howell K, Scheffer IE. Natural history studies and clinical trial readiness for genetic developmental and epileptic encephalopathies. *Neurotherapeutics* 2021; **18**: 1432-44.

Palmer EE, Sachdev R, Macintosh R, Melo US, Mundlos S, Righetti S, et al. Diagnostic yield of whole genome sequencing after nondiagnostic exome sequencing or gene panel in developmental and epileptic encephalopathies. *Neurology* 2021; **96**: e1770-e82.

Park J, Koko M, Hedrich UBS, Hermann A, Cremer K, Haberlandt E, et al. KCNC1-related disorders: new de novo variants expand the phenotypic spectrum. *Annals of Clinical and Translational Neurology* 2019; **6**: 1319-26.

Peron A, Catusi I, Recalcati MP, Calzari L, Larizza L, Vignoli A, Canevini MP. Ring chromosome 20 syndrome: genetics, clinical characteristics and overlapping phenotypes. *Frontiers in Neurology* 2020; **11**: 613035.

Poduri A, Evrony GD, Cai X, Elhosary PC, Beroukhim R, Lehtinen MK, et al. Genetic diagnoses in epilepsy: The impact of dynamic exome analysis in a pediatric cohort. *Neuron* 2012; **74**: 41-8.

Sheidley BR, Malinowski J, Bergner AL, Bier L, Gloss DS, Mu W, et al. Genetic testing for the epilepsies: a systematic review. *Epilepsia* 2022; **63**: 375-87.

Smedley D, Smith KR, Martin A, Thomas EA, McDonagh EM, Cipriani V, et al. 100,000 genomes pilot on rare-disease diagnosis in health care - preliminary report. *New England Journal of Medicine* 2021; **385**: 1868-80.

Soldovieri MV, Freri E, Ambrosino P, Rivolta I, Mosca I, Binda A, et al. Gabapentin treatment in a patient with KCNQ2 developmental epileptic encephalopathy. *Pharmacology Research* 2020; **160**: 105200.

Symonds JD, Elliott KS, Shetty J, Armstrong M, Brunklaus A, Cutcutache I, et al. Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. *Brain* 2021; **144**: 2879-91.

Symonds JD, McTague A. Epilepsy and developmental disorders: next generation sequencing in the clinic. *European Journal of Paediatric Neurology* 2020; **24**: 15-23.

Trump N, McTague A, Brittain H, Papandreou A, Meyer E, Ngoh A, et al. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. *Journal of Medical Genetics* 2016; **53**; 310-17.

Turner TJ, Zourray C, Schorge S, Lignani G. Recent advances in gene therapy for neurodevelopmental disorders with epilepsy. *Journal of Neurochemistry* 2021; **157**: 229-62.

Vezyroglou A, Varadkar S, Bast T, Hirsch E, Strobl K, Harvey AS, et al. Focal epilepsy in SCN1A-mutation carrying patients: is there a role for epilepsy surgery? *Developmental Medicine and Child Neurology* 2020; **62**: 1331-35.

von Spiczak S, Helbig KL, Shinde DN, Huether R, Pendziwiat M, Lourenço C, et al. For the Epi4K Consortium, and the EuroEPINOMICS-RES NLES Working Group. DNM1 encephalopathy: a new disease of vesicle fission. *Neurology* 2017; **89**: 385-94.

Weckhuysen S, Marsan E, Lambrecq V, Marchal C, Morin-Brureau M, An-Gourfinkel I, et al. Involvement of GATOR complex genes in familial focal epilepsies and focal cortical dysplasia. *Epilepsia* 2016; **57**: 994-1003.

Wengert ER, Wagley PK, Strohm SM, Reza N, Wenker IC, Gaykema RP, et al. Targeted augmentation of nuclear gene output (TANGO) of SCN1A rescues parvalbumin interneuron excitability and reduces seizures in a mouse model of Dravet syndrome. *Brain Research* 2022; **1775**: 147743.

Wolff M, Johannesen KM, Hedrich UBS, Masnada S, Rubboli G, Gardella E, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. *Brain* 2017; **140**: 1316-36.

Zhang J, Yang Y, Niu X, Chen J, Sun W, Ding C, et al. Clinical phenotype features and genetic etiologies of 38 children with progressive myoclonic epilepsy. *Acta Epileptologica* 2020; **2**: 14 (access through: https://aepi.biomedcentral.com/articles/10.1186/s42494-020-00023-z)

Zimmern V, Minassian B, Korff C. A review of targeted therapies for monogenic epilepsy syndromes. *Frontiers in Neurology* 2022; **13**: 829116.

epilepsy action

epilepsyspace.org.uk

The Epilepsy Space

The mobile friendly website is a helping hand for 16-25 year olds to live their best life with epilepsy

The Epilepsy Space will help young people to:

- Manage their epilepsy
- Feel less alone
- Increase their confidence
- Get the support they need

There's lots of epilepsy facts, tips and stories from young people sharing their experience.

The content is short and interactive. It's not all reading, there's video and young people can share their own quotes, stories and videos too.

It's been created with young people and reviewed by epilepsy nurses.

Take a look at:
epilepsyspace.org.uk

Leaflets about The Epilepsy Space to give to young people can be requested by emailing:
nurseorders@epilepsy.org.uk

Registered charity in England and Wales (No. 234343)

© Copyright Epilepsy Action 2020

Epilepsy Action
Information you can trust

Find out more
epilepsy.org.uk/trust

Recently published papers

This section highlights recently published papers. Hopefully this will be very useful to all, helping to keep everyone up to date with the latest developments. It will certainly save you research and reading time, not having to search so many journals.

There are many (often over 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded and as many review papers as possible have been included. We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

SKOTTE L, Fadista J, Bybjerg-Grauholm J, Appadurai V, Hildebrand MS, Hansen TF, Banasik K, Grove J, Albiñana C, Geller F, Bjurström CF, Vilhjálmsson BJ, Coleman M, Damiano JA, Burgess R, Scheffer IE, Pedersen OBV, Erikstrup C, Westergaard D, Nielsen KR, Sørensen E, Bruun MT, Liu X, Hjalgrim H, Pers TH, Mortensen PB, Mors O, Nordentoft M, Dreier JW, Børglum AD, Christensen J, Hougaard DM, Buil A, Hviid A, Melbye M, Ullum H, Berkovic SF, Werge T and Feenstra T.
Genome-wide association study of febrile seizures implicates fever response and neuronal excitability genes
Brain. 2022 Apr 18;145(2):555-568.
doi: 10.1093/brain/awab260.

PANGALILA R and van der Meulen I.
What is the effect of pharmacological treatment for continuous spike-wave during slow wave sleep syndrome and Landau-Kleffner syndrome? A Cochrane Review summary with commentary
Dev Med Child Neurol. 2022 Apr;64(4):411-412.
doi: 10.1111/dmcn.15137.

WANG J-Y, Li Y, Lv Y-Y and Jiang L.
Screening and identification of novel candidate biomarkers of focal cortical dysplasia type II via bioinformatics analysis
Childs Nerv Syst. 2022 May;38(5):953-960.
doi: 10.1007/s00381-022-05454-2.

LEAL-PARDINAS F, Truty R, McKnight DA, Johnson B, Morales A, Bristow SL, Pang TY, Cohen-Pfeffer J, Izzo E, Sankar R, Koh S, Wirrell EC, Millichap JJ and Aradhya S,
Value of genetic testing for pediatric epilepsy: Driving earlier diagnosis of CLN2 Batten disease
Epilepsia. 2022 Apr 26.
doi: 10.1111/epi.17269.

SOH MS, Bagnall RD, Semsarian C, Scheffer IE, Berkovic SF and Reid CA.
Rare sudden unexpected death in epilepsy SCN5A variants cause changes in channel function implicating cardiac arrhythmia as a cause of death
Epilepsia. 2022 Apr 9.
doi: 10.1111/epi.17254.

BJURULF B, Reilly C, Sigurdsson GV, Thunström S, Kolbjer S and Hallböök T.
Dravet syndrome in children-A population-based study
Epilepsy Res. 2022 May;182:106922.
doi: 10.1016/j.eplepsyres.2022.

LEE C-C, Hung S-C, Chen Y-H, Chen H-H, Chen C, Chen C-J, Wu H-M, Lin C-P and Peng S-J.
Structural connectivity in children after total corpus callosotomy
Epilepsy Res. 2022 May;182:106908.
doi: 10.1016/j.eplepsyres.2022.106908.

MAHAJAN SS, Prakash A, Sarma P, Niraj N, Bhattacharyya A and Medhi B.
Efficacy, tolerability and safety of perampanel in population with pharmacoresistant focal seizures: A systematic review and meta-analysis
Epilepsy Res. 2022 May;182:106895.
doi: 10.1016/j.eplepsyres.2022.106895.

KNUPP KG, Coryell J, Singh RK, Gaillard WD, Shellhaas RA, Koh S, Mitchell WG, Harini C, Millichap JJ, May A, Dlugos D, Nickels K, Mytinger JR, Keator C, Yozawitz E, Singhal N, Lockrow J, Thomas JF and Juarez-Colunga E.
Comparison of Cosyntropin, Vigabatrin, and Combination Therapy in New-Onset Infantile Spasms in a Prospective Randomized Trial
J Child Neurol. 2022 Mar;37(3):186-193.
doi: 10.1177/08830738211073400.

HANDOKO M, Karakas C, Gadgil N, Wilfong A, Riviello J, Curry D and Ali I.
Comparison of Surgical Outcomes in Individuals With Hypothalamic Hamartoma Alone or With Other Potentially Epileptogenic Focal Lesions
Pediatr Neurol. 2022 Apr 9;131:13-19.
doi: 10.1016/j.pediatrneurol.2022.03.004.

ÁLVAREZ DAS, Marcos ES, de Lucas Collantes C, Extremera VC, Insuga VS and López CA.
Fanconi Syndrome Secondary to Sodium Valproate Therapy: Experience and Literature Review
Pediatr Neurol. 2022 May;130:53-59.
doi: 10.1016/j.pediatrneurol.2022.03.001.

KIM HJ, Koo YS, Yum M-S, Ko T-S and Lee S-A.
Cleft size and type are associated with development of epilepsy and poor seizure control in patients with schizencephaly
Seizure. 2022 Apr 6;98:95-100.
doi: 10.1016/j.seizure.2022.04.002.

HERZOG, AG
Association between family history of alcohol use disorder and catamenial epilepsy
Epilepsia. 2022 Apr 15.
doi: 10.1111/epi.17261.

SCHOONJANS A-S, Roosens L, Dewals W, Paelinck BP and Ceulemans B.
Therapeutic drug monitoring of fenfluramine in clinical practice: Pharmacokinetic variability and impact of concomitant antiseizure medications
Epilepsia. 2022 Mar;63(3):686-696.
doi: 10.1111/epi.17162.

BERMAN E, Noyman I, Medvedovsky M, Ekstein D and Eyal S.
Not your usual drug-drug interactions: Monoclonal antibody-based therapeutics may interact with antiseizure medications
Epilepsia. 2022 Feb;63(2):271-289.
doi: 10.1111/epi.17147.

LEONARD H, Junaid M, Wong K, Aimetti AA, Knight EP and Downs J.
Influences on the trajectory and subsequent outcomes in CDKL5 deficiency disorder

Epilepsia. 2022 Feb;63(2):352-363.
doi: 10.1111/epi.17125.

XU Y, Wan L, He W, Wang Y-Y, Wang Q-H, Luo X-M, Liu K, Yang X-Y, Wang J, Shi X-Y, Yang G, Han F, Gao J and Zou L-P.
Risk of vigabatrin-associated brain abnormalities on MRI: A retrospective and controlled study
Epilepsia. 2022 Jan;63(1):120-129.
doi: 10.1111/epi.17121.

SULLIVAN J, Specchio N, Devinsky O, Auvin S, Perry MS, Strzelczyk A, Gil-Nagel A, Dai D, **Galer BS and Gammaitoni AR.**
Fenfluramine significantly reduces day-to-day seizure burden by increasing number of seizure-free days and time between seizures in patients with Dravet syndrome: A time-to-event analysis
Epilepsia. 2022 Jan;63(1):130-138.
doi: 10.1111/epi.17106.

PUKA K, Jones M and Mathern GW.
Functional cognitive and language outcomes after cerebral hemispherectomy for hemimegalencephaly
Epilepsia. 2021 Dec;62(12):2932-2940.
doi: 10.1111/epi.17088.

LAYER N, Brandes J, Lührs PJ, Wuttke TV and Koch H.
The effect of lamotrigine and other antiepileptic drugs on respiratory rhythm generation in the pre-Bötzinger complex
Epilepsia. 2021 Nov;62(11):2790-2803.
doi: 10.1111/epi.17066.

SWINNEN L, Chatzichristos C, Jansen K, Lagae L, Depondt C, Seynaeve L, Vancaester E, Van Dycke A, Macea J, Vandecasteele K, Broux V, De Vos M, Van Paesschen W.
Accurate detection of typical absence seizures in adults and children using a two-channel electroencephalographic wearable behind the ears
Epilepsia. 2021 Nov;62(11):2741-2752.
doi: 10.1111/epi.17061.

SCHEFFER IE, Halford JJ, Miller I, Nabbout R, Sanchez-Carpintero R, Shiloh-Malawsky Y, Wong M, Zolnowska M, Checketts D, Dunayevich E and Devinsky O.
Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial
Epilepsia. 2021 Oct;62(10):2505-2517.
doi: 10.1111/epi.17036.

TAN G, Li X, Niu R, Wang H, Chen D, Gong Q and Liu L.
Functional connectivity of the thalamocortical circuit in patients with seizure relapse after antiseizure medication withdrawal
Epilepsia. 2021 Oct;62(10):2463-2473.
doi: 10.1111/epi.17014.

FREDWALL M, Terry D, Enciso L, Burch MM, Trott K and Albert DVF.
Outcomes of children and adolescents 1 year after being seen in a multidisciplinary psychogenic nonepileptic seizures clinic
Epilepsia. 2021 Oct;62(10):2528-2538.
doi: 10.1111/epi.17031.

VAWTER-LEE M, Natarajan N, Rang K, Horn PS, Pardo AC and Thomas CW.
Topiramate Is Safe for Refractory Neonatal Seizures: A Multicenter Retrospective Cohort Study of Necrotizing Enterocolitis Risk
Pediatr Neurol. 2022 Apr;129:7-13.
doi: 10.1016/j.pediatrneurol.2021.12.003.

SEGAL E, Wheless J, Moretz K, Penovich P, Patten A and Malhotra M.
Perampanel in real-world clinical care of adolescent and adult patients with epilepsy: Results from the retrospective Phase IV PROVE Study
Seizure. 2022 Feb 26;98:87-94.
doi: 10.1016/j.seizure.2022.02.011.

SHAWAHNA R and Zaid L.
Concentrations of antiseizure medications in breast milk of lactating women with epilepsy: A systematic review with qualitative synthesis
Seizure. 2022 Mar 27;98:57-70.
doi: 10.1016/j.seizure.2022.03.017.

SPERLING MR, Wheless JW, Hogan RE, Dlugos D, Cascino GD, Liow K, Rabinowicz AL, Carrazana E and DIAZ 001.05 Study Group
Use of second doses of Valtoco® (diazepam nasal spray) across 24 hours after the initial dose for out-of-hospital seizure clusters: Results from a phase 3, open-label, repeat-dose safety study
Epilepsia. 2022 Apr;63(4):836-843.
doi: 10.1111/epi.17177.

YANG X-R, Ginjupalli VKM, Theriault O, Poulin H, Appendino JP, Au P-Y and Chahine M.
SCN2A-related epilepsy of infancy with migrating focal seizures: report of a variant with apparent gain and loss of function effects
J Neurophysiol. 2022 Apr 13.
doi: 10.1152/jn.00309.2021.

CHASSOUX F, Mellerio C, Laurent A, Landre E, Turak B and Devaux B.
Benefits and Risks of Epilepsy Surgery in Patients With Focal Cortical Dysplasia Type 2 in the Central Region
Neurology. 2022 Apr 13;10.1212/WNL.0000000000200345.
doi: 10.1212/WNL.0000000000200345.

ARSKI ON, Martire DJ, Young JM, Wong SM, Suresh H, Kerr EN, Ochi A, Otsubo H, Sharma R, Widjaja E, Snead OC, Jain P, Donner EJ, Smith ML and Ibrahim GM.
Connectomic Profiles and Cognitive Trajectories After Epilepsy Surgery in Children
Neurology. 2022 Apr 11;10.1212/WNL.0000000000200273.
doi: 10.1212/WNL.0000000000200273.

ARMENO M, Caballero E, Verini A, Reyes G, Galarza N, Cresta A, Caraballo RH.
Telemedicine- versus outpatient-based initiation and management of ketogenic diet therapy in children with drug-resistant epilepsy during the COVID-19 pandemic
Seizure. 2022 Apr 4;98:37-43.
doi: 10.1016/j.seizure.2022.03.023.

SADAK U, Honrath P, Ermis U, Heckelmann J, Meyer T, Weber Y and Wolking S.
Reduced REM sleep: a potential biomarker for epilepsy - a retrospective case-control study
Seizure. 2022 Apr 2;98:27-33.
doi: 10.1016/j.seizure.2022.03.022.

BOOP S, Barkley A, Emerson S, Prolo LM, Goldstein H, Ojemann JG and Hauptman JS.
Robot-assisted stereoelectroencephalography in young children: technical challenges and considerations

Childs Nerv Syst. 2022 Feb;38(2):263-267.
doi: 10.1007/s00381-021-05384-5.

GADIAN J, Eyre M, Konstantoulaki E, Almoyan A, Absoud M, Garrood I and Lim M.
Neurological and cognitive outcomes after antibody-negative autoimmune encephalitis in children
Dev Med Child Neurol. 2022 May;64(5):649-653.
doi: 10.1111/dmcn.15101.

MO A, Snyder LG, Babington O, Chung WK, Sahin M and Srivastava S.
Neurodevelopmental profile of HIVEP2-related disorder
Dev Med Child Neurol. 2022 May;64(5):654-661.
doi: 10.1111/dmcn.15100.

WILLARD A, Antonic-Baker A, Chen Z, O'Brien TJ, Kwan P and Perucca P.
Seizure Outcome After Surgery for MRI-Diagnosed Focal Cortical Dysplasia: A Systematic Review and Meta-analysis
Neurology. 2022 Jan 18;98(3):e236-e248.
doi: 10.1212/WNL.0000000000013066.

HURLEY EN, Ellaway CJ, Johnson AM, Truong L, Gordon R, Galettis P, Martin JH and Lawson JA.
Efficacy and safety of cannabidivarin treatment of epilepsy in girls with Rett syndrome: A phase 1 clinical trial
Epilepsia. 2022 Apr 1.
doi: 10.1111/epi.17247.

HEGER K, Skipsfjord J, Kiselev Y, Burns ML, Aaberg KM, Johannessen SI, Skurtveit S and Landmark CJ.
Changes in the use of antiseizure medications in children and adolescents in Norway, 2009-2018
Epilepsy Res. 2022 Mar;181:106872.
doi: 10.1016/j.eplepsyres.2022.106872.

ASADI-POOYA AA, Bazrafshan M and Farazdaghi M.
Long-term medical and social outcomes of patients with Lennox-Gastaut syndrome
Epilepsy Res. 2021 Dec;178:106813.
doi: 10.1016/j.eplepsyres.2021.106813.

DING J, Wang L, Wang C, Gao C, Wang F and Sun T.
Is vagal-nerve stimulation safe during pregnancy? A mini review
Epilepsy Res. 2021 Aug;174:106671.
doi: 10.1016/j.eplepsyres.2021.106671.

YOUN SE, Jung DE, Kang H-C and Kim HD.
Long-term results of vagus nerve stimulation in children with Dravet syndrome: Time-dependent, delayed antiepileptic effect
Epilepsy Res. 2021 Aug;174:106665.
doi: 10.1016/j.eplepsyres.2021.106665.

MYTINGER JR, Vidaurre J, Moore-Clingenpeel M, Stanek JR and Albert DVF.
A reliable interictal EEG grading scale for children with infantile spasms - The 2021 BASED score
Epilepsy Res. 2021 Jul;173:106631.
doi: 10.1016/j.eplepsyres.2021.106631.

SONODA M, Rothermel R, Carlson A, Jeong J-W, Lee M-H, Hayashi T, Luat AF, Sood S and Asano E.
Naming-related spectral responses predict neuropsychological outcome after epilepsy surgery
Brain. 2022 Apr 18;145(2):517-530.
doi: 10.1093/brain/awab318.

CACIAGLI L and Bassett DS.
Epilepsy imaging meets machine learning: a new era of individualized patient care
Brain. 2022 Apr 29;145(3):807-810.
doi: 10.1093/brain/awac027.

SOFIA F.
Quality of lives matters in developmental and epileptic encephalopathy
Dev Med Child Neurol. 2022 Mar 22.
doi: 10.1111/dmcn.15219.

YANG T, Ren J, Zhang Y, Zhang T, Zhou H, Yang M, Li L, Lei D, Gong Q and Zhou D.
Pretreatment topological disruptions of whole-brain networks exist in childhood absence epilepsy: A resting-state EEG-fMRI study
Epilepsy Res. 2022 May;182:106909.
doi: 10.1016/j.eplepsyres.2022.106909.

Lin S, Liao J, Zhao X, Hu Y, Chen L, Chen Y, Liu G, Yao Y, Su Q, Scheffer IE and Wen F.
Focal Epilepsy in Children With Tuberous Sclerosis Complex: Does Vigabatrin Control Focal Seizures?
J Child Neurol. 2022 Mar 23;883073821104832 6.
doi: 10.1177/0883073821104832 6.

Paediatric Epilepsy is published by: Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY, UK
Date of preparation: September 2021

Epilepsy Action is a working name of British Epilepsy Association. British Epilepsy Association is a Registered Charity in England and Wales (No. 234343) and a Company Limited by Guarantee (No. 797997).

The authors, editors, owners and publishers do not accept any responsibility for any loss or damage arising from actions or decisions based on information contained in this publication; ultimate responsibility for the treatment of patients and interpretations of published material lies with the health practitioner. The opinions expressed are those of the authors and the inclusion in this publication of material relating to a particular product, method or technique does not amount to an endorsement of its value or quality, or of the claims made by its manufacturer.

© 2022 Epilepsy Action ISSN 2631-7400
New Anstey House, Gate Way Drive, Yeadon,
Leeds LS19 7XY, UK
tel: 0113 210 8800 | fax: 0113 391 0300 | Epilepsy Action Helpline freephone: 0808 800 5050
email: epilepsy@epilepsy.org.uk epilepsy.org.uk
To subscribe, email: editor@epilepsy.org.uk