epilepsy action

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New drug targets

New microRNA targets for epilepsy medicines

David Henshall

Diagnosis in children – Richard Appleton

River epilepsy – Robert Colebunders

Smoking and CECTS – Brown | Wang | Xu

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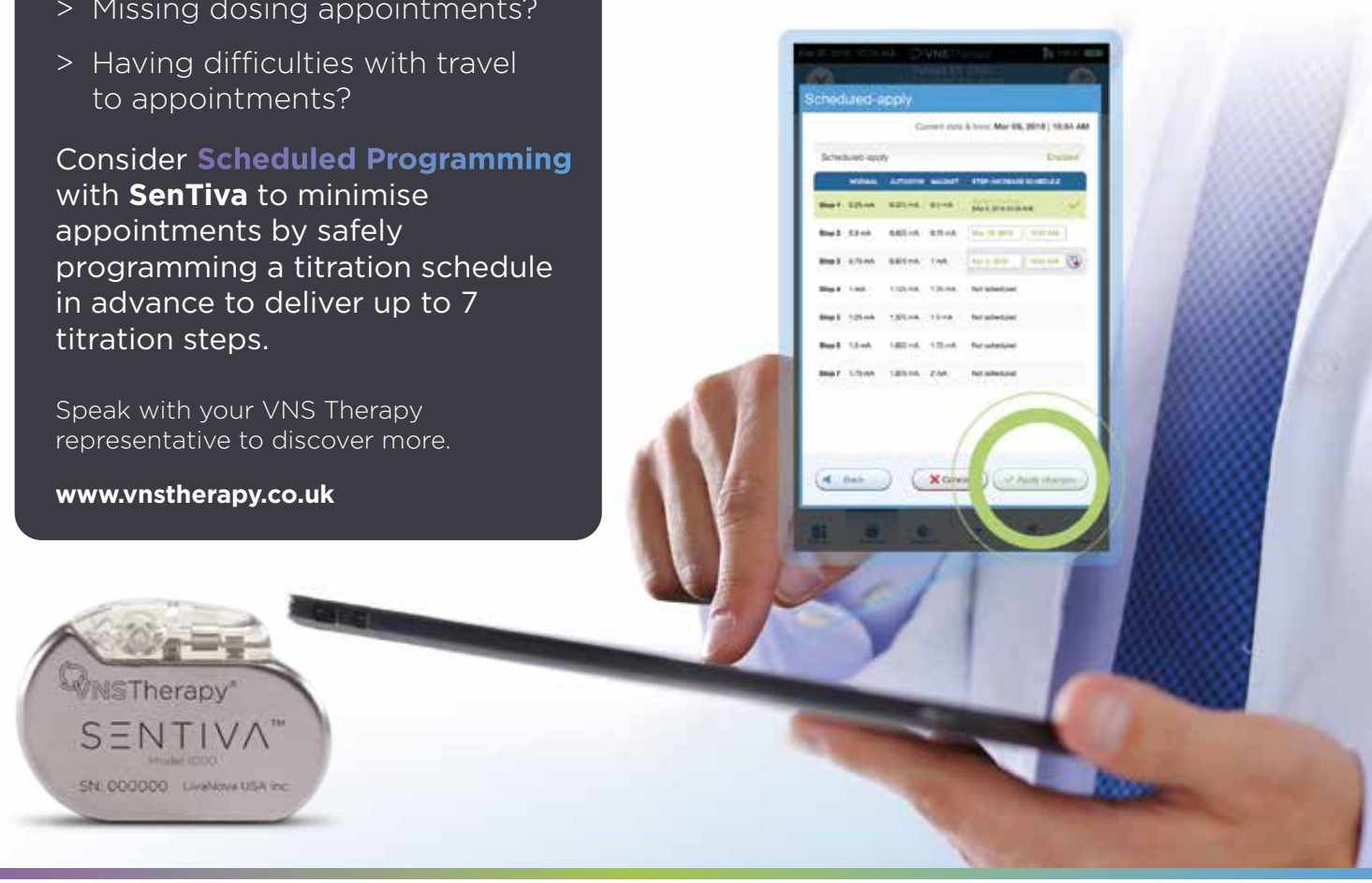

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Health innovation that matters

When training, I was always told the tale of the anaesthetist's light. When operating, the surgeon may bark an order to his colleague, the anaesthetist, to adjust the light and improve visibility for whichever oozing cavity he or she is exploring. The light is angled above the bed on an awkward frame, and adjusting the light is like manipulating the rear-view mirror. Whatever you do, it is crooked, and you often have to make do with the 'least worst' positioning. All the anaesthetist must do is move the light far out of the way, plunging the surgeon's view into abject gloom and count to three, abiding the tut-tutting or gasp of frustration. Then they just return the light to the very same position where it started. Invariably the surgeon will announce that this is 'much better' and will not make the same request again.

My hope is that COVID-19 and the pandemic has been our anaesthetist's light. In returning to work 'as normal' later this year, I hope we find that everything is pretty much as we left it, but with a new view on things. I hope we have a greater love and respect for the in-person clinical medicine we have missed so much of. With this grand aspiration, I introduce four cracking articles which do not reference Br**it, CO*ID or indeed Tr**p.

The first allows us to widen our horizons and look at treatable causes of epilepsy, specifically 'nodding syndrome'. (Nodding syndrome is not the name given to the keen agreement of medical students and juniors following the aforementioned surgeon into theatre in the apocryphal anecdote). Professor Robert Colebunders studies onchocerciasis, a communicable disease endemic to parts of Africa such as Uganda, Tanzania and the Republic of South Sudan. No spoilers from me here, you will want to read the interview in full, but this is an evolving story and one with the potential for more twists in the tale.

Smoking is bad. Smoking is always bad. Except for when it is not, like with ulcerative colitis, or when it is hard to prove it is not. But maternal smoking is an attractive avenue to explore when looking for risk factors that predict the development of neurodevelopmental syndromes such as epilepsy. We could soon be collecting sufficient data and with sufficient quality to look at gene versus environment correlations for common epilepsies. If you pardon the pun, Prof Matthew Brown, Geng Wang and Prof Huji Xu describe a smoking gun associating the nicotinic acetylcholine receptor with CECTS.

There is clearly a critical need for change in our design for anti-seizure therapies and Dr David Henshall has been studying the potential of microRNAs – the 'multi-tasking molecules'. He describes a raft of pre-clinical discoveries which could be laying the groundwork for transformative therapies.

Finally, a favourite article type of mine, a series of invaluable clinical lessons brought to us by a senior and respected colleague. Prof Appleton talks us through how to discuss epilepsy diagnosis with children and their families. If there is a short-cut to hard-earned education produced by experience, it is following the structure and guides in this paper, which is peppered with tips for us all.

I defy you not to have learned something new from these four super articles. Or perhaps you may have only learned the lesson of the anaesthetist's light.

Rhys Thomas
Consultant neurologist
Chief medical adviser
Epilepsy Professional

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Prof Colebunders tells Kami Kountcheva about a preventable major public health problem that needs multidisciplinary collaboration and more awareness

As the light glistens at the end of the long, dark tunnel that is the COVID-19 pandemic – albeit still a small flicker in the distance – it brings with it the thoughts of life after COVID. Aside from the many other things COVID-19 took from us, one thing that stopped – at least for me – was looking forward. For months, looking forward felt like gazing into a fog. But as the vaccine continues to slowly pull us out of our quicksand, it's nice to look outside ourselves, our present and our immediate vicinity. We could think about holidays, plan birthday meet-ups or look forward to that first hug with a loved one. And, as well as that, we can consider life after COVID-19 professionally too.

On page 22, Prof Colebunders speaks to us about his work in onchocerciasis and nodding syndrome. He shares how he uncovered a big, but preventable, public health crisis in some African villages that has gone unnoticed for too long. Recently, it's been imperative to focus on our present and pressing crisis, but it's important to start to look more widely again, as these communities need us to.

Two of our other articles delve into interesting pieces of research offering answers and the potential for more treatment options in the future. On page 10, Dr Henshall describes some potential new drug targets for future exploration and on page 28, Prof Brown, Mr Wang and Prof Xu discuss their research on the role of parental smoking in CECTS. Finally, on page 16, Prof Appleton shares some tips for disclosing a diagnosis of epilepsy to a child and their family. He believes this should be done in person – and hopefully soon there will be no reason for hesitation.

We hope you enjoy this issue, and let's keep looking forward.

Kami Kountcheva
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SUDEP deaths double in pregnant and post-natal women

A "concerning doubling" in maternal deaths due to sudden unexpected death in epilepsy (SUDEP) was seen between 2016-18 compared to 2013-15, a new report has shown.

Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) published their report 'Saving Lives, Improving Mothers' Care 2020 in January 2021. Of the 2.2 million women who gave birth over the two years, 547 women died during pregnancy or up to one year afterwards. The report found that generally, pregnancy remains very safe in the UK.

However, it said a "key focus" in this year's report is the fact that the number of women with epilepsy dying during pregnancy or the year after pregnancy from SUDEP had doubled. According to the report, "in many instances, these deaths are linked to inadequate medications management for these women either before or during their pregnancy".

The report stressed that SUDEP needs to be discussed. It found that "most women with epilepsy who had died had clear risk factors for SUDEP, but had not had risk or prevention measures discussed with them".

MBRRACE-UK advises that women have a pre-pregnancy discussion with their epilepsy team well before considering pregnancy, to agree a plan. The report suggests that women with epilepsy need to be aware of the risks of SUDEP and epilepsy and how they can be reduced. A free app called EpSMon (available at *sudep.org/epsmon*) can be used to help with this.

MBRRACE-UK is also calling on healthcare professionals to support women with epilepsy with their pregnancies as early as possible. Health professionals should check that conversations have been had about minimising SUDEP risk and about the valproate Pregnancy Prevention Programme, it says. They should use a standardised safety tool, such as the SUDEP and Seizure Safety Checklist (*sudep.org/checklist*). The report also highlights the importance of joined up working between different specialists in maternity and epilepsy services.

Philip Lee, Chief Executive at Epilepsy Action, said: "It is extremely concerning to hear of the findings of the MBRRACE report, which found that the number of women with epilepsy dying during, or after pregnancy has increased from 13 in 2013-15, to 22 in 2016-18.

"The report shows the need for pre-conception counselling has never been more urgent, so women fully understand the risks around pregnancy and epilepsy-related death, and how to minimise them.

"We support the recommendations and urge healthcare professionals to work together to ensure issues are fully discussed and women are appropriately supported."

The report has also found that outcomes also differ across different areas and ethnicities for women. Those who are from more deprived areas, and those of Asian, Black or Mixed ethnic groups are at a higher risk of dying in pregnancy. Heart disease remains the leading cause of death in pregnancy, followed by blood clots.

The full report from MBRRACE-UK is available online at *www.npeu.ox.ac.uk/mbrrace-uk*

Neonatal seizures classification

The ILAE Task Force on Neonatal Seizures has developed a modification to the ILAE's 2017 change to the classification of seizures and epilepsies, which is relevant to neonates.

The Task Force explained that neonatal seizures have characteristics that may mean they don't fit well in classification models developed for adults or older children. This led to the need for a modification to the classification developed in 2017.

One of the features of the neonatal classification framework is that it is developed to emphasise the role of EEG in the diagnosis of seizures in neonates. It also includes seizure types more relevant to this age group. This includes electrographic-only seizures, as many neonatal seizures don't have evident clinical features.

The Task Force also explained that neonatal seizures have been shown to have focal onset, so it's not necessary to have a subdivision for generalised onset as you might have in adults and older children. They added that the classification allows for the appropriate level of detail to be noted, including different motor, non-motor and sequential presentations.

The full paper with details of the modified classification system is available at: *www.epilepsy.org.uk/neonatalclassificationILAE*

The Netherlands government to honour UK Bedrocan oil prescriptions

The Netherlands government has confirmed it will continue to supply Bedrocan oil (cannabis-based medicine) for existing UK prescriptions until 1 July 2021, the Department of Health and Social Care (DHSC) has said.

This comes after Brexit took effect on 1 January 2021, and led to prescriptions issued in the UK no longer being honoured and dispensed by EU member states.

This left around 40 children with severe epilepsy, who currently have UK prescriptions for cannabis oil that they source from the Netherlands, in a serious and vulnerable position. A problem with the supply of these medicines would put them at risk of more frequent, more severe or prolonged seizures.

The DHSC added that it will use the time between now and July to come up with a more permanent solution.

Philip Lee, chief executive of Epilepsy Action, said: "We are pleased to see the action taken by the DHSC to secure continued access to finished Bedrocan oils for those with UK prescriptions on a temporary basis. But this is only a short-term fix in more ways than one.

"There is now a new deadline of 1 July 2021 to find a permanent solution to these supply issues. The government also needs to apply the same effort and urgency to address the wider issues faced by families trying to access cannabis-based medicines for children with intractable epilepsy – namely a lack of NHS access and funding.

"Some families are still having to find up to £2,500 every month to cover the costs of private prescriptions. Epilepsy Action has written to the Prime Minister urging him to take comprehensive action to remove barriers to accessing these products on the NHS and a long-term funding settlement for those who are currently accessing privately.

"Swift, comprehensive action, and a system of financial support, will give those affected the certainty and reassurance they so desperately need. We will continue to work with the families involved to find a long-term solution."

There is more information at *epilepsy.org.uk/cannabis*

Pregabalin linked to respiratory depression

Pregabalin has been associated with some reports of severe respiratory depression in people taking the medicine, the Medicines and Healthcare products Regulatory Agency (MHRA) said last month.

A recent European review of the safety data around pregabalin (brand name Lyrica) found that the action of pregabalin on the central nervous system (CNS) could cause respiratory depression. In some cases, this was without concomitant opioid treatment.

The MHRA advises that prescribers and healthcare professionals consider adjusting the dose or regimen for people at higher risk of this complication. This includes people with compromised respiratory function, respiratory or neurological disease or renal impairment. It also includes people taking other CNS depressants, including medicines containing opioids, and people aged over 65.

Suspected adverse events linked with pregabalin should be reported using the Yellow Card Scheme, available at: *yellowcard.mhra.gov.uk*

The MHRA has said it will include new warnings about this side-effect in pregabalin's product information leaflet.

Pregabalin is licensed as an adjunctive therapy for focal seizures with or without secondary generalisation. It is also given for pain caused by the nervous system and for anxiety disorder. In 2019, pregabalin and gabapentin were reclassified as Class C substances under the Misuse of Drugs Act 1971. The MHRA update is available at *www.epilepsy.org.uk/pregabalinGOV*

Teratogenic effects of AEDs

Several anti-epileptic drugs (AEDs) carry risks when taken in pregnancy, a review, published on 7 January by the Medicines and Healthcare products Regulatory Agency (MHRA), has found.

The review, from the Commission on Human Medicines, looked at all the available safety data about 10 of the most commonly prescribed AEDs.

Sodium valproate is known to have teratogenic effects and this prompted the review of the risks for other AEDs.

The review found that four out of the 10 AEDs increased the risk of a baby being born with a physical birth abnormality if taken during pregnancy. These were carbamazepine (Tegretol), phenobarbital, phenytoin (Epanutin) and topiramate (Topamax).

Some of the AEDs also increased the risk of children having learning or thinking difficulties later in life, or of babies being born smaller than average, the review found. None of these AEDs carried as high a risk of teratogenicity as sodium valproate, according to the findings.

Lamotrigine (Lamictal) and levetiracetam (Keppra) were found to be safer in pregnancy than other AEDs.

A further 11 AEDs were included in the review, but there was not enough evidence to reach a conclusion about their safety when used during pregnancy.

Louise Cousins, director of External Affairs at Epilepsy Action, said: "It is imperative that this information is circulated to doctors and nurses widely and quickly. Past mistakes must not be repeated. We know that the consequences of women not knowing information such as this can be devastating. No woman or girl should be taking an anti-epileptic medication without them, or their family, being aware of the risks.

"Women with epilepsy often face difficult choices when they consider how to manage their condition through pregnancy. It is essential that they receive pre-conception counselling so they can work with their health professionals to make an informed choice.

"The review was unable to establish the risk in pregnancy of more epilepsy medications than those it was able to reach conclusions about. This is deeply concerning. We are urgently calling for more research looking into the risks of epilepsy medicines in pregnancy, including the risks of taking more than one medication at once – something many people with epilepsy have to do."

Epilepsy Action says this information could affect the choices of thousands of women with epilepsy, as well as raise concerns about the effects of these AEDs if they've been taken during pregnancy in the past.

The organisation has written to Health Secretary Matt Hancock, calling for the reintroduction of pre-conception counselling for all women with epilepsy as an indicator in the Quality and Outcomes Framework (QOF). This will encourage GPs to talk to women about their options and the risks associated with these before becoming pregnant.

Virtual clinics research

Epilepsy Action and Epilepsy Research UK are jointly funding a new research project comparing remote and face-to-face seizure clinic consultations.

The research, led by Prof Markus Reuber, will aim to help clinicians improve how they communicate in remote clinics and avoid pitfalls in this type of appointment.

The study will be carried out by the University of Sheffield in the UK in early 2021.

The coronavirus pandemic caused virtual consultations to become widespread and they will likely continue to take place after the pandemic is under control.

The study will look to understand why remote seizure consultations appear to be generally shorter. It will also shed light on how clinicians can reduce the risk of misunderstandings and how to best involve patients in making decisions about their healthcare when they are not talking face-to-face.

Other urgent research programmes funded by Epilepsy Research UK will look at other aspects of remote care provision enforced by the pandemic. Dr Rhys Thomas is lead investigator of the epilepsy risk reduction and e-education (ERRE) study. The study will look at the effects of bespoke risk-management tools for people with epilepsy and provide risk-management videos outside of epilepsy clinics, aimed at vulnerable groups. Prof Sameer Zuberi is also leading a project evaluating a new clinical service for secure video sharing and remote care for people with epilepsy.

There is more about this and other research projects at *epilepsy.org.uk/virtualclinicsERUK*

Government responds to safety review recommendations

The UK government is planning to appoint a Patient Safety Commissioner to advocate for patients, after recommendations made in last year's safety review into valproate, Primodos and vaginal mesh.

The government is responding to the recommendations made by the Independent Medicines and Medical Devices Safety (IMMDS) Review published in July last year. The recommendations were made to improve patient safety, after the review found major failings by the healthcare system over three "public health scandals".

The government is putting together a Valproate Safety Implementation Group. This will work to reduce the number of women prescribed valproate and support those women for whom valproate is the only option.

This group will include clinical specialists in neurology and mental health, data experts and system leaders. Other aims for the group include raising awareness of the issues around taking valproate during pregnancy, and trying to ensure the Pregnancy Prevention Programme (PPP) is followed.

A Valproate Safety Register has also been created to monitor the use of valproate, adherence to the PPP and babies born to women taking valproate. The first data from the registry, recently published, showed some progress in reducing valproate prescriptions to women and girls of childbearing age. It also showed that some pregnant women were prescribed valproate.

The government is also responding to recommendations to improve data collection on medicines and medical devices. The Medicines and Healthcare products Regulatory Agency (MHRA) has created an Expert Working Group on Optimising Data on Medicines used During Pregnancy to ensure better data collection and analysis.

A Safer Medicines in Pregnancy and Breastfeeding Consortium has also been set up, made up of 16 organisations, including NHS, regulator and charitable organisations. In addition, the government is putting steps in place to create a UK-wide medical device information system to collect data on medical devices.

Health Secretary Matt Hancock has said that research is ongoing into maternity and neonatal services. He added that the National Institute for Health Research (NIHR) welcomes funding applications for research, including into the use of epilepsy medicines in pregnancy.

Recent findings from a safety review by the MHRA suggest that other anti-epileptic drugs (AEDs) aside from valproate can also have teratogenic effects. Organisations such as Epilepsy Action have called for more research into these and other AEDs.

The Health Secretary said that there are no plans to introduce a PPP for other epilepsy medicines. The government said that "neither the magnitude nor the nature of the risks observed with the reviewed epilepsy medicines are as severe as [those] associated with the use of valproate during pregnancy".

The government is also still considering a number of the recommendations including a call for more transparency about the relationships between healthcare professionals and medical device and pharmaceutical companies.

LD guidance report

New guidance was launched in 2020 to improve epilepsy treatment for people with learning disabilities.

The guidance report, Step Together, reveals that huge variations in levels of care might be failing people with epilepsy and a learning disability.

Four out of every 10 people with epilepsy also have a learning disability and are at a higher risk of premature death than the general population.

The guide describes good quality integrated services for people with a learning disability and epilepsy. It allows commissioners to assess whether needs are met by the current services. It also offers examples of ways to increase joint working, improve services and reduce the variation of levels of care.

The report was created jointly by a number of organisations. They include Epilepsy Action, the International League Against Epilepsy – British Chapter, the Royal College of Psychiatrists, Research in Developmental Neuropsychiatry and the Epilepsy Specialist Nurses Association UK.

Dr Rohit Shankar, consultant neuropsychiatrist and project lead for Step Together, said the guidance should be used to transform services and be ambitious for good epilepsy management.

The full report is available at *epilepsy.org.uk/steptogether*

David Henshall

New drug targets

Researchers identify new microRNA targets for epilepsy medicines

Dr Henshall describes a new class of multi-tasking molecules called microRNA, which may offer the best chance yet to treat or prevent one of the most common and drug-resistant epilepsies in adults.

The majority of people with epilepsy control their seizures by taking anti-epileptic drugs (AEDs). There are more than 20 in general use. They are typically small molecule compounds that can be taken orally as a pill, often several times a day. While they are effective in around two thirds of people with epilepsy, a sizeable minority continue to experience seizures. This treatment gap requires ongoing efforts to discover new targets and therapies. Moreover, virtually all current AEDs work in a similar way. They bind to ion channels and neurotransmitter systems altering their function to dampen brain excitability, either boosting inhibitory transmission or reducing excitatory transmission. But AEDs only provide symptom control; a patient will need to continuously take the drug or seizures return. This is not good enough.

So, what will be the medicines of the future? Increasingly, researchers, clinicians and patients want disease-modifying treatments. We want drugs that actually change the underlying pathophysiology so that seizures decrease over time and eventually stop altogether. Interestingly, although there has been a precipitous drop in active epilepsy drug development programmes in large pharma, new molecules and targets would be expected to re-ignite companies to engage in new epilepsy drug development.

For certain patients with specific genetic mutations, we have the promise of gene therapy, perhaps delivered via a virus to repair or replace a faulty gene. But the number of patients who have single gene causes of their epilepsy is relatively small. The most common form of drug-resistant epilepsy in adults is temporal lobe epilepsy (TLE). Here, genetics has a smaller role to play. TLE is thought to be caused by an earlier insult to the brain such as trauma, prolonged febrile seizure, infection or cerebrovascular event. The hippocampus, deep within the temporal lobe, appears to be a key site driving seizures. Indeed, surgical resection of the hippocampus in TLE patients can lead to seizure freedom. When a resected hippocampus is studied, for example by a neuropathologist, they typically find select neuron loss, gliosis, neuroinflammation and microscopic and macroscopic changes to neuronal networks. This complex pathophysiology presents a challenge to treat. Targeting any one individual pathway or process may not be sufficient to correct the various causal pathways that give rise to intractable epilepsy. So, new types of target are needed.

Anti-epileptic drugs only provide symptom control; a patient will need to continuously take the drug or seizures return. This is not good enough

Role of microRNA

But what is the right target? A discovery during an investigation of the development of the roundworm *C elegans* led to the uncovering of a new layer controlling gene expression [Lee *et al*, 1993]. The molecule belonged to a class of ribonucleic acids (RNA) that were later called microRNA. An explosion of scientific interest followed, with over 100,000 publications to date. About 15 years after being discovered, they came to the attention of the epilepsy research community, in part because of their unique mechanism of action. In short, microRNA are the ultimate 'multi-tasker' molecule.

David Henshall

MicroRNAs are short RNA molecules present in all cell types [Bartel, 2018]. There are about 2,500 different microRNAs in humans. They are essential for organisms to develop as demonstrated in mice when the key enzyme involved in their generation, Dicer, was deleted resulting in non-viable embryos [Brennan & Henshall, 2020].

The primary function of microRNAs is to negatively regulate protein levels in cells. More specifically, they buffer or fine-tune amounts of proteins within cells [Bartel, 2018]. This confers precision to cellular protein 'noise' and lowers protein levels of the messenger RNA (mRNA).

MicroRNAs are 'multi-tasking' because individual microRNAs can have dozens, and perhaps hundreds, of targets. This means that an individual microRNA can produce effects on several targets within the same pathway or several targets in different pathways. Likewise, a single mRNA often has binding sites for multiple different microRNAs, and when several microRNAs target the same mRNA, the effects are stronger (more reduced protein output). This feature is just the kind of property that could be helpful in TLE. You could identify a microRNA which has effects on several targets each contributing to the development or maintenance of the epileptic state. And that way you could have a way to disrupt a complex process through a single target.

We can create a 'drug' targeting microRNAs by designing an antisense oligonucleotide (ASO) complementary to a large part of the molecule. First reported in 2005 and termed 'antagomirs', these ASOs lock onto the microRNA and prevent it from functioning or promote its degradation [Krutzfeldt *et al*, 2005]. One of the most interesting features was that antagomirs produced very long-lasting knockdown of the microRNA. For example, levels of the microRNA being targeted remain reduced for weeks, and even months, after a single injection of antagomir. Another feature, however, created a major problem for their use in brain diseases: their size meant they cannot pass from the circulation through the blood brain barrier (BBB). For brain diseases such as epilepsy, antagomirs will likely have to be given by a route that circumvented the BBB, such as intrathecally.

The first reports on microRNA in epilepsy emerged about a decade ago. Since then, more than a hundred different microRNAs have been reported to show a difference in the brain of humans or animals with epilepsy. To keep track of this, we established the first database on microRNA and epilepsy, called EpimiRBase [Mooney *et al*, 2016]. Soon after the first studies reported altered levels of microRNAs in epilepsy, functional studies began to emerge. These reported that seizures or neuropathological consequences of seizures, such as neuronal death, could be prevented in rodents given antagomirs targeting specific microRNAs. To date, more than a dozen microRNAs have been reported to modulate seizures upon their manipulation by an antagomir [Brennan & Henshall, 2020].

You could identify a microRNA which has effects on several targets each contributing to the development or maintenance of the epileptic state

Narrowing down TLE targets

So, microRNAs could represent a new class of drug target for epilepsy. But key issues remain. How many microRNAs are potential targets for epilepsy? How do we best identify 'new' ones? Also, most studies to date have been led by a single team and used a single model or species. Cross-validation of findings becomes increasingly important before drug development can commence. To tackle these issues and advance the field, we led an EU-funded large collaborative project called EpimiRNA. One of the key objectives was to carry out a multi-laboratory, multi-model systematic investigation to identify all the microRNAs that were functional as epilepsy develops and once spontaneous seizures become chronic. These data would then be used to rationally design antagomir inhibitors to the shared ones and screen these for anti-seizure effects in preclinical models. Later research within FutureNeuro, an Ireland-based multi-institutional research centre focused on chronic and rare neurological diseases, completed the study. The results were recently published [Venø *et al*, 2020]. A key technical advance we used was to first extract the Argonuate protein, which binds to the microRNAs to create a complex that 'searches' for targets, from brain samples. This allowed us to identify just the functional microRNAs, thus enriching for 'active' microRNAs. We also used three different animal models, to minimise bias when relying on a single model. Finally, we collected tissue samples from video-EEG monitored rodents so we were assured which developed epilepsy and we sampled six time points including the day of the first spontaneous seizure. Epilepsy was induced either chemically using kainic acid or pilocarpine in mice, or by electrical stimulation of the afferent fibre bundle that runs into the rat hippocampus (perforant pathway). After the Argonaute protein was extracted it was mixed with chemicals to extract any bound small RNA and then sequenced. Overall we identified more than a billion RNA molecules.

About 400 microRNAs were found to be active in the brain in each model and more than half of these showed a significant change at one or more time points in the models. At every time point we found common-to-all model microRNAs undergoing up- or down-regulation. We compiled a database which contains quantitative data on every microRNA detected and how it changed in the three models. We sense-checked our data for microRNAs previously linked to epilepsy and found many reported before were also changed in our dataset. However, we had data on many other microRNAs that had not been linked to epilepsy before. Some microRNAs showed modest and gradual changes over the course of epilepsy development whereas others showed abrupt changes in levels at specific time points. We also saw that the highest number of microRNAs changed during the early period of epileptogenesis but there was still extensive dysregulation on the day of the appearance of the first spontaneous seizure and in chronic epilepsy. Sets of microRNAs exist that are common to all models of TLE but some are changed at multiple time points while others appeared just at certain times. This tells us that specific populations of microRNAs are being recruited to regulate gene expression at different phases of the disease. This could have direct therapeutic implications – pick the wrong time point to intervene and you may miss the microRNA you are trying to target. Thus, disturbance to the

microRNA pool is a feature of all stages of the disease.

We next focused on manipulating some of the novel microRNAs. The high numbers of microRNAs changing in all models of epilepsy raised the challenge of how to reduce this to a number that would be manageable. We therefore applied a set of criteria that a microRNA had to meet to be retained for antagomir targeting. First, the microRNA had to be fully conserved in humans. No point designing antagomirs to a microRNA only present in rodents. Next, it had to be changed in all three models in the same direction. Then, we set a threshold for how much they had to go up, dropping any microRNAs that showed small and possibly less-meaningful changes. Because our interests lay foremost in identifying new targets for drug-resistant epilepsy we decided to design inhibitors to the upregulated microRNAs common to all models in the final (chronic) phase. Eight microRNAs fitted the criteria. Because two on the list had already been studied in some detail we focused on the remaining six. We designed antagomirs to all six microRNAs and then injected them into separate groups of mice. We then triggered seizures in the mice and recorded their brain activity using a simplified EEG system. We found that seizure severity was reduced by three of the six antagomirs. This suggests that three of the new microRNAs may function in the brain to promote excitability. We also analysed seizure-induced brain injury in the mice. Here, we found that five antagomirs reduced neuronal death in the hippocampus. This suggests that inhibiting some microRNAs can protect neurons from seizures even though the seizures themselves are unchanged, a potentially direct neuroprotective action. We also checked whether the protective antagomirs had any adverse effects in rodents by making recordings from neurons in brain slices from treated rodents. This showed they did not alter the general excitable properties of the brain, meaning they can prevent hypersynchronous discharges of neurons while sparing normal brain function. Together, this suggested that these common-to-all model upregulated microRNAs were a rich source of anti-seizure target.

The anti-seizure effects of the antagomirs may be mediated by altering this pathway and the TGFβ pathway, in addition to these microRNAs, becomes a potential new target in epilepsy

In the final part of our study we investigated whether the new microRNA inhibitors could prevent spontaneous seizures. The earlier antagomir tests had used a chemical, kainic acid, to trigger seizures. Could the antagomirs prevent seizures in an animal with pre-existing epilepsy? Because that type of experiment is much more labour-intensive we decided to pool together the three best antagomirs from the earlier part of the study and inject a single "cocktail" of the antagomirs to mice in which drug-resistant TLE had been induced weeks earlier by status epilepticus. The antagomir cocktail proved effective at reducing spontaneous seizures in mice indicating potential for the treatment of drug-resistant epilepsy.

To try and understand the mechanism by which targeting the

microRNAs had these effects we performed bioinformatics analysis, looking for targets that might be shared in common between the three microRNAs. We found that all three microRNAs we were targeting converged on transforming growth factor β (TGFβ). This is an intercellular signalling molecule known to regulate extensive gene networks, glial and microvascular responses to injury. Analysis of brain tissue samples revealed that TGFβ pathway components were decreased in epilepsy, consistent with the upregulation of the microRNA that we were targeting with antagomirs. Further, we found that injecting the antagomirs reversed this change, restoring levels of the TGFβ pathway. Thus, the anti-seizure effects of the antagomirs may be mediated by altering this pathway and the TGFβ pathway, in addition to these microRNAs, becomes a potential new target in epilepsy.

Next steps

What are the next steps? While all three microRNAs we targeted are fully conserved in humans, we did not investigate the expression of them in human brain tissue. This is an important next step to validate the target. The three individual antagomirs could be entered into preclinical development either alone or as a combination for epilepsy. It would be prudent to test them in other epilepsy models and check in more detail for safety and toxicity. It would also be interesting to investigate whether targeting these microRNAs can have effects on the early changes and development of epilepsy. Attracting industry interest will help accelerate preclinical development. There are several microRNA therapeutics companies, although not many with current central nervous system (CNS) interests. Beyond the potential therapeutic use of the findings, we have learned more about this exciting class of molecules. The datasets we generated certainly contain more targets for exploration and our group as well as others will begin to unpick these in the coming months and years.

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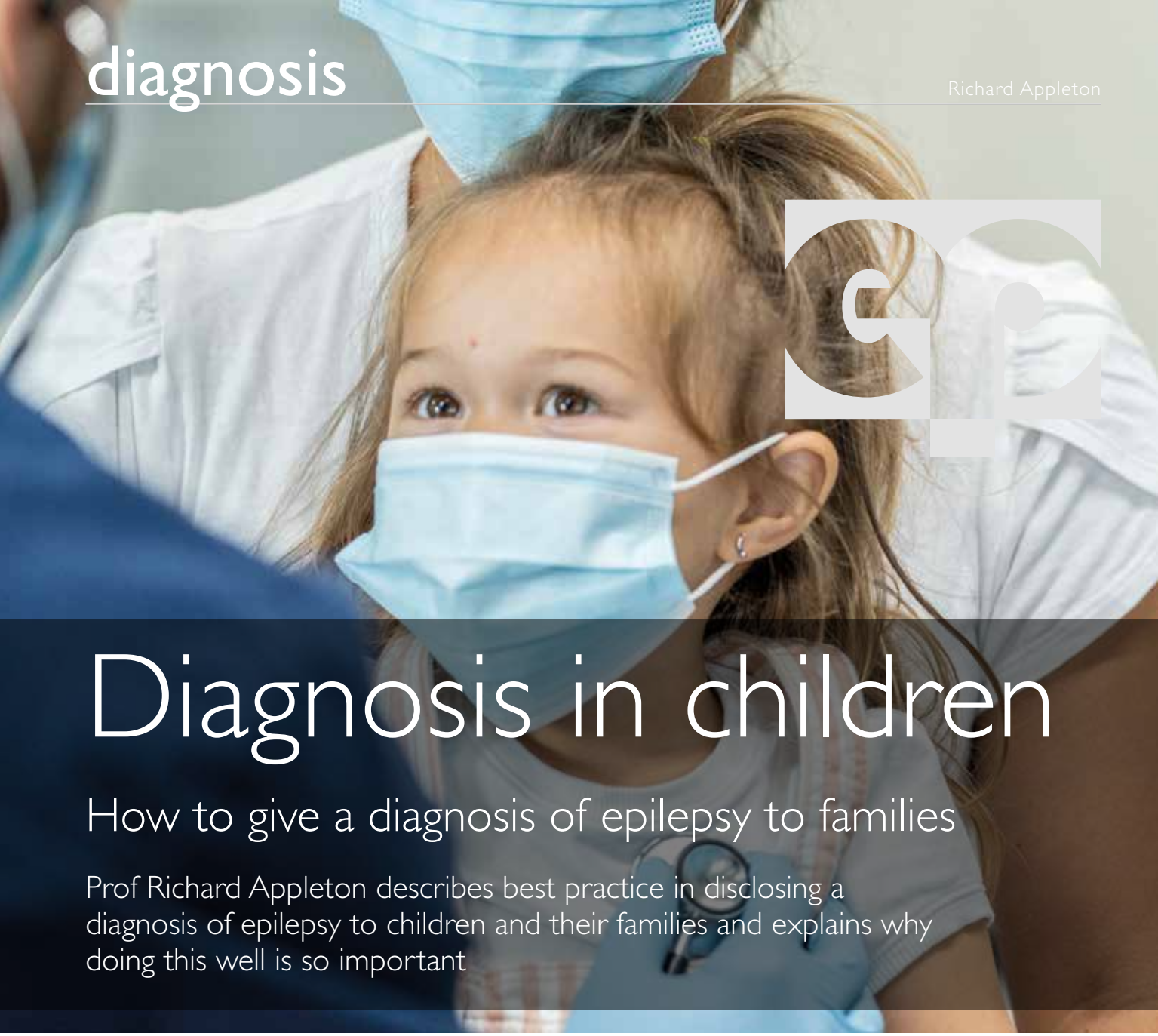
Richard Appleton



Diagnosis in children

How to give a diagnosis of epilepsy to families

Prof Richard Appleton describes best practice in disclosing a diagnosis of epilepsy to children and their families and explains why doing this well is so important

A child with a potentially life-long condition, including epilepsy, provides opportunities and challenges for everyone involved in their care. The first begins with giving the diagnosis to the child and their family. This may be relatively straightforward or it may be difficult, depending on the circumstances. Factors include the epilepsy syndrome or type of epilepsy, the age at which it develops and whether the child has additional physical or learning difficulties (such as severe cerebral palsy, autism, tuberous sclerosis complex or Dravet syndrome). Some doctors may find this a comfortable experience, although others might find it uncomfortable or even stressful [Fallowfield and Jenkins, 2004].

Disclosure that is done well can prevent or reduce parental confusion, dissatisfaction and fear. It can also help to establish important and trusting parent–healthcare professional relationships at a crucial time and also for what may become a long-term process, including through transition and into adulthood. Finally, this process should always be a dialogue, the basis of good communication. It is inevitable that parents, the child and potentially other members of the extended family will have questions about the diagnosis and its implications, as well as management and prognosis. These must be answered.

An editorial in the *British Medical Journal* published 30 years ago, entitled 'It isn't epilepsy is it, doctor?', focused on the importance of establishing a correct diagnosis of

epilepsy using clinical (not EEG) criteria [Brett, 1990]. However, the anxiety − implicit, if not obvious − in this question highlighted the negative emotions inherent in this diagnosis. For some, it's a diagnosis to be feared. These fears reflected, in part, parents' beliefs that a child could die in a febrile convulsion [Baumer *et al*, 1981], which could equally apply to a non-febrile convulsion. A secondary fear was that their child would have suffered brain damage. Fortunately, this fear, perpetuated in the 20th century through ignorance and stigma, has been greatly reduced. But despite the welcome reduction in the mythology and fear about epilepsy, it remains important that the initial disclosure of its diagnosis is clear, knowledgeable and truthful, while also realistic and sensitive.

A paper was published in *Seizure* almost 20 years ago, called 'Epilepsy – giving the diagnosis: A survey of British paediatric neurologists'. This sought opinions on how epilepsy was disclosed to families by UK paediatric neurologists, with the hope this might lead to a consensus statement on best practice [Cunningham *et al*, 2002]. It was a questionnaire-based survey sent to 32 consultant paediatric neurologists, which represented approximately 75% of those in practice in the UK in 2001. Sixteen (50%) questionnaires were completed. Seven recurring factual points emerged from the brief free text sections in the completed questionnaires.

1. It was important to say it is epilepsy
2. There was the need to explain that seizures and 'fits' and some convulsions are all the same (clearly, in 2021 this requires some qualification)
3. That recurrent seizures are called epilepsy – and that this is all the term means
4. Seizures can happen to anyone in certain circumstances
5. Having a seizure is very common: the brain is still working all right and is not usually damaged by the seizure
6. It may not be persistent
7. There are different types of epilepsy with different implications and prognoses

The most striking impression was the general lack of consensus in both the thoughts of, and approaches to, the disclosure of the diagnosis. The respondents considered that intuition determined the pattern of the disclosure. The lack of consensus was felt to reflect, in part, the method of information gathering (an imperfect questionnaire). However, it was also due to the heterogeneity of the epilepsies (which prevented a single or 'one size fits all' approach to disclosure) and the status of disclosure practice. This latter point clearly reflected the experience and the personality of the consultant giving the diagnosis.

The most striking impression was the general lack of consensus in both the thoughts of, and approaces to, the disclosure of the diagnosis

There have been a far greater number of papers on how to give a diagnosis of cancer than ones on how to give a diagnosis of a serious or progressive neurological disorder. A study published in 2000 outlined a six-step algorithm in how to give a diagnosis of a cancer [Baile *et al*, 2000]. This was given the acronym, 'SPIKES', which represented:

- **Setting** the interview
- Assessing the patient's **perception**
- Obtaining the patient's **invitation**
- Giving **knowledge** and information to the patient
- Addressing the patient's **emotions** with empathic responses
- **Strategy** and **summary**

A very recent paper published in early 2020 undertook a scoping review of studies on diagnosis-disclosure to adults with a progressive neurological disease (motor neurone disease, multiple sclerosis and Parkinson's disease) [Anestis *et al*, 2020]. The authors identified 47 studies. Although patients were generally satisfied with diagnosis delivery or disclosure, a considerable proportion was still dissatisfied with aspects of the consultation. This was particularly around the information given, the time provided (the duration of the consultation) and the doctor's approach – specifically, their lack of empathy.

Interestingly, more has been published on how the families of children with a new diagnosis of epilepsy themselves then proceed to disclose and share the diagnosis with others outside the immediate family. This includes grandparents, friends, teachers and others who may at some point be involved with the children (such as during school or in out-of-school activities). A study from Ireland explored the challenges parents of children with epilepsy experienced when disclosing their child's epilepsy diagnosis to others [Benson *et al*, 2017]. The authors used a qualitative exploratory design and conducted interviews with 34 parents (27 mothers and seven fathers) of 29 children aged six to 16 years. The families were recruited from a neurology clinic of a specialist children's hospital and from a national epilepsy association. Five themes emerged, identified by the families,

which led to concealment of the diagnosis or sharing only selective aspects of the diagnosis:

- Seeking or trying to maintain normalcy for the child
- The invisibility of epilepsy
- Negative reactions to disclosure
- Dealing with poor public perceptions of epilepsy
- Coming to terms with the diagnosis themselves

Clearly, this was only a single study with a small number of participants and from a single country. However, an earlier systematic review of 17 studies published by the same group [Benson, O'Toole *et al*, 2015], reported similar findings. They identified the important barriers to disclosure were:

- Prior negative responses to disclosure
- Parental fear of:
  - Stigmatisation
  - The child being treated differently
  - Imposition of unnecessary restrictions on the child

Cultural, religious and societal issues are important factors in the role and effect of stigma on the disclosure of epilepsy and its wider discussions. We must acknowledge that stigma may be both real and perceived. Both need to be addressed to facilitate children's and their family's understanding, acceptance of, and adjustment to the condition.

As healthcare professionals we must be comfortable about how we give a diagnosis of epilepsy before we are then best able to help families, children and young people to do the same. If we have difficulties in disclosing the diagnosis, or give it in an awkward or emotionally-charged way, this may adversely impact the family's desire and ability to disclose the diagnosis to others.

It is often eye-opening and salutary when we have the experience of sitting on the other side of the desk: not as a doctor or nurse, but as a patient, parent or grandparent. It's a valuable perspective when we are the recipients of a diagnosis that may have life-long or life-shortening consequences on ourselves or a family member. On returning to the safety and comfort of our side of the desk, we should never forget our own less comfortable and perhaps distressing experiences. We should let that inform how we disclose the diagnosis of epilepsy to the next family we see.

We must acknowledge that stigma may be both real and perceived

In the current climate of virtual and online consultations, it is my opinion that all healthcare professionals should strive to ensure that the initial disclosure of a diagnosis of epilepsy be face-to-face. I cannot conceive of any scientific or public health reason to do otherwise.

Clearly, families may react differently to how a diagnosis is received and this will require a degree of flexibility as to how and when it is done. Although the following themes or domains may seem intuitive, if not obvious, this may not apply to everyone. It may be a useful checklist, particularly to those more inexperienced in giving diagnoses, and particularly when the child's epilepsy is likely to be severe and difficult to control.

1. Allow adequate time to undertake the disclosure

It is difficult, if not impossible and perhaps even inappropriate to prescribe a specific time period over which this should be done. This is

because of the heterogeneity of the epilepsies, the underlying cause (if known) and the response of individual families to the disclosure. However, my experience would suggest a minimum of 45 and probably a maximum of 60 minutes is reasonable. This allows time to give the diagnosis and discuss the immediate management plan and relevant lifestyle issues. Many families are likely to require a second appointment, probably within a few weeks of the initial disclosure. They may want to 'retrace their steps' in what might have been a challenging and confusing initial disclosure, or to ask questions that were not asked at the first appointment.

2. Seek a family's understanding of epilepsy before this is explained in detail

An early exploration of where the family are in their understanding of their child's symptoms and subsequent diagnosis is important. It enables the clinician to identify the child's and their family's fears but also any myths and misunderstanding they might express if they already believe their child has epilepsy. It also allows the family to show the doctor what they have found and downloaded from the internet – this is likely to reflect the family's postcode and background. This knowledge will enable a more appropriate and individual approach to the disclosure. It shows the family that the doctor is aware of the importance of communication as a dynamic, two-way dialogue. This question-and-answer approach should continue throughout the consultation to ensure the family and child can proceed at a rate with which they are comfortable.

3. Speak honestly with the family and child but framed with optimistic realism

This emphasises the importance of knowing about epilepsy. This includes the different seizure types and syndromes, possible underlying causes (particularly a genetic disorder or a potentially surgically-treatable lesion), available treatment options based on their efficacy and safety data, and likely prognoses. A specialist in paediatric epilepsy from a tertiary centre must be involved if there is any doubt over the initial diagnosis of epilepsy or the specific epilepsy syndrome [NICE 2012]. Providing inaccurate, skewed or inappropriately optimistic information represents poor clinical medicine. The situation is further compounded if the inaccurate or skewed information is given in an engaging, eloquent and charming style and in what seems to be an excellent bed-side manner. In his remarkable book, Talking Sense, Dr Richard Asher wrote: "It is a greater medical triumph to leave the patient feeling better, but thinking little of the doctor, than to leave him worse, but deeply impressed." [Asher, 1972]. Clearly, the ultimate goal and triumph would be to have the patient feeling better **and** deeply impressed with the doctor. A good doctor recognises the importance of both the science (a sound knowledge and understanding of the condition) and the art (how to communicate this knowledge and understanding) of medicine. Focusing on the art while ignoring or misrepresenting the science risks

"It is a greater medical triumph to leave the patient feeling better, but thinking little of the doctor, than to leave him worse, but deeply impressed"

leading the child and family into a false sense of security and trust. If this becomes a reality, it may result in a significant adverse long-term impact on their relationship with the doctor, if not the wider medical profession.

4. Be sensitive in the disclosure

As doctors and nurses, we are encouraged not to become emotionally involved with our patients. This is difficult to avoid when we have known the child and the family for many years and over a period of time during which everyone has grown together. Clearly, emotional involvement is far less likely in the early stages of a potential long-term doctor-patient journey. However, this does not mean we should not show empathy and sensitivity when we talk with the child and their family. Finally, we need to view and treat the child as a person with epilepsy and not as a person whose seizures we must control, as this will not always be possible. We should keep in focus what the children themselves think, "I don't want them to look at me and think of my illness, I just want them to look at me and see me" [Benson, Lambert *et al*, 2015]. This clearly emphasises treating patients (of all ages) holistically.

5. Provide the family with literature or websites from where they can obtain more information

It is very likely and probably inevitable that families will want confirmation and further information on what they had heard during the consultation. Some will have been too shocked or not have known which questions to have asked at the disclosure visit, or both. It is not appropriate to simply suggest the family go to the internet or consult 'Dr Google', because of the risk they will find inappropriate or confusing information. I also don't consider that they should rely on a copy of the clinic letter, as the family may not receive this for some weeks (possibly longer) and it may contain medical jargon. All epilepsy clinics should provide families with printed information sheets on the relevant epilepsy syndrome and anti-epileptic medication(s). Details of reliable and up-to-date websites from where they can obtain additional information should be included. I believe it is important that the families leave the clinic with this 'real' (rather than virtual) information, even if this is limited. This should still be possible in a continuing COVID-19 situation.

Patient experiences of any consultation are clearly important. This was picked up and explored by the Picker Institute over 15 years ago. It is an organisation and charity that evaluates the development of valid measures to assess patient experiences. The Institute has worked with the Healthcare Commission on a number of projects, including an assessment of the day-case and inpatient experience of young people and their parents. Their early research identified the following eight domains that were considered important in patient experiences [Picker Institute, 2005]:

1. Fast access to reliable health advice
2. Effective treatment delivered by trusted professionals
3. Involvement in decisions and respect for preferences
4. Clear information, communication and support for self-care
5. Attention to physical and environmental needs
6. Emotional support, empathy and respect
7. Involvement and support for family and carers
8. Continuity of care and smooth transitions

Getting the disclosure of an epilepsy diagnosis right will help to reduce confusion and misunderstanding early in the child's management

It is surprising that there was no specific domain on diagnosis-disclosure. It is possible this was considered too narrow a subject to justify a specific domain. However, I would argue that the initial disclosure of a diagnosis is a very important, if not crucial, first step in the building and development of a patient (and family) experience.

Conclusion

The disclosure of a diagnosis of epilepsy is an important first step in the management of epilepsy in any individual. In a child, this may be more complex because the disclosure involves not only the child but their family. It may also develop in a child with pre-existing physical or learning difficulties, which some families may consider 'the final straw'. Potentially life-changing epilepsy will also impact on the child's parents and siblings [Hames and Appleton, 2009] which may have a long-term adverse impact on their own lives.

Getting the disclosure right will help to reduce confusion and misunderstanding early in the child's management. It is likely to facilitate future professional doctor-child and doctor-family relationships, which is important for the patient experience.

Communication is crucial to this process. It must always be a two-way process to allow the child, young person and family to respond and progress at a rate with which they are comfortable.

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Robert Colebunders

Village workers remove vegetation at the Maridi dam in South Sudan

River epilepsy

Epilepsy associated with onchocerciasis

Professor Robert Colebunders tells Kami Kountcheva about a preventable major public health problem that needs multidisciplinary collaboration and more awareness.

Epilepsy Professional: Can you tell us a bit about how you came to research onchocerciasis and epilepsy in the first place?
Robert Colebunders: Around 2012 there was a lot of buzz around nodding syndrome. It was considered a very mysterious disease. This is a form of epilepsy that was initially considered to only occur in Uganda, Tanzania and the Republic of South Sudan. This epilepsy is characterised by head nodding seizures, often associated with cognitive deterioration, and sometimes stunted growth. Children were often malnourished and severely intellectually disabled – a terrible situation.

Research was initially mainly done by the Centres for Disease Control and Prevention (CDC) and the World Health Organisation (WHO), but nobody could really find the cause of this disease. There were around 20 hypotheses that were suggested and explored. Blood samples and cerebrospinal fluid were examined, but the only thing that came out was that there was a link with onchocerciasis, also called river blindness. Onchocerciasis is a tropical disease caused by a worm which is transmitted by black flies. This disease is well known to cause skin lesions and eye problems (and eventually blindness), but until recently, it was not considered to result in epilepsy.

It was found that a lot of these children had been in contact with onchocerciasis. But it was unclear how the worm could cause epilepsy, as it was considered that the worm could not penetrate the brain.

I was approached by the government of South Sudan to try to help with a terrible epidemic of epilepsy in a region of South Sudan affected by onchocerciasis. In 2014 I obtained a grant from the European Research Council for €2.5million to identify the cause of nodding syndrome and ways to stop epilepsy in areas affected by onchocerciasis. I chose a multi-country, multi-disciplinary approach.

EP: Can you tell me a bit about your research?
RC: In the past, people have looked for nodding syndrome in Uganda, Tanzania and South Sudan, but not really in other places. If you think there's a relationship with onchocerciasis, you have to go everywhere where there's onchocerciasis. So, in my research, I went to all those countries – north Uganda, South Sudan, Tanzania, Cameroon and the Democratic Republic of Congo (DRC). DRC is where most of the onchocerciasis is. I worked with neurologists, as well as epidemiologists, parasitologists and entomologists. I wanted to look at the broader picture, not only nodding syndrome but also epilepsy in general in areas affected by onchocerciasis. We found that there were indeed many areas in the DRC, often areas of unrest, where onchocerciasis was not well controlled. There were a lot of children ranging from three to 18 years – but particularly aged 10-12 – with epilepsy. Some of the children presented with nodding seizures, others other forms of seizures, while others had epilepsy with severely stunted growth, a condition called Nakalanga syndrome. Where there were children with nodding syndrome, often their siblings would have some other form of epilepsy too. What we found was that nodding syndrome was just the tip of the iceberg. In some villages affected by onchocerciasis we found that more than 4% of the population had epilepsy.

EP: You said the mechanism of how onchocerciasis is linked to epilepsy is not known, but are there hypotheses about what it could be?
RC: We are exploring this. We believe onchocerciasis is the trigger because this form of epilepsy only occurs when onchocerciasis is not treated. Onchocerciasis can be treated with a drug called ivermectin. In areas where there has been unrest and war, in places like South Sudan and the north of Uganda, there have been periods when nothing was done to treat onchocerciasis. In such areas, an epilepsy epidemic can appear. On the other hand, we also documented in Uganda that if onchocerciasis is eliminated, this form of epilepsy disappears.

We do not think the worm can penetrate the brain. It could be an immunological reaction, antibodies against the worm that are neurotoxic attacking the brain. It could also be secretions from the worm. They secrete a lot of proteins, which could have an effect on the brain.

There are a lot of areas in medicine where we don't know how exactly a disease develops or how a treatment works. But if the treatment is working, you give it. We have shown that if you eliminate onchocerciasis, then no new children will develop this form of epilepsy. Therefore, it is important to increase the effort against onchocerciasis in areas where there is a lot of epilepsy.

EP: Nodding syndrome was the original 'mysterious disease' that sparked an interest in this health problem. Why are some cases nodding syndrome and some other forms of epilepsy?
I think the main factor is the number of worms and the age at which children are infected. I believe children with nodding syndrome and Nakalanga disease became infected at a very early age. We found that if left untreated they end up with a large number of worms and develop the most severe form of epilepsy.

Genetics may play a role, as in all infectious diseases, but are not the main factor.

All infectious diseases present with a spectrum of disease manifestations.

Consequence of lack of anti-seizure treatment: severe burns after falling in a fire during a seizure


Prof Colebunders working in Titule in the Bas Uélé in the Democratic Republic in the Congo

This is true in a lot of diseases. In HIV, you have people with AIDS and people who have no symptoms or a minor form of the disease. It's the same with COVID-19. I think that's an error that we made in the past, placing too much focus on these nodding seizures that were thought to be so special.

EP: Why does it seem to affect children from three years old, and why does the epilepsy tend to present at 10-12 years old?
RC: I think there are two reasons for this. When you are bitten by an infected fly, it injects larvae in your body, which grow into adult worms and produce small worms (microfilariae), and these small worms cause the disease. In children living in onchocerciasis-affected areas, you see a sharp increase in the number of worms in the body between the ages of three and 18. At a certain level of infection, a child will be at risk for developing epilepsy. Moreover, around the ages of 10-12, the brain is possibly also more susceptible to developing epilepsy. We know that there are juvenile epilepsies in Europe that start around this age.

EP: How are individuals and communities affected by these forms of epilepsy?
RC: It's a disaster. In South Sudan, I've been to villages where the epilepsy prevalence is more than 4%. In one village, close to the Maridi dam where the blackflies were breeding – because there's a lot of oxygen in the water there – 11% of the population had epilepsy. About half of them have intellectual disabilities, and therefore many cannot work. They are stigmatised and discriminated against. Children are the social security for the older people, but these children will likely die before the older people. For these villages, epilepsy is the main health problem.

These areas are also not equipped to deal with this. There are few doctors, certainly no neurologists. They are very poor and it's quite difficult to get there as well.

EP: What is the solution to this major public health problem?
RC: There are two ways to eliminate this disease. One is by giving everyone the drug ivermectin once a year. I think it would be better to give it twice a year in areas where there's a lot of epilepsy. This is relatively easy to do because it's given free from the pharmaceutical company Merck & Co. They decided to do this as long as there's onchocerciasis. There is a cost associated with its distribution but that's a relatively minor cost.

The other way is to try to eliminate the blackflies. This has been very successful in west Africa, with the use of insecticides, and in other places where onchocerciasis has been eliminated. But since ivermectin became available, the use of insecticides has been abandoned because it's considered more difficult and expensive. There are, however, cheaper ways to do this, using a technique called 'slash and clear'. This way we can remove the vegetation in rivers, so the black flies can't lay their eggs on the leaves. We have started to do this now in South Sudan.

A challenge in these remote onchocerciasis-affected areas is to provide uninterrupted anti-seizure medication. The cheapest drugs are phenobarbital and carbamazepine. Currently in Europe it's not thought of as an ideal treatment, but treatment with these drugs would already make a big difference.

EP: What other challenges are there in implementing this?
RC: Regarding the prevention of this form of epilepsy, it's important that affected populations are informed about the importance to take ivermectin in order to eliminate onchocerciasis.

With epilepsy treatments, in Africa, many people have no access to medicines, or only access for a short amount of time. Often, people only take anti-seizure medication when they have seizures but stop them when the seizures disappear. Also, the treatment of epilepsy is often started

too late, at a stage when there is already intellectual disability.

Organisations like the WHO are making a lot of effort to eliminate onchocerciasis, but I don't think they're focusing enough on the worst-affected areas. I think places like remote areas of South Sudan and the DRC should be prioritised, because this is where there is a lot of epilepsy that could be treated and prevented.

We also need to do much more to raise awareness that there is a way to prevent and treat this significant health problem. A lot of people are not aware that this form of epilepsy exists. There is also little communication between persons with epilepsy from high- and low-income countries. There isn't the kind of solidarity that you get out of sharing experiences. There doesn't seem to be enough cross-country communication between epilepsy associations. There's not enough international awareness between people with epilepsy and between epilepsy specialists. There are also not enough advocates for epilepsy. Having well-known people who speak openly about epilepsy is destigmatising, which is very important in these remote areas of Africa, where stigma and misconceptions are still widespread.

I think the main challenges are a lack of international awareness, the lack of solidarity and the treatment gap. My struggle is trying to communicate that we really need to do something about this.

EP: What's the role of the Western epilepsy community?

Raising international awareness about this problem and the fact that it is treatable and preventable at a relatively low cost, is really important. We need to support these affected communities in Africa and listen to their voices. Importantly, we need to increase international solidarity to decrease the epilepsy treatment gap in Africa. Finally, understanding the mechanism of this epilepsy in onchocerciasis-affected regions may also lead to new insights in the causes of epilepsy elsewhere in the world.

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Highlights

Top picks from *Seizure*

Editor of the journal *Seizure*, Professor Markus Reuber highlights his key papers from the latest editions

We are all creatures of habit. It requires much less mental effort to stick with an established routine than to deviate from it and approach a given task differently. However, as clinicians we must remain prepared to learn throughout our working lives. We have to review the way we manage illness regularly, and we must force ourselves to change when medical knowledge has moved on. While this may not be controversial in principle, the decision whether to change a well-established treatment method or to stick with a familiar, time-honoured approach is rarely clear-cut.

The use of carbamazepine (CBZ) as an anti-epileptic drug (AED) is a good example. This compound was first synthesised in the 1950s – at a time when vinyl was still competing with shellac records. Does this and the fact that there are so many more recent AED choices mean that CBZ is now past its sell-by date? Is it ethical to prescribe CBZ when there are alternatives with fewer side-effects and drug interactions? Conversely, is it ethical to use more expensive alternatives (including eslicarbazepine) when funds are limited and there are so many other health problems to tackle? Is it better to prescribe a drug with known side-effects or one with an unknown long-term safety profile, especially in pregnancy? Is oxcarbazepine (OXC) a sensible middle way?

My editor's choice from issue 83 of *Seizure*, a narrative review by A. Beydoun *et al* [2020], provides the information readers need to decide what choice they should make in relation to the use of CBZ. Readers are not only encouraged to read this comprehensive review article, but then to test their own conclusions by going on to read three editorials on the subject CBZ 'Oldie but goodie?' by Roy Beran [2020], Charlotte Lawthom [2020] and Martin Brodie [2020].

Perhaps readers will conclude that they don't want to change their treatment approach (yet). But maybe the review article and these editorials demonstrate that it would not be appropriate to continue using CBZ out of habit alone. Clinicians need to weigh up the arguments and come to a considered judgement on this important aspect of their practice.

Discharge against medical advice

Previous studies suggest that around 3% of patients with epilepsy leave hospital against medical advice [Raja *et al*, 2020]. Seizures are one of the three most common symptoms leading to A&E presentations which ultimately end in Discharge Against Medical Advice (DAMA) [Hoyer *et al*, 2019].

DAMA gets in the way of proper discharge planning, and may lead to medication errors, repeated seizures and other poor health outcomes. It is, therefore, no surprise that patients who decide to leave hospital prematurely are at a strongly increased risk of being re-admitted to hospital within 30 days [Raja *et al*, 2020]. Not least because of the high risk of readmission, DAMA also represents a financial challenge for health and social care systems.

My editor's choice from issue 84 of *Seizure* is an original research paper by Parul Agarwal *et al* [2021], which seeks to explore the causes and predictors of DAMA. Their study uses the National Inpatient Sample (NIS) from the years 2003 to 2014. The NIS includes all inpatient discharges across 44 states and the District of Columbia, representing more than 96% of the US population. It is a nationally representative database maintained by the Agency for Healthcare Research and Quality. The large case numbers and the availability of data spanning a period of 12 years allow detailed assessment and the exploration of temporal trends. For the purpose of their analysis, Agarwal *et al* split the available sample of inpatient admissions into those that ended in DAMA and those where the final discharge occurred with the clinicians' approval.

The figures from 2014 provide an impression of the size of the problem. Out of 7,071,762 admissions, 187,850 were coded as related to epilepsy, 3,783 of whom (2.01%) were identified as ending in DAMA. Of the variables which distinguished between the two outcomes in univariate analyses, a number of predictors continued to make a significant contribution to a multivariate model. Black patients had higher odds of DAMA than white patients and admissions of patients from poorer households were more likely to end in DAMA. Also, more Medicaid than Medicare and self-pay admissions were associated with DAMA. Weekend admissions ended in DAMA more commonly than weekday admissions. A lower risk of DAMA was associated with older age, higher levels of comorbidity, female sex, Hispanic extraction, elective admissions, and hospital location in the Midwest compared to the Northeast US.

Discharge Against Medical Advice (DAMA) gets in the way of proper discharge planning, and may lead to medication errors, repeated seizures and other poor health outcomes

Although epilepsy patients whose admissions ended with DAMA had fewer recognised comorbidities overall, some specific comorbidities were associated with an increased risk of DAMA. These were alcohol and drug abuse disorders, as well as mood disorders. Alcohol-related disorders were among the top five causes of admission in people with epilepsy who left against medical advice.

The proportion of epilepsy-related admissions ending in DAMA increased substantially between 2003 and 2014, from 1.13% to 2.01%.

The findings of this study can only provide an initial impression of the causes and predictors. However, the potential of DAMA to fragment care provision, put patients at risk and waste limited healthcare resources are very clear. This study should serve as a wake-up call not only to health but also to social service providers. The near doubling of DAMA since 2003 is particularly troubling. Further research into what actually motivates patients to leave hospital against medical advice is urgently required. The largely social risk factors identified in this study suggest that DAMA is not simply an ending of one particular episode of inpatient care. They suggest an expression of a much more profound estrangement between an important group of patients with epilepsy and those providing medical care for them.

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Smoking and CECTS

Maternal smoking and the risk of childhood epilepsy with centrotemporal spikes

Prof Matthew Brown, Geng Wang and Prof Huji Xu discuss the possible underlying causes of CECTS and the potential role of parental smoking in exacerbating the condition or slowing its remission.

Childhood epilepsy with centro-temporal spikes (CECTS), also known as benign Rolandic epilepsy or benign epilepsy with centrotemporal spikes (BECTS), is the most common form of idiopathic epilepsy in children. It accounts for 8-23% of epilepsy in children less than 16 years of age [Tedrus *et al*, 2010; Verrotti *et al*, 2017]. The typical age of onset is between three and 14 years, and the condition typically resolves by the early teenage years, hence the use of the term 'benign'. Affected children are usually neurodevelopmentally normal. However, the condition has been associated with varying degrees of neuropsychological damage, and can be associated with sociological and behavioural problems in adulthood [Ciumas *et al*, 2014]. The causes of CECTS are unknown, with – to date – no known environmental or specific genetic risk factors that have been established for the disease, which is common to most types of epilepsy.

In many cases, epilepsy can be clearly causally related to obvious diseases, particularly of the central nervous system (CNS), such as tumours, infection, stroke, and head injury. But in roughly two-thirds of cases, no obvious cause can be identified [Hauser *et al*, 1993]. Genetic causes have been identified for several different rare forms of epilepsy, often where the epilepsy occurs as part of a complex syndrome along with other medical issues. The genetic aetiology of common forms of epilepsy has been shown to involve common, low-penetrance genetic polymorphisms [International League Against Epilepsy Consortium on Complex, 2018], rare variants of high penetrance [Epi and Epilepsy Phenome/Genome, 2017], and copy number variants [Niestroj *et al*, 2020]. Current understanding of the genetics of epilepsy has recently been comprehensively reviewed by Perucca *et al* [2020].

CECTS is known to run in families, suggesting that either shared environmental factors or genetic factors are involved in its pathogenesis

The role of genetics in CECTS

While genetic variation is clearly a significant contributor to epilepsy risk, the overall heritability of epilepsy is not known. CECTS is known to run in families, suggesting that either shared environmental factors or genetic factors are involved in its pathogenesis (reviewed by Xiong and Zhou [2017]). A major international twin study identified only discordant twin pairs (ie where one twin had CECTS, the other twin did not), suggesting that non-inherited, and non-familial factors must be involved in its pathogenesis [Vadlamudi *et al*, 2006]. However, this study was quite small, with only 18 twin pairs studied, where at least one twin had CECTS. The study is therefore unable to exclude a small to moderate genetic contribution to CECTS. A further potential disadvantage to twin studies is that they can be influenced by ascertainment bias. That is, that twins participating in the studies may not be randomly recruited from the

population. In this study, more identical (monozygotic) twins were recruited than non-identical (dizygotic) twins (monozygotic twins share 100% of their genome and dizygotic twins share 50% of their genome on average). Dizygotic twins occur roughly twice as frequently as monozygotic twins, suggesting that this study was affected by ascertainment bias.

Recently, methods have been developed using apparently unrelated cases and controls to measure distant relatedness between the cases and the controls. According to the common variant-common disease hypothesis, cases with common diseases have inherited genetic variants that arose in common ancestors many generations previously. The hypothesis says they are thus more closely related than individuals without the disease. Using genome-wide association study (GWAS) data, the relatedness between cases, and between controls, can be assessed and compared, giving a measure of heritability due to genetic variants captured by the genotyping method. Typically, GWAS data only involves common variants, with minor allele frequencies >1%, often >5%. Thus, the heritability measured by this approach only assesses common genetic variants (either single base changes (also called SNPs) or copy number variants), not rare mutations or rare structural variants.

We have recently reported a GWAS of CECTS children, involving 1,800 Chinese Han CECTS patients, and 7,090 controls [Shi *et al*, 2020]. Using the method described above, we demonstrated that the heritability of CECTS due to common genetic variants was 10-17%. This is roughly half the common variant heritability of rheumatoid arthritis or one third that of coronary artery disease, determined using the same method [Stahl *et al*, 2012; Nikpay *et al*, 2015]. However, CECTS likely represents many different diseases, with different causes leading to clinically similar outcomes, and our approach does not account for that heterogeneity. Consequently, it likely underestimates the role of common variants in the disease. Therefore, these findings provide a major spur to further GWAS research in CECTS, and more broadly in genetics.

According to the common variant-common disease hypothesis, cases with common diseases have inherited genetic variants that arose in common ancestors many generations previously

Using genetic studies to investigate environmental causes of disease

Traditional observational epidemiologic approaches to the investigation of the role of environmental factors in disease are subject to confounding and biases that make it difficult to produce robust definitive findings. In this context, confounding is where a third variable leads to an apparent association between two other variables. This has led to large scale clinical trials being unable to demonstrate beneficial effects of interventions predicted from observational studies. For example, reports that vitamin E was protective for coronary heart disease [Rimm *et*

al, 1993] led to trials of vitamin E interventions. But they ultimately demonstrated no beneficial effect [Eidelman *et al*, 2004], presumably because of confounding influencing the original epidemiological studies.

The development of Mendelian Randomisation (MR) approaches to leverage the developments of GWAS has enabled causal investigations to be performed without many of these biases [Smith and Ebrahim, 2003; Lawlor *et al*, 2008]. Simply put, this approach leverages the fact that if two genetically determined diseases or traits are not related, they will not occur together more often than by chance. Conversely, genetic correlation between diseases suggests a causative relationship between them [Smith and Ebrahim, 2003]. This approach has now been used to identify or confirm the association of many different diseases with potentially therapeutically targeted factors. For example, in multiple sclerosis, MR has confirmed that low vitamin D levels increase the risk of the disease [Mokry *et al*, 2015]. This was suggested by earlier GWAS data [Australia and New Zealand Multiple Sclerosis Genetics, 2009], and shows the association is not due to confounding with other factors.

Our analysis shows that maternal smoking around birth is associated with 3.9 times increased risk of CECTS

In our CECTS GWAS, association was observed at the locus CHRNA5, involving SNPs that affect transcription of this gene in the brain. CHRNA5 encodes a nicotinic acetylcholine receptor. Microinjection of acetylcholine into the brain can cause seizures in mice, suggesting that acetylcholine, as a neurotransmitter, may play an important role in the development of epilepsy [Duga *et al*, 2001; Ketzef and Gitler, 2014]. While not definitive, these data support a role for this locus and a possible link between nicotine/cholinergic neurostimulation and CECTS, raising the hypothesis that anticholinergic therapies may be effective in CECTS. Further research will be required to test this.

SNPs in and nearby this gene are associated with cigarette smoking, nicotine dependence, and smoking-associated lung diseases [Saccone *et al*, 2007; Amos *et al*, 2008; Berrettini *et al*, 2008]. Therefore, we applied MR to the dataset to investigate the role of smoking in CECTS risk. Although it is unlikely the patients, at their age of onset, were smoking themselves, they could have been exposed to second-hand smoking. For this analysis, we used data from the UK Biobank (*ebi.ac.uk/gwas/*), which included genetic variants associated with risk of perinatal maternal smoking (no data was available about perinatal paternal smoking). Our analysis shows that maternal smoking around birth is associated with 3.9 times increased risk of CECTS. Our study cannot exclude that the CHRNA5 variants influence CECTS through a non-smoking related mechanism (ie. pleiotropy). However, our finding is supported by suggestive evidence that smoking increases the risk of epilepsy overall [Dworetzky *et al*, 2010], and that perinatal maternal cigarette smoking was associated with febrile seizure [Cassano *et al*, 1990; Rong *et al*, 2014].

Conclusions

This study suggests that CECTS is another reason why parents should

not smoke while pregnant. It indicates that this advice is likely to be even more relevant to families already with children affected by CECTS. It suggests that further research should be carried out to study the potential role of paternal smoking, and of passive smoking in children already affected by CECTS. It is possible that parental smoking or other exposure to passive smoking may exacerbate CECTS or slow its natural remission.

Perhaps more importantly, the study shows that clinically relevant findings can be made from GWAS data in epilepsy through MR. This is as opposed to using the higher risk and longer duration functional genomics approaches typically used to translate findings into clinical applications. Our study also confirms that common genetic variants are responsible for a significant fraction of CECTS risk. These variants should therefore be identifiable by GWAS, which currently remains a far cheaper investigational tool than sequencing based approaches, using either whole exome or whole genome sequencing.

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Reflecting on the last year

What a year and what a great deal of change we have all lived through. As we start to come out of the horrible second wave of the COVID-19 pandemic, I'm sure we are all hoping that this will be the last wave. We hope that our lives will soon start to return to some semblance of normality.

We have all been through a lot. Our work has been stopped. Our patients have waited or been afraid to come forward and put more pressure on the NHS and some have come to harm because of this. We have been redeployed and forced to find new ways of working. We have lost colleagues, friends and loved ones.

We have also seen amazing things. The NHS, universities and the pharmaceutical industry have mobilised to create vaccines and new treatments. We have found ways of working to try and minimise the effect of the pandemic on our patients.

There have been improvements. The option of more telephone and video consultations opens up our virtual doors to patients who have struggled to access us. Videoconferencing has enabled more access to multidisciplinary meetings, grand rounds and other governance and educational events. They've made space and distance less of an issue.

There is a lot to process, we are still not out of trouble, but I hope we will be soon. We must all take time to reflect, rest and recuperate. There are backlogs building, but we will not be in a position to tackle them if we do not look after ourselves and our colleagues.

Once we have had a time to rest, we must learn the lessons of treating epilepsy during a pandemic. We must build on the good and change our practice to be more responsive and inclusive.

Hopefully the goodwill shown towards healthcare professionals during the pandemic will endure and will be translated into better health policy and decision making at all levels of government and society. I hope this leads to better working conditions for us and better overall care for our patients.

Dates for the diary

Dates and events may be subject to change – please check on the relevant websites.

2021

23 April
Irish Epilepsy League Annual Meeting
ilae.org/regions-and-countries/national-chapters/ireland

20-22 May
13th International Epilepsy Colloquium (IEC)
Virtual event
epilepsy-colloquium2021.com/

28 August – 1 September
34th International Epilepsy Congress
Virtual congress
epilepsycongress.org/iec/

9-12 September
11th International Summer School for Neuropathology and Epilepsy Surgery (INES 2021)
Erlangen, Germany
ilae.org/files/dmfile/INES-2021-Flyer.pdf

23-24 September
ILAE British Branch Virtual Annual Scientific Meeting
Virtual congress
www.ilaebritishconference.org.uk/

2022

28 April - 2 May
14th European Paediatric Neurology Society Congress (EPNS)
Glasgow, UK
epns-congress.com/

9-13 July
14th European Epilepsy Congress
Geneva, Switzerland
epilepsycongress.org/eec

Next issue:

Sameer Zuberi

Prof Zuberi describes a new clinical service to allow secure video-sharing and remote care for epilepsy

Jacon Pellinen

Dr Pellinen discusses the potential for missed diagnoses of focal seizures

If you are interested in submitting a research paper for inclusion in *Epilepsy Professional,* please contact the Editor: *kkountcheva@epilepsy.org.uk*

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