Epilepsy in 2020 – a new dawn

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2020 will be a remembered as the year when COVID19 put life on hold. As in all areas of medicine, not only did clinical care delivery to our epilepsy patients have to change, but as staff were redeployed and universities closed, research was paused. That aside we had much to learn, not least from new ways of working through online platforms. Epilepsy patients and their carers however reported difficulties in accessing routine health care and medication[1]. Surveillance studies have highlighted that over and above the risk of illness related seizures, there is no specific risk to those with epilepsy beyond that of the recognised comorbidities that of course may be experienced by those with epilepsy[2]. In the event of a pandemic, we must ensure ongoing care of chronic disease, and so avoid a parallel pandemic of ongoing needs in our patients.

Despite the hold on research, several exciting studies have been reported over the year. In the first instance strides forward in the treatment of Dravet syndrome, a developmental epileptic encephalopathy the result of a SCN1A mutation, with poor prognosis for seizure and neurodevelopmental outcome. Secondly studies utilising big data to gain insights into underlying mechanisms and outcomes from interventions.

Fenfluramine, previously utilised in obesity but now off licence in view of concern about cardiac toxicity, has been shown to be effective in the treatment of Dravet syndrome. After the finding that the genotype phenotype of many responders from early use was SCN1A positive Dravet syndrome, two RCTs were undertaken[3,4]. Patients showed significant benefit when treated with fenfluramine compared to placebo, whether add on to stiripentol or stiripentol naive – however the 54-62% difference in percent reduction in convulsive seizures between fenfluramine and placebo groups was far greater than that seen in any previous antiepileptic drug studies. Whether this effect is specific to Dravet syndrome through action on serotonin metabolism[5], or applicable to other epilepsies remains to be seen. No cardiac toxicity has been reported. Fenfluramine appears to be a potential game changer in the treatment of Dravet syndrome.

Studies have also been published highlighting the real possibility of genetic therapy for Dravet syndrome. Han and colleagues used Targeted Augmentation of Nuclear Gene Output (TANGO) technology to increase Scn1a gene and protein expression in a mouse model. They showed that a single intracerebroventricular dose of an ASO at postnatal day 2 or 14 reduced the incidence of electrographic seizures and SUDEP, with increased expression of SCN1A transcript and protein in brains of treated mice[6]. Colasante and colleagues showed catalytically dead Cas9 (dCas9)-mediated Scn1a gene activation could rescue Scn1a haploinsufficiency in a mouse Dravet syndrome model and restore physiological levels of its gene product[7]. A specific sgRNA was identified that increased Scn1a gene expression levels in cell lines and primary neurons. Nav1.1 protein levels were augmented, as was the ability of wild-type immature GABAergic interneurons to fire action potentials. They then delivered the Scn1a-dCas9 activation system to Dravet syndrome pups using adeno associated viruses. Parvalbumin interneurons recovered their firing ability, and febrile seizures, a characteristic

of the disease, were significantly attenuated. Both studies offer the real potential for genetic therapies in humans.

However, whereas these studies relate to one rare genetic epilepsy, large collaborations have utilised big data to address research questions. The Epi25 collaborative, a global effort to collect genetic cohorts primarily for the three major classes of non-lesional epilepsies (Developmental Epileptic Encephalopathies (DEE), Genetic Generalised Epilepsies (GGE) and , and Non Acquired Focal Epilepsies (NAFE)) reported on CNV analysis in 17458 subjects, demonstrating increase in CNV burden in GGE and DEE, with 15q13.3 deletion being the strongest CNV for GGE[8]. In all common epilepsy types, 1.5–3% of patients were shown to carry epilepsy-associated CNVs. Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA), a global initiative of combining individually collected images into a single large-scale study, celebrated 10 years of collaboration. Specifically, in the epilepsies they published on white matter changes, showing abnormalities in the corpus callosum, cingulum and external capsule, with differing severity across epilepsy syndromes[9]. They suggested these data provide detailed insights into the pathological substrates that may explain cognitive and psychiatric co-morbidities in the epilepsies, that could be utilised in future biomarker studies of treatment outcomes and/or genetic research.

The European Epilepsy Brain Bank reported on data from 9147 patients for whom seizure outcomes were available in 8191 (89·5%) at 2 years, and 5577 (61·0%) at 5 years[10]. Such data demonstrated histopathological diagnosis, age at surgery and duration of epilepsy to be important predictors of outcome, with children more likely to be seizure free off medication at 5 years.

Phenotypic and genotypic insights have made major strides towards a mechanistic approach in the treatment of monogenic epilepsies, whereas big data and data sharing are changing the way we undertake research and ultimately will have an impact on epilepsy care.

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