Navigating the genetic landscape of childhood epilepsy- a new perspective?

Over the past decade, the genomic revolution has led to an explosion in genetic discovery in the childhood epilepsies. In particular, *de novo* dominant variants in genes encoding a variety of synaptic proteins and channels have been implicated.[1] For clinicians attempting to interpret genetic results, this can appear a confusing genetic landscape. More importantly, there remains a significant lag between the advances in our diagnostic capabilities and the development of novel therapies; these children still have treatment-resistant epilepsy and significant neurodisability.[2] Indeed, after 20 years of new antiepileptic drug development, 30% of people with epilepsy suffer uncontrolled seizures.[3]

In this issue, Gatalullina *et al* propose a new way of thinking about the monogenic epilepsies of childhood, combining data from experimental models and knowledge of gene function with electroclinical features.[4] The childhood epilepsies are classified as NMDA-pathies, phasic GABA-pathies or tonic GABA-pathies, and they suggest this can direct treatment choice.

For the NMDApathies, a number of different genetic aetiologies are described as leading to perturbed glutamatergic signaling as a final common endpoint. For some there is robust functional evidence, such as altered NMDA receptor subunit expression patterns in *TSC1* and *CDKL5* animal models and mutations in *GRIN2B* encoding GluN2 subunits, all resulting in West syndrome. However for others such as *PRRT2, KCNT1* and *KCNQ2* direct evidence of NMDApathy is not available and it is rather imputed from gene function or clinical features.

There is a strong body of evidence to support the concept of *SCN1A*-related Dravet syndrome as a phasic GABApathy and this is further supported by mutations in $GABA_A$ receptor subunit genes leading to a Dravet-like phenotype. Conversely, *SMC1A*-and *PCDH19*-related epilepsies, for which the mechanisms of epileptogenesis are not understood, are proposed as GABApathies based on clinical features.

The role of tonic GABAergic inhibition mediated by extrasynaptic GABA receptors is emerging as an important area in epilepsy. There are intriguing phenotypic similarities between patients with myoclonic astatic epilepsy (MAE) due to mutations in *GAT1*, the voltage-dependent neuronal GABA transporter responsible for synaptic re-uptake of GABA, and Angelman syndrome due to *UBE3A* mutations which lead to abnormal clathrin-coated vesicle cycling and which may also result in increased extrasynaptic GABA. For some time it has been noted that vigabatrin, which inhibits GABA transaminase amongst other actions, can worsen seizures in both MAE and Angelman syndrome. Therefore this clinical observation links neatly to the concept of both these disorders being mediated by excessive extra-synaptic GABA tone.

Indeed, the strength of this approach is borne out by the similarities in clinical and EEG features shared by the electroclinical syndromes placed into each phenotypic grouping.
But does this approach provide any new insights for current or future treatments? Suppression of specific NMDA receptor subunits in tuberous sclerosis (TS) is discussed as a

potential treatment avenue. However, while this process may contribute to early epilepsy in TS, it is one of many mTOR-dependent effects and early suppression of perturbed mTOR signalling with everolimus or other compounds may be a more efficient approach.[5] The authors also cite the use of sodium channel blockers in *SCN2A* and *SCN8A* related epilepsies and quinidine in *KCNT1* related epilepsies, but these are driven by the underlying genetic aetiology rather than addressing excessive glutamatergic signalling. On the other hand, considering genetic generalised epilepsy in the same category of phasic GABApathy as Dravet syndrome leads to the interesting suggestion of extending the use of stiripentol to other syndromes.

With the ever-increasing number of individually rare genetic aetiologies for the childhood epilepsies, the search for common disease mechanisms is important. Recent advances in the field have focussed on gene-specific treatments and the proposed classification prompts us to consider extending these to other epilepsies. Whether the reverse is possible- repurposed or novel therapies which target a pathway common to multiple genetic aetiologies - remains to be seen.

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