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CHALLENGES IN INVESTIGATING CLINICALLY RELEVANTTAXONOMIC AND FUNCTIONAL SHIFTS IN THE GUT MICROBIOTA OF CHILDREN WITH SEVERE EPILEPSY ON KETOGENIC DIET

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Epilepsy is a heterogeneous collection of neurological conditions and syndromes characterized by recurrent, unprovoked, paroxysmal seizure activity. Children with epilepsy experience difficulty in aspects of functioning, including social competence, academic achievement, and family life, with effects extending into adulthood (Camfield and Camfield 2010). Different forms of sleep disturbance, emotional and behavioural problems have been reported in patients with epilepsy, depending on the type of seizure disorder (Stores 2013).

The international League against Epilepsy defines drug-resistant epilepsy as a failure of adequate trials of two (or more) tolerated, appropriately chosen, and appropriately used antiepileptic drug regimens to achieve freedom from seizures. A community-based study in southern France estimated that there are up to 22.5% of patients with drug resistant epilepsy (Picot et. al. 2008). These patients have increased risks of premature deaths, injuries, psychological dysfunction and reduced quality of life (McCagh et. al. 2009). A randomized, controlled trial showed that the number of seizures in drug resistant epilepsy fell by more than 50% in approximately half of children after 1 year on the ketogenic diet and the diet seems to be effective for all seizure types. (Neal et. al. 2008).

Gut microbiota has been thought to play a central role in normal neurological functioning and germ-free mice display deficits in brain development and behaviour (Heijtz et. al. 2011). This "microbiome–gut–brain axis" is a bidirectional communication system between the intestinal microbiome and the central nervous system involving neural, endocrine, and immune pathways (Cryan and Dinan et. al. 2012). It has been shown that gut microbiota is necessary for the anti-seizure effect of ketogenic diet in mice (Olson et. al. 2018).

Ketogenic diet in drug resistant epilepsy changes the taxonomic and functional profiles of gut microbiota (Lindefeldt et. al. 2019). *Identifying which microbial taxa, functions and metabolic substrates may be correlated to a positive effect of the diet in patients could lead to a better understanding of mechanism of action of ketogenic diet. Furthermore, this knowledge can lead to the development of oral formulations of prebiotics and probiotics for non- responders to increase their chance of response to the intervention.*

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