The Rare Epilepsy Network

The Rare Epilepsy Network (REN) is a consortium of partners committed to conducting research to improve outcomes of rare conditions associated with epilepsy and seizures. REN is a Patient Powered Research Network funded by PCORI and part of PCORnet. Led by The Epilepsy Foundation, in collaboration with Research Triangle Institute International and Columbia University, REN includes organizations representing more than 35 rare-epilepsies. We are committed to addressing the urgent health challenges of our rare epilepsy community by engaging patients and caregivers to participate in patient-centered and patient-driven research, making data available to researchers, and investigating causes and consequences of rare epilepsies in order to improve diagnosis, treatment, and find cures.

The REN survey has eleven modules that address demographics, epilepsy diagnosis, seizure history, development of the affected person, comorbidities, seizure treatment, surgeries and devices, genetic testing, birth and maternal symptoms, and quality of life. EEG, MRI, video EEG reports can be uploaded. A follow-up survey collects longitudinal data. Caregivers and cognitively able adults enter data into the REN survey and choose whether their de-identified data is shared with researchers. Researchers interested in projects in the REN can complete a one-page form, evaluated by the REN Executive Committee, and voted on by the REN Steering Committee.

Demographics

Nine-hundred and thirty-two people entered data at baseline and 269 entered data at follow-up.

- Age and gender at baseline and follow-up were evenly distributed.
- Non-Hispanics and Whites predominated (89% and 86%-90%, respectively).
- More than 47% had an annual household income of $75,000-$100,000.

Analyses Conducted in the REN

Comorbidities across 10 rare epilepsies:
Baseline data are used. The 10 rare epilepsies were Aicardi, CDKL5, Dravet, Dup15q, Hypothalamic hamartoma, Infantile spasms, Lennox-Gastaut, Phelan McDermid, and Tuberous Sclerosis. The comorbidity classes were sleep, mental health, learning disability, vision, hyper/hypotonia, brain abnormality, skin, pulmonary, mitochondrial, immune system, hearing, endocrine, digestion, dental, cardiac and bone.

We used a heat map to graphically display the prevalence of each comorbidity class (0%-100%) for each of the 10 rare epilepsy syndromes. This allowed us to see whether the prevalence of each comorbidity showed commonalities or differences across the 10 rare epilepsies.

i. A set of low prevalence comorbidities (ranging from 0% to 20%), included skin disorders (except for Tuberous Sclerosis, 100% prevalence), pulmonary disorders, hearing, mitochondrial disorders, and immune system disorders. With the exception of TS skin disorders, the set of low prevalence comorbidities was similar across the 10 rare epilepsies.

ii. A set of medium prevalence comorbidities (ranging from 20%-70%), includes endocrine, digestion, and cardiac conditions that varied across rare epilepsies. For example, cardiac conditions were most
prevalent in CDKL5, Aicardi, infantile spasms, and LGS, whereas cardiac conditions were less prevalent in Dup15Q, PCDH19, and Phelan McDermid.

iii. A set of variable prevalence comorbidities ranged from 20%-100%, although sleep, mental health disorders, hypo/hypertonia, brain abnormality, and learning disability had the highest prevalence. Vision in Aicardi was 100% and 80% for CDKL5. Learning disability was highly prevalent in Aicardi, CDKL5, Dravet, Dup15Q, LGS, and Phelan McDermid. A medium prevalence of learning disability ranged from 20%-50%, in hypothalamic hamartoma, PCDH19, Infantile spasms, and Tuberous Sclerosis. Hyper/hypotonia had a high prevalence in Aicardi and CDKL5, a medium prevalence in Phelan McDermid, Infantile Spasms, LGS, and Dup15q, and a low prevalence in Dravet, Hypothalamic Hamartoma, TS and PCDH19. Brain abnormality was found in 100% for hypothalamic hamartoma and 60-80% for Aicardi and Tuberous Sclerosis.

iv. Problems with sleep ranged from 50%-100%. A high prevalence was found in all but IS, which had a lower prevalence (~50%).

v. The prevalence of mental health disorders ranged from 40%-100%. Dup16q and Phelan McDermid had the highest prevalence, 70% and 90% respectively. Those conditions that appear to be more variably affected were Tuberous Sclerosis, LGS, PCDH19, Hypothalamic hamartoma, Dravet, CDKL5 and Aicardi.

**Risk factors for pneumonia in the rare epilepsies:** We have developed hypotheses for a causal pathway for pneumonia in the rare epilepsy populations and examined risk factors for pneumonia, defined as aspiration or recurrent pneumonia and both pneumonias, across rare epilepsies in baseline data.

Carbonic anhydrase inhibitors and antiepileptic drugs with strong sedation effects (e.g. Clobazam) were associated with non-significant 3.5-fold increased prevalence odds ratio (pOR) of both types of pneumonia. Hyperventilation and neuromuscular scoliosis, using a breathing device during sleep, and swallowing issues (e.g., aspiration of food into the lungs) were each significantly associated with aspiration or recurrent pneumonia (pORs=4.7-11.2) and with both types of pneumonia (pORs=10.4-18.1).

Hyperventilation was mediated by swallowing problems (p<0.001), neuromuscular scoliosis was mediated by hyperventilation (p=0.016), gross motor delay was mediated by aspiration of food into the lungs (p<0.001) and by swallowing problems (p<0.01), both topiramate and zonisamide were mediated by aspiration of food into the lungs (p=0.03 for topiramate and p=0.04 for zonisamide).

People with a rare epilepsy are at risk for developing pneumonia. These complex epilepsy syndromes require a care coordination model in a medical home open 7 days a week that can deliver multidisciplinary care to prevent adverse outcomes such as pneumonia among patients with rare epilepsy syndromes.
Future Plans
We will be embarking on a population-level validation of deidentified data in the REN and in the Tuberous Sclerosis natural history data, comparing caregiver-entered data in the REN to physician-entered data in the TS Alliance Natural History Database.

Strategic Priorities
The REN organizations voted on short- and long-term priorities.

Short-term priorities
• Validation of REN data
• Analyses of caregiver priorities and perspective

Long-term priorities
• Continuing to build REN infrastructure as a clinical trials and studies network for pragmatic clinical trials and to feed into IND/IDE studies
• Create a priority list of treatment recommendations based on genetic signatures
• Apply for funding and/or collaborate to collect bio specimens and tissues
• Review and expand the list of explicit research question for groups of syndromes and continue to refine the questions over time:
  • Which therapy works best?
  • Which side effects are most common?
  • How should REN connect families to organizations and researchers?
  • Are there logical collections of syndromes that make sense for drug development?