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Editorial

Rare epilepsies — Shared challenges & immense opportunity

Daniel…

Daniel was a very healthy 22-year-old Stanford graduate working as a financial analyst who suddenly felt ill. Found unresponsive, he was rushed to the hospital where he began to have reoccurring seizures accompanied by a high fever. Multiple antiepileptic drugs were administered and failed. Daniel was placed in an induced coma to protect his brain. Subsequently, ketogenic diet and intravenous immunoglobulin (IVIG) proved futile. On day 79, palliative care was started. An hour later, Daniel died.

Daniel had no history of epilepsy, and there was no history of epilepsy in his family. His doctors have since attributed his illness to new onset refractory status epilepticus or NORSE[1] which is defined as an acute, prolonged illness in which one seizure follows another without recovery of consciousness and with no known cause. It is frequently a diagnosis of exclusion after other causes are ruled out. There is no established treatment for NORSE, and by definition, it does not respond to standard AED interventions. However, it requires urgent treatment and coordinated medical care of ICU, epilepsy, and other specialty teams.

One-third of patients diagnosed with NORSE die, another third suffer profound morbidity, and another third recover varying function but typically live with recurring epilepsy for life. Multiple specialists from the ICU, epilepsy department, and neurology managed Daniel's care, but at times, it felt like there was no quarterback or effective communication between the teams, especially during team transitions and holidays. Reflecting on this time period, Daniel's family wished his NORSE had been readily documented and communicated and that a path forward had been lain out with the spectrum of possibilities, so the family could both understand the care strategy and begin to prepare. It was startling to go from trying to cure Daniel to palliative care to his ultimate death.

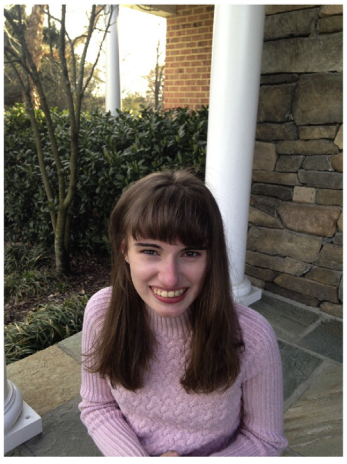
Ellie…

Ellie was just 3 months when her mom noticed she was turning her head as if she was tracking something on a wall. After this behavior repeated several times the next day, Ellie was sent by her pediatrician to the hospital where seizures started coming hourly. Ellie's EEG was normal, but an MRI showed a missing corpus callosum and an intracranial cyst. It was recommended that an ophthalmologist do an eye exam to rule out Aicardi syndrome (AS) — a rare neurological disorder.

Following the eye exam, Ellie's parents were given a diagnosis of AS, bleak survival statistics, and discharge papers and essentially told to make an appointment with one of the local neurologists in 1 month. Furthermore, they were told to call the ER if things worsened in the interim. In this single moment, Ellie's family's life changed permanently, yet they were left to their own resources to understand the diagnosis, navigate the medical system, and maintain hope for their newborn baby girl. They entered the hospital with a seemingly thriving baby girl and left with a rag doll in an AED stupor.

At first, hope came easy as baby Ellie continued to meet milestones despite the effects of the AEDs and the doctor's prognosis. It was hard to imagine that she would ultimately regress. Her parents focused their attention on another rare child with AS who was high functioning and avoided stories about those who were not. By age 6, Ellie was potty trained, signing, and walking and had developed akin to 36 months when the regression started. Two brain surgeries at ages 7 and 8 arrested the regression, but skills lost were not regained.

It is hard for Ellie's mom to look at the early pictures and videos of how Ellie was. Today, Ellie is 17, and seizures occur weekly instead of multiple daily thanks to cannabidiol oil. Life with Ellie has been filled with joy but also a rollercoaster for her family as they navigate each new challenge. The only consistency has been the need to continuously adjust and readjust expectations.



[1] http://rarediseases.org/rare-diseases/new-onset-refractory-status-epilepticus-norse/.

http://dx.doi.org/10.1016/j.yebeh.2016.07.001

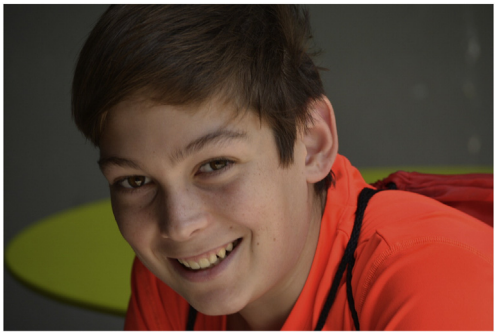
Mark…

Ice-skating with his father, four-year-old Mark fell down and could not get up. Suddenly, after 4 years of misdiagnosis, it clicked with his dad, an orthopedic surgeon by training, that Mark was postictal and had experienced a seizure. His EEG was normal. An MRI was ordered to rule out the bad stuff. It too read as normal. As a courtesy, the radiologist asked Mark's parents what symptoms led the neurologist to request an MRI. When they described the smirking, laughing, swallowing, and staring behaviors, the radiologist took a second look at the imaging.

Armed with those key clinical details, he uncovered a rare tiny tumor called a hypothalamic hamartoma (HH). But for the communication between the radiologist and Mark's parents, the diagnosis would have been altogether missed. Suddenly, the cute laughing Mark had exhibited since he was born was diagnosed as gelastic seizures, the swallowing as automatisms, and the staring and spacing out were identified as absence seizures. Soon thereafter, Mark started experiencing complex partial seizures with regularity and one very prolonged tonic-clonic seizure.

Obtaining an accurate diagnosis was only just the beginning. The MRIs were sent to dozens of neurosurgeons internationally. Top neurosurgical centers questioned the diagnosis altogether. Some recommended surgery to remove the tumor, others argued that experimental gamma knife surgery (GKS) was the only safe option given the deep location and small size of the tumor, and finally, others advocated a "watch & wait" approach.

Mark had GKS surgery at age 5, which was not successful. Newer, less invasive therapies have since been developed for which Mark, now 14, is not currently a candidate. Though seizures in most persons with HHs are refractory to AEDs, luckily, Mark's seizures are fairly well controlled, and his family watches and waits all the while quarterbacking a team of specialists spanning Arizona, Texas, Maryland, and France.



Rare diagnosis — common journey & shared challenges

Daniel, Ellie, and Mark's stories shed a common light on the many patients and families navigating rare epilepsies, like AS, NORSE, and HHs. Despite disparate diagnoses, these conditions share many similarities and challenges in each patient's journey to a timely and accurate diagnosis; access to specialized, multidisciplinary, coordinated care and up-to-date treatment; disease management and cure; and access to caregiver emotional and other supports for the stress and challenge of prolonged care and uncertain prognosis.

In 2014, ten rare epilepsy organizations connected to form the Rare Epilepsy Network (REN)[2] — a PCORI-funded registry that cuts across all rare epilepsies. Currently, 37 rare epilepsy organizations are participating in the REN with patient populations ranging from 1 to 248. Seventy-one epilepsy genes[3] have been identified because of advances in gene sequencing with the potential for many more. As a result, the list of newly discovered rare epilepsies continues to grow.[4]

Despite the unique origin of each rare epilepsy, patients and their caregivers consistently seek many of the same solutions including defining conditions and establishing diagnosis, treatment, and management guidelines; professional support at disease diagnosis; better information dissemination; and long-term care solutions, roadmaps, and supports for patients that will never live independently. A movement is afoot within the rare epilepsies to change the total diagnosis, management, care, and support paradigm.

Defining conditions & establishing guidelines

Diagnosis was delayed for Mark and Daniel. For Daniel, one ICU doctor's hunch was not communicated across multiple specialty teams caring for Daniel. In Mark's instance, neurologists, pediatricians, and other doctors did not recognize the symptoms. When diagnoses are delayed, critical interventions are also delayed.

Educating neurologists, ER doctors, pediatricians, nurses, and social workers to ask the right questions in order to recognize symptom clues like a gelastic seizure must be a priority. Building consensus definitions of the rare epilepsies, keeping the list current, and disseminating them widely are key toward their recognition. The NORSE was only first defined in 2005 — a first step toward educating providers that a condition exists and must be treated. Establishing diagnostic, care, and treatment guidelines and protocols built upon the experience of doctors expert with these conditions and broadly disseminating them is the only way to ensure expedited and high quality care for patients like Mark, Daniel, and others.

Navigating care, maintaining hope

A common theme for families who receive a rare diagnosis is the triple challenge of first, reconciling the shock and disbelief of the diagnosis; second, quickly transitioning from parent to child health advocate to rare disease expert; and third, maintaining hope, especially when given a life-changing or -threatening diagnosis. Repeatedly, families share how emotional – angry, sad, and confused – they felt in the moment of diagnosis followed by a mourning process that occurs when the expectations you have for your child's future are instantly shattered.

Ellie, Daniel, and Mark's parents all shared that shedding light on the spectrum of even the rarest conditions with what is known and what is unknown would have given them the opportunity to understand the worst case scenarios while still holding onto hope for the best outcomes. Ellie's family easily accessed information about the kids with AS who never sat up, walked, or talked while seizing for life. It was important to Ellie's parents to avoid leaping forward, assuming the worst was going to be their experience. There is tremendous need for more nurse navigators and social workers specialty trained in the field of epilepsy. Families need immediate access to a dedicated professional with both compassion and the time and ability to help them navigate the diagnosis, treatment, management options, support resources, and their own processing.

Information silos

It turns out that, as Daniel laid in an induced coma, an experimental drug for super refractory status epilepticus was being developed by a company just a stone's throw away from his hospital, in conjunction with a neurologist who was colleagues with Daniel's doctors. But Daniel's parents learned about this drug not through his medical team but through friends and colleagues. The drug was acquired on a compassionate use basis, but by the time this process was completed, Daniel was too ill to have it administered. Too often, epilepsy specialists work in silos within their departments, their hospital, and consortiums.

[2] http://www.ren.rti.org.
[3] http://www.cureepilepsy.org/egi/genes.asp.
[4] http://www.rightdiagnosis.com/e/epilepsy/subtypes.htm.

They are unaware of drugs or other developments across the country and sometimes even at neighboring institutions.

The same was true for Mark's path to a treatment plan; given the small number of patients with HH treated by disparate doctors dispersed internationally, there is lack of communication toward establishing the best practices and protocols that become widely disseminated. Resultantly, some patients with HH are recommended for tests that have no bearing and even antiquated harmful surgical procedures that have been replaced by cutting age, less invasive interventions.

All too often, parents research the diagnosis and become more expert than many of the medical team, especially if they also have access to other similar parents on social media or other support groups. Parents become educators of their healthcare team — both with the experience of living with these diseases day-to-day as well as experiential information discussed among similarly situated families. Banking parental knowledge has infinite value but is too often dismissed.

The information age and transformative technology must be harnessed in ways to enable better sharing among disparate people — both medical professionals and lay people. Imagine if we could build bodies of data across individuals, institutions, and borders to get a clearer clinical picture of these rare conditions, the efficacy of interventions, and the comorbidities.

Continuum of care rollercoaster

Once the crisis moment passes as it did for both Ellie and Mark, the task at hand is living with the diagnosis. With refractory epilepsy, there rarely is a long-lasting normal, as seizures increase and decrease. Medications have adverse effects, some interventions wreak havoc, and comorbidities arise impacting cognition, education, physical abilities, and many other body systems. Early data from the REN show a high proportion of patients with autism spectrum disorder, developmental regression, and sleep issues in both patients and caregivers.[5] The child's natural development brings on new stressors that impact family dynamics and increase parental stress as children age out of school and other support systems. Many parents' new normal is a life of stress and constant change with no established roadmaps or systems that include qualified, ongoing support, and respite care. Each family is left to navigate this tumultuous road often times very much alone. The impact of stress on the health outcomes for caregivers is well documented, yet supports and resources for the family are rarely addressed in the pediatric setting.

Conclusion

With international readership across multiple medical disciplines, *Epilepsy & Behavior* is uniquely positioned to advance understanding, awareness, and research of these rare epilepsies. The Rare Epilepsy Network and expansive PCORnet network provide a novel framework to tackle these most pressing challenges. We ask you, as clinicians, to become educated on the growing number of rare epilepsies, as well as their symptoms and treatments. We encourage you to refer your new and returning patients with rare epilepsy for participation in the REN. We hope that editorials like this one will spark interest in new interdisciplinary research and cross-institutional collaborations. We have the potential to study the rare epilepsies, which share many common phenotypes, pathways and comorbidities; identify people with rare epilepsy yet to be diagnosed; and undertake new research across multiple disorders and disciplines. Finally, we urge you to engage in dialogue with patients and their advocates to identify important research questions and new processes for culling experiential-based information. The rare epilepsy advocates stand ready, and we hope that all epilepsy professionals will take up this charge.

Conflict of interest

The authors declare that they have no conflict of interest.

About the Author. Ilene Miller is cofounder and President of Hope for Hypothalamic Hamartomas. *Special thanks to parents Barbara Kroner, Aicardi Syndrome Foundation, and Nora Wong, The NORSE Institute, for sharing their stories and contributions to this editorial. Thanks also to all of the Rare Epilepsy Network partners and families seeking answers and support. The REN is actively recruiting patients and researchers. For more information, visit: ren.rti.org.*

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[5] Across the 14 rare epilepsies with at least 10 people per syndrome reporting, the REN finds that 1%–52% have autism spectrum disorder only, 1%–20% have developmental regression only, and 1%–19% have both. Sleep issues are also common across rare epilepsies with restless sleep, frequent awakenings during the night, and difficulty falling asleep predominating. Among caregivers, restless sleep, frequent night awakenings, excess daytime sleepiness, and difficulty falling asleep are issues of concern as well.