




CASE REPORT

On the edge—A diagnostic odyssey

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Abstract

The diagnostic odyssey of a child with epileptic encephalopathy was resolved by rapid whole genome sequencing. This identified a rare form of pyridoxine responsive epilepsy due to a pathogenic variant in *PLPBP*. Access to such potentially life-changing diagnostic technology needs to expand in a thoughtful and equitable manner.

KEYWORDS

diagnostic odyssey, narrative medicine, *PLPBP*, pyridoxine responsive seizures

What do you do when your child lives on the edge of modern medicine, when physicians tell you that “he is beyond medical help” and that the “medical field is not this advanced yet”?

Cammdon is a little boy whose existence was thrown into jeopardy by an inexplicable illness. He pushed doctors to do things they had never done before and was ultimately saved by the opportune availability of an advanced genetic test. This is the story of Cammdon and his family's diagnostic odyssey; their journey to find a diagnosis raises important questions, and their experience teaches us many important lessons.

In the summer of 2017, Cammdon, who was 14 months of age, first presented to the emergency department for abnormal eye movements. At the time of this initial presentation, electroencephalographic abnormalities were found and Cammdon was started on the anticonvulsant

medication levetiracetam. However, this treatment failed to resolve the symptoms, and within a few days he was admitted to the pediatric intensive care unit (PICU). Genetic testing was performed to look for what could be causing his symptoms, and a variant of uncertain significance (VUS) was identified on the standard epilepsy gene panel. Despite finding this variant, a definitive diagnosis remained elusive. This identified VUS did not provide any real relief to Cammdon or his family, and indeed it may have contributed to his care team not asking more questions, and thus an extension of what would turn into an arduous diagnostic odyssey. After an adverse reaction to levetiracetam, Cammdon was started on topiramate and entered into a period of relative stability marked by outpatient visits instead of emergency room visits.

Cammdon would take a turn for the worse in summer of 2018 as his symptoms began again. Summer through

The information contained in the following narrative was obtained from multiple interviews with family and care providers.

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winter of 2018 was consumed with multiple admissions, a life flight trip from their hometown to the regional children's hospital in Salt Lake City (a trip of about 60 miles), and the first time a physician told Cammdon's parents that he may not make it to the end of the year. Cammdon's seizure frequency increased when he had any other illnesses, and he was repeatedly admitted to the hospital. At the start of 2019, Cammdon again improved, with a decline in admissions to the hospital. However, July of 2019 would mark a turn of events eerily similar to the previous two summers. Seizure frequency would gradually increase, at first manageable at home with rescue medication, and then his parents would eventually have to start driving him to their local hospital, all the way to Primary Children's Hospital (the regional children's hospital) or calling ambulances. Their local hospital would do everything they could to help, but the family would end up describing the local hospital as merely a means to the end of arranging transport to Primary Children's. On one occasion, insufficient IV phenobarbital in the local hospital pharmacy prompted such a transfer to Primary Children's Hospital. Throughout this process, Cammdon's family had worked closely with the palliative care team at Primary Children's Hospital, called Rainbow Kids. These relationships would prove to be a much-needed source of constancy and comfort for Cammdon's family as they endured an ever-rotating cast of attendings, residents, nurses, and other staff.

I just think about the uncertainty and that was the most difficult thing for them, and I don't know how to fix the uncertainty other than just acknowledging it and being honest.

(Nurse Practitioner, Palliative Care)

As summer of 2019 dragged into winter of 2019, the pattern of admissions triggered by uncontrollable seizures would continue and Cammdon experienced further developmental regression with each exacerbation of seizures. By this time, he had been labeled with a variety of diagnoses: Dravet syndrome, mesial temporal sclerosis, and Lennox-Gastaut syndrome. He had tried an overwhelming number of medications, including the following: levetiracetam, topiramate, lorazepam, divalproex sodium, clobazam, midazolam, zonisamide, intravenous immune globulin, epidiolex, phenobarbital, and lacosamide. For refractory status epilepticus, he had repeatedly received fosphenytoin, phenobarbital and propofol, and ultimately ketamine. Late in December of 2019, Cammdon would be admitted to Primary Children's for the final time before his diagnosis would be discovered. He would remain in the hospital for 49 days. His problem list included the following: Refractory status epilepticus, intractable drug-resistant epilepsy, mesial temporal sclerosis, developmental delay, pneumatosis,

possible pneumonia, worsening pancreatitis, pancytopenia, and full body edema. Between his inpatient and home list, there were over 40 medications in his chart, including fentanyl and ketamine. The ketogenic diet had been initiated but had to be withdrawn due to complications, and the team was contemplating epilepsy surgery in the few days just before his diagnosis. He was 3 years old (Figure 1).

Families who are in an ICU are grieving constantly, even if things go well there is grief.

(Social Worker, Palliative Care)

Part of it too was ... how difficult his seizures were to watch, and I did not understand this until I saw it myself, his seizures were incredibly difficult to witness...I mean seizures are scary, I have seen lots of them, they can look intense, but his were really different because he would get this look of extreme fear in his eyes, and sit up and just scream, and it was really hard for everyone... One of the PICU residents even told me, 'after a day shift with him I just had to step out and go cry in the hallway...

(Pediatric Neurology Resident)



FIGURE 1 Cammdon at 3 and a half years of age, 2 months before his final hospitalization

“One of the ICU doctors told us at one point that he is beyond medical help at this point, like our medical field is not this advanced yet.

(Cammdon's Mom and Step-Dad)

A lot of my co residents were very disturbed by it because it looked like he was in pain or uncomfortable...we suspect that he is unconscious while this is happening, that is kind of what the neurologists have told me, but I think people worried he was suffering.

(Pediatric Resident)

Simultaneous to Cammdon's distressing decline at the end of 2019, the Primary Children's Center for Personalized Medicine was being established. A collaboration between Primary Children's Hospital, University of Utah Health, and Intermountain Precision Genomics this center aims to provide advanced personalized healthcare and advanced genetic testing to the sickest children, who may benefit from more advanced genetic evaluation.

The initial epilepsy gene panel performed at 13 months of age explored 189 potential epilepsy genes. Three VUS were found, only one of which—in the *SCN2A* gene—appeared to be a potential explanation for Cammdon's early-onset epilepsy. Several efforts were made to test parents for the same variants, but for reasons including breakdowns in communication, this was never accomplished. During each hospitalization, further genetic testing would be proposed but somehow failed to occur.

During an inpatient multidisciplinary family care conference in November of 2019, whole exome sequencing was again proposed, and the help of the pediatric neurology division's genetic counselor was enlisted. Preauthorization for the testing with the insurance company was denied on December 5 and was subsequently appealed. By the time provisional approval for whole exome sequencing had been obtained on January 7, 2020, rapid whole genome sequencing had already been obtained through the newly established Center for Personalized Medicine Program. Preliminary results of the rapid whole genome sequencing finally brought this three-year mystery to a close on January 13, 2020.

The rapid whole genome sequencing revealed two distinct deleterious mutations in the *PLPBP* gene, each inherited from one parent resulting in compound heterozygous mutations in the *PLPBP* gene, consistent with a very rare form of pyridoxine dependent epilepsy¹. At this junction, it is useful to consider the diagnostic context of Cammdon's condition.

Currently, a child such as Cammdon would be described as having an “early-onset epileptic encephalopathy

(EOEE)”². This category usually implies onset of difficult to control (“intractable”) seizures “early in childhood.” It also typically presupposes associated neurodevelopmental impairments, which are often severe. What this term does not provide is any specificity. There are hundreds of unique conditions that can lead to EOEE², and identification of a specific cause or “etiology” is difficult. Over the last two decades, it has become increasingly apparent that many of these conditions are the result of particular genetic mutations and the tools needed to identify the causative pathogenic variants are increasingly accessible in clinical practice.

Cammdon's condition is the consequence of a specific type of EOEE known as “pyridoxine dependent epilepsy” (PDE), a group of rare severe childhood epilepsies in which seizure control is achieved or markedly improved by pyridoxine (vitamin B6) supplementation alone^{3,4}. PDE was recognized well before any sophisticated genetic testing was available. Diagnosis of PDE was previously based on a clinical “pyridoxine trial” which demonstrated seizure control and clinical improvement in response to high-dose pyridoxine³. Based on this approach, early, and probably conservative, estimates of the birth incidence of “pyridoxine dependent seizures” suggest an incidence of 1/313,000 live births³. Three genetic conditions are now recognized as the most common causes of pyridoxine dependent epilepsy: *ALDH7A1*, *PNPO*, and *PLPBP* gene mutations, all of which are autosomal recessive conditions⁴. The relative contribution of each of these specific disorders to PDE is not precisely known, but most experts state that *ALDH7A1* is the most prevalent. In a recent study from China, only 2 cases of *PLPBP* mutation were identified in a cohort of 33 children with PDE⁵.

Finally, we also know that the vast majority of children with PDE and specifically with *PLPBP* mutation present with epilepsy in infancy. As of this writing, 35 patients including Cammdon have been reported in the literature with PDE/encephalopathy due to pathogenic variants in *PLPBP*. Of those 35 patients, only one, Cammdon, experienced onset of seizures after one year of age. Based on the above, we can roughly estimate the rarity of Cammdon's specific circumstance as occurring about 1 in 181 million births. In short, Cammdon's experience was substantially rarer than 1 in a million.

Cammdon's unusually late presentation and the potentially misleading early genetic testing results both contributed to physicians not considering treatment with supplemental pyridoxine earlier. The initial gene panel had excluded the more common *ALDH7A1* and *PNPO* gene changes as the cause of his seizures. In the end, more than 2 and half years after his initial presentation, treatment with pyridoxine was initiated and Cammdon has been seizure free since.

I don't know if we would be where we are if we hadn't had educated ourselves and advocated for him, Cammdon may have passed away last year

(Cammdon's Mom and Step-Dad)

"Probably the single most valuable lesson is to listen to the parents...

(Pediatric Neurology Attending)

If one out of a thousand tests we send has an outcome like Cammdon's then I think it is worth it

(Pediatric Resident)

I mean, he pushed us to do things, because his seizures were so terrible and we couldn't get them under control, like we did things that we had never done before like putting him on a ketamine drip for days and days, like just pushing the boundary of things we were all comfortable with...

(Pediatric Neurology Resident)

Although the cause of and treatment for Cammdon's seizures have been found, important questions remain. Is his story a medical miracle or a disappointment? Is his experience a testament to the power of genetic testing to save families from needless suffering and hospitals from unnecessary expense, or a warning about the power of technological access to decide who lives and who dies? And how can we do better in our care of future patients with rare or enigmatic conditions moving forward?

The story of Cammdon and his family is a touching reminder that while medicine is increasingly powerful, offering additional hope and inspiration, there are always more ways to learn and to improve. Access to technology needs to expand in a thoughtful and equitable way that accounts for barriers that patients may face because of socioeconomic status, race, educational background, and other sociodemographic factors. Interdisciplinary teams must consistently value clear communication with their colleagues and with families. The support that social workers and palliative care can provide needs to remain prioritized for families going through medical trauma. In a field such as pediatric neurology where answers and diagnoses have historically been difficult if not impossible to find, we must work to cultivate hope and exploit the potential of early genetic testing. We must also avail ourselves of the wisdom afforded by the power of teams and the experience

of seasoned clinicians. The system we have created is capable of finding explanations for previously inexplicable conditions and offering advanced state of the art or even novel treatments. At the center of all this technology, testing and scientific advancement is a patient and a family who have never before had to navigate the medial ambiguity and suffering surrounding a rare diagnosis. Cammdon's journey reminds us that, in addition to the countless medical and scientific advancements, human connection and compassion are essential elements of our approach to a diagnostic odyssey.

I talk about what happened with his care because of the challenges with trying to have one united team for him and understanding that your colleagues have limitations, and they're doing the best they can, and the best way to take care of our patients and to make people feel safe is to have good communication and to instill that trust in the other parts of the team with the family.

(Pediatric Resident)

There are things in medicine, there are delayed diagnoses in medicine, there are treatments that are hurtful that have been done, medicine is not perfect, we are not perfect, and trying to understand that, I think that's a harder thing to deal with than being an intensivist...

(Pediatric Critical Care Attending)

The epilepsy gene responsible for Cammdon's seizures will be added to the standard epilepsy gene panel that was initially employed in his diagnostic journey. While that change to one particular diagnostic test may catch and save another child in future, the lessons learned by all those involved in Cammdon's care will undoubtedly have a positive impact on a countless number of future patients and their families.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Hailey McLean reviewed/collated all clinical data, conducted all interviews, and wrote the manuscript. Rachel

Palmquist led interpretation of genetic data, lead genetic counselor for the Primary Children's Center for Personalized Medicine, and manuscript review. Lincoln Nadauld was the leader of Intermountain Precision Genomics and contributed to data interpretation and manuscript review. Sabrina Malone Jenkins was the leader, Primary Children's Center for Personalized Medicine, and involved in data interpretation and manuscript review. Joshua Bonkowsky, director, Primary Children's Center for Personalized Medicine, contributed to data interpretation and manuscript review. Francis Filloux mentored Hailey McLean, reviewed/collated clinical data and involved in writing of manuscript.

ETHICAL APPROVAL

IRB approval for the project was obtained.

CONSENT

Written informed consent was obtained from the patient's parents to publish this report in accordance with the journal's patient consent policy. The child's first name is used specifically at the request of his family, and parents kindly provided the photograph used in the figure.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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