

How Does KCNT1 Present

Children with KCNT1-related epilepsy can initially present with minor seizures such as a twitch in one limb, infantile spasms, or seizures during sleep, and then progress to continuous seizures that move from one side of body to the other. KCNT1-related epilepsy is commonly associated with intractable seizures (40-100 per day) and developmental delay. Some patients do not learn to walk and have minimal ability to communicate. The consequences of the variants can include cortical visual impairment, gastroesophageal reflux, constipation, neurogenic bladder and hypotonia and dystonia. Some children develop pulmonary collaterals and cardiac arrhythmias which can increase the risk of mortality. Children are at risk for sudden unexpected death in epilepsy (SUDEP). There are 300 diagnosed cases but it is estimated that there are 3,000 people in the world with KCNT1 related epilepsy.

KCNT1-Related Epilepsy Syndromes

KCNT1 is a channel that affects the flow of electricity in the brain and in the heart. Mutations in KCNT1 result in increased electrical flow through these potassium channels. This primarily results in problems in electric electrical activity in the brain, which can cause seizures. KCNT1-related epilepsy syndromes include: 1) early onset seizures, either epilepsy of infancy with migrating focal seizures EIMFS, also known as migrating partial seizures of infancy MMPSI, or 2) it can cause an epileptic encephalopathy EE. There is also 3) a later onset form of KCNT1 related epilepsy which is often known as autosomal dominant nocturnal frontal lobe epilepsy ADNFLE, recently renamed as autosomal dominant sleep-related hyper motor epilepsy (SHE). Reports have identified children who exhibit symptoms from multiple phenotypes, while some people carry a gene mutation but have no seizures. Other syndromes associated with KCNT1 can include Ohtahara and West syndromes.

KCNT1 is expressed in the heart and in the blood vessels coming out of the heart. This can sometimes result in cardiac arrhythmias or in the formation of abnormal blood vessels called major aortopulmonary collateral arteries (MAPCAs) that go from the heart to the lungs. It is believed these collaterals form to compensate for poor circulation of blood supply to the lungs due to underdeveloped native pulmonary arteries. It is estimated that 10% of patients with a KCNT1 mutation have this rare type of congenital heart defect which can be life threatening.

EIMFS or MMPSI– Onset Before 6 Months

Seizures often begin before 6 months of age and increase in frequency and severity, negatively impacting neurodevelopment and often resulting in regression and severe developmental disabilities. Other names: Epilepsy of Infancy with Migrating Focal Seizures (EIMFS), Early Infantile Epileptic Encephalopathy, MMPSI or Migrating Partial Epilepsy of Infancy. Seizures may be difficult to detect but the child may get hiccups, stop

breathing, turn blue, or sweat moderately. Seizures in EIMFS are resistant to medication and can become continuous by the age of six to nine months. This can result in prolonged seizures or status epilepticus.

ADNFLE – Onset After 6 Months

The KCNT1 mutation can cause clusters of nocturnal seizures that vary from simple arousals to very physical thrashing movements. These seizures happen during sleep and can be mistaken as night terrors. This phenotype is referred to as Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) seizures typically start later than EIMFS.

Diagnosis

The diagnosis is established in a patient with intractable epilepsy and with identification of a heterozygous pathogenic variant in KCNT1 through genetic testing from a certified lab. The patients with MMPSI syndrome are most often de novo KCNT1 mutations, and most with ADNFLE are inherited from one parent. Several genetic testing companies include the KCNT1 gene in their epilepsy panels. It is preferred that genetic tests are certified by the American Board of Medical Genetics and Genomics.

Treatment

Treatment for KCNT1-related epilepsy initially focuses on reducing or stopping the number of seizures. Unfortunately, many traditional anti-convulsant medications don't work very well so you must work with your physician to try different options. The types of seizures experienced by these children are so variable that surgical intervention is not an option although some patients have Vagus nerve stimulating (VNS) device surgically implanted with limited success. Many parents report that a ketogenic diet is one of the most effective ways to reduce seizures followed by Phenobarbital, Topamax Tegretol. Quinidine has been used as an off-label anticonvulsant with success in some patients, but careful monitoring is necessary due to possible negative effects on the heart. Some parents report some improvement with cannabidiol but there is not sufficient research in this area.

In addition to reducing seizures, treatments focus on addressing symptoms that are often associated with low muscle tone and sedation from the medications. These can create issues with feeding and swallowing, gastrointestinal difficulties, constipation, urinary tract issues. Often parents are faced with a decision of whether to supplement their child's nutrients through the placement of a temporary feeding tube, or a more permanent G-tube. Some children have issues with their heart and lungs, particularly the development of potentially dangerous blood vessels called major aortic and pulmonary collaterals that must be carefully monitored to ensure they do not rupture. In some cases of pulmonary collaterals embolization is recommended. Breathing issues and managing oral secretions can also be an issue. Sleep apnea and seizures during sleep require monitoring with different devices and alarms. Parents also must consider special beds, supportive chairs, and standing walkers to aid the development of bones and muscles. Creative parents and therapists have adapted toys, tables, and devices to find ways to provide entertainment for their children as well as a means of stimulating cognitive and visual development. Caring for the special needs of your child requires a great deal of effort but having a coordinated medical team and supportive community can help parents effectively manage their child's care. More treatment info is available at kcnt1epilepsy.org

New Treatments Under Development

Several pharmaceutical companies are testing potential treatments for KCNT1 related epilepsy. One is a traditional small molecule drug and the other is an Antisense Oligonucleotide (ASO) which would block the expression of the diseased portion of the KCNT1 gene. It will be several years before these will be available, but the community is helping to prepare for clinical trials by contributing data to help document the progression of symptoms of this rare disease.

Contact the KCNT1 Epilepsy Foundation

The KCNT1 Epilepsy Foundation U.S. based non-profit organization created by parents of children diagnosed with KCNT1 gene mutation. Our vision is to create a community of parents, researchers, and supporters of those affected by KCNT1-related epilepsies and support research for clinical treatments. We have a KCNT1 patient registry and want to find people affected by KCNT1 across the globe. We can work with researchers to utilize this information to find treatments and a cure. More information is available at our website: <https://kcnt1epilepsy.org> or contact info@kcnt1epilepsy.org

Enroll in the Patient Registry

The KCNT1 Epilepsy Foundation sponsors a patient registry for those with “likely-pathogenic” or “pathogenic mutations” in the KCNT1 gene. When you sign up, you will see that all the data is private and secure. We are hopeful that the community can collect enough data to be useful by the FDA in the approval of several drugs that are currently being developed specifically for KCNT1. We recognize that participating takes time and commitment, but your information will help move research forward! Please go to www.kcnt1epilepsy.org Registry menu. This will take you to the LunaDNA website where you will create a Minor or Ward account for your child. Adults may also create an account.

Associated Medical Conditions

Intellectual disability• Autism spectrum disorder• Cerebral palsy (spasticity, hypotonia)• Movement disorders (dystonia, ataxia)• Cortical visual impairment• Gastroesophageal dysfunction and dysbiosis• Neuropathic pain• Sleep disorders• Speech and language deficits• Behavioral and emotional issues• Urology problems (retention, infections)• Respiratory issues

Specialists Frequently Required

• Complex care• Developmental pediatrician• Endocrinologist• Epileptologist• Gastroenterologist• Geneticist• Neurologist• Neuropsychologist• Occupational therapist• Ophthalmologist• Orthopedist• Palliative care• Psychologist• Psychiatrist, physical therapist• Pulmonologist• Speech pathologist• Urologist• Vision therapist Patients with KCNT1 benefit from a multi-disciplinary team approach with numerous specialists involved to deliver comprehensive care.

What to Discuss with Your Doctor

1. Ask for a copy of genetic reports and discuss whether parents or siblings should get tested.
2. Discuss the types of seizures your child has and how many to expect, and what to do during and after a seizure. Keep a seizure/medication journal.

3. Establish an emergency plan for home if child has numerous or extraordinarily strong seizures.
4. Request a heart checkup with EKG.
5. Ask for a letter to present hospital staff in case you must go to the Emergency Room.
6. Discuss how to prepare for problems with feeding, breathing, low muscle tone, communication, sleep, or social behaviors.
7. Inquire about the ketogenic or related diet.
8. Discuss risk of SUDEP (sudden unexpected death in epilepsy) and how to monitor.
9. Request prescriptions for speech, occupational, physical and vision therapy.
10. Ask whether there are any support groups in the area.
11. Register your child in the KCNT1 Registry.

For more suggestions and resources: <https://kcnt1epilepsy.org/parents-caregivers>

KCNT1 is a potassium ion channel gene located on chromosome 2. It encodes a subunit of the voltage-gated potassium channel located in the brain but also expressed in smooth muscle and other locations in the body. These channels help control a cell's ability to generate and transmit signals. A change in the gene can alter the function of the channel and affect the way the neuronal impulses are conducted. Gain-of-function mutations in the KCNT1 gene can affect brain development and cause intractable epilepsy.