

SLC13A5 Epilepsy

Also known as: SLC13A5 Deficiency, SLC13A5 Citrate Transporter Disorder, Citrate Transporter Disorder, Early Infantile Epileptic Encephalopathy 25 (EIEE25), Developmental Epileptic Encephalopathy 25 (DEE25), Kohlschütter-Tönz syndrome (non-ROGDI), NaCT, Indy, mIndy, GARD: 12901, OMIM: 608305

Overview

SLC13A5 epilepsy (a citrate transporter disorder) is a rare form of intractable epilepsy that begins in infancy and proceeds with accumulating disability that significantly impacts individuals throughout their lifetime. SLC13A5 epilepsy is a genetic disorder with autosomal recessive inheritance. Seizures begin shortly after birth and may persist throughout life, although some families are able to control the seizures with antiseizure medications, especially later in life. Common symptoms associated with SLC13A5 epilepsy include: frequent seizures (up to hundreds or more daily), prolonged seizures (lasting minutes or hours), movement and balance problems, behavioural and developmental delays, severe difficulty with speech production with better ability to understand language, sleeping difficulties, and eating difficulties. Children and adults with SLC13A5 epilepsy often need help with the following: bowel and bladder care, feeding, dressing, ambulation, moving in/out of bed, bathing, oral hygiene, grooming, accompaniment to medical appointments, and protective supervision. Overall, they require 24-hour care throughout child and adulthood.

Incidence and prevalence

SLC13A5 epilepsy is an ultra-rare disease. It was first described in 2014, and the incidence and prevalence are still unknown. The full extent of contributing alleles remains unknown. 1% of the Icelandic population are heterozygous carriers of the SLC13A5 G219R disease allele.

Aetiology

SLC13A5 epilepsy is a citrate transporter disorder. So far around 54 variants have been identified among the patient population. All variants are suspected to be a loss of function meaning that there is an inability to move citrate into the cell. SLC13A5 epilepsy is an autosomal recessive disorder.

Diagnosis

Diagnosis is made based on the results of genetic testing. There are several genetic tests available to confirm SLC13A5 epilepsy. These tests can be performed on either blood or saliva samples. Genetic tests include Whole Exome Sequencing (WES), epilepsy gene panel (SLC13A5 is included in many epilepsy panels) or targeted testing. Only if both copies of the child's SLC13A5 gene are mutated, is it considered to be disease causing. SLC13A5 epilepsy is an autosomal recessive (inherited) disorder that affects both boys and girls of all races and ethnicities.

Other diagnostic test might be helpful prior to the genetic testing, although EEG results show a relatively well-preserved background for age, even in case of frequent seizures. Brain MRI is usually normal or shows signal changes in the in the white matter in some cases. Elevated citrate levels in blood and cerebrospinal fluid are present.

Age of onset

First seizures manifest in neonates, usually within first few days of life.

Seizure types at presentation

Seizures first appear in neonates with different seizure types present including: focal, focal to bilateral, myoclonic, and tonic-clonic seizures. Even at the early age seizures can evolve with the manifestation of prolonged seizure i.e. status epilepticus. Seizures are often triggered by fever or acute illness.

How may seizures change over time?

Seizures during the neonatal period are often severe with prolonged hospitalization necessary in some of the patients. The seizure semiology is similar to a typical neonatal seizure hence it is difficult to distinguish them from more common causes of neonatal seizures. Beyond the newborn period, patients typically have multiple seizure types present but the majority are motor seizures, with predominance of myoclonic and tonic-clonic seizures. It is important to note that patients tend to have more seizures with acute illness, and they can experience prolonged bouts of status epilepticus. Therefore, a seizure rescue plan is warranted for patients with SLC13A5 epilepsy. Seizure frequency is daily with patients experiencing over hundreds of seizures per day, but there appears to be an age-related improvement in seizure control during adolescence although it is not present in all individuals, nor it is clear why older patients are more likely to be seizure free. Regardless of achieving seizure freedom, almost all patients remain on anti-seizure medications.

EEG features

Patients with SLC13A5 epilepsy start experiencing seizures within hours to days after birth. Despite frequent seizures, SLC13A5 epilepsy patients have EEG results showing normal background for age, but in some cases a slow background activity can be seen (Matricardi et al. 2020, Yang et al. 2020). This contrasts with many other epileptic encephalopathies which have more disordered backgrounds and frequent interictal spiking. Focal, multifocal or diffuse epileptiform abnormalities can be found in EEG testing.

Comorbidities

In addition to epilepsy, the following symptoms are commonly associated with SLC13A5 epilepsy:

Movement Disorder

- Low muscle tone (hypotonia). Infants and young children experiencing this symptom are often described as “floppy”
- Lack of muscle control and/or coordination of voluntary movements, such as walking or picking up an object (ataxia)
- Episodes of body stiffening or weakness lasting a few minutes to a few hours

Developmental Delay

- Severe difficulty with speech production (expressive language delay), with better ability to understand language (receptive language)
- Motor delay
- Cognitive delay

Other characteristics of SLC13A5 epilepsy include poor development of teeth (hypodontia) or weakness of teeth enamel, and excessive drooling.

It is important to highlight that the disease phenotype is variable so that even siblings with the same genetic mutation can show variability in the severity of symptoms, including differences in the seizure types and frequency, and differences in developmental milestone timeline.

Treatment

At this time, there are no specific treatments that cure the disease. Currently treatment options are focused on treating the symptoms and include antiseizure medications. There is no mono or polytherapy that is beneficial for all individuals with SLC13A5 epilepsy. However, phenobarbital, valproic acid, acetazolamide and topiramate may be more successful than other drugs. Antiseizure medication is usually prescribed based on the seizure types present. In some cases, Vagal Nerve Stimulation (VNS), Deep Brain Stimulation (DBS) or ketogenic dietary treatment might be helpful but still there is a lack of strong evidences.

Other therapies individuals require include: physical therapy, occupational therapy, speech therapy, and sometimes placement of feeding tubes. Many patients seem to benefit from augmentative communication devices.

Individualized emergency protocol

Seizure rescue plan with emergency medications is warranted for patients with SLC13A5 epilepsy. It is important to note that patients tend to have more seizures with the presence of fever or acute illness, and they can experience prolonged bouts of status epilepticus.

Review the impact of seizures, drugs and comorbidities on:

- Day-to-day activities
- Overall well-being
- Mental health
- Physical health
- Independence
- Biological and psychiatric health
- Behaviour

Provide patient and/or carer with:

- Contact information of patient organisations/support groups
- Seizure action plan/emergency protocol (including prescription for rescue medications)
- Possibilities of registry enrolment
- Genetic counselling
- SUDEP risk management
- Transition to adult care
- Individualised rehabilitative program (occupational, physical and speech therapy, and schooling)
- Patient, carer & employer support requirements (neuropsychological evaluation, guidance, potential psychiatric support).

Literature

- Matricardi S, De Liso P, Freri E, et al. Neonatal developmental and epileptic encephalopathy due to autosomal recessive variants in SLC13A5 gene. *Epilepsia*. 2020;61(11):2474-2485. doi:10.1111/epi.16699
- Yang QZ, Spelbrink EM, Nye KL, Hsu ER, Porter BE. Epilepsy and EEG Phenotype of SLC13A5 Citrate Transporter Disorder. *Child Neurol Open*. 2020;7:2329048X20931361. Published 2020 Jun 8. doi:10.1177/2329048X20931361

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Overview

SLC13A5 epilepsy is a rare form of intractable epilepsy that begins in infancy and proceeds with accumulating disability that significantly impacts individuals throughout their lifetime. SLC13A5 epilepsy is an autosomal recessive (inherited) disorder caused by the mutation on SLC13A5 gene, that affects both boys and girls of all races and ethnicities. Seizures begin shortly after birth and may persist throughout life, although some families are able to control the seizures with seizure medications, especially later in life. Common symptoms associated with SLC13A5 epilepsy include: frequent seizures (up to hundreds or more daily), prolonged seizures (lasting minutes or hours), movement and balance problems, behavioural and developmental delays, severe difficulty with speech production with better ability to understand language, sleeping difficulties, and eating difficulties. Children and adults with SLC13A5 epilepsy often need help with the following: bowel and bladder care, feeding, dressing, ambulation, moving in/out of bed, bathing, oral hygiene, grooming, accompaniment to medical appointments, and protective supervision. Overall, they require 24-hour care throughout child and adulthood.

How common is SLC13A5?

SLC13A5 is a very rare, genetic cause of epilepsy. It is not yet known how common it is nor how many individuals are affected globally.

When do symptoms first appear?

Affected children present with seizures beginning within hours or few days after birth. Multiple seizure types might be present, and occurrence of status epilepticus in early stages of life can be seen in most patients. The seizures may continue throughout life. Besides the seizures, individual may have difficulties with speech production, limited and slow motor progress with issues standing or walking independently. Almost all the affected children have abnormalities in their tooth enamel.

What are the types of seizures seen in SLC13A5?

Individuals with SLC13A5 epilepsy may have multiple, different seizure types present, including focal and generalized seizures, and status epilepticus. Seizures may vary in how they look and how long they last. Usual seizure type present is asymmetric focal clonic bilateral seizure that may become bilateral tonic-clonic. Some may have arrest of activity or asymmetric tonic seizures. In many cases, seizures are triggered by common trigger factors such as fever or acute illness.

Is SLC13A5 linked to any other epilepsy syndromes or conditions?

SLC13A5 epilepsy is a citrate transporter disorder with a genetic cause, hence it is a unique form of epilepsy. Mutations on the SLC13A5 gene are suspected to cause a change in production of protein called citrate transporter which leads to inability to move citrate into the cells.

Although symptoms may overlap with other conditions, unlike many other epileptic syndromes EEG results show a relatively well-preserved background for age, even in case of frequent seizures. Brain MRI is usually normal or shows signal changes in the in the white matter in some cases. In individuals with SLC13A5 epilepsy, elevated citrate levels in blood and cerebrospinal fluid are present.

How do seizures change over time?

Seizures soon after birth are often severe with prolonged hospitalization necessary in some patients. Frequency and duration of seizures varies greatly amongst patients, with seizures being more frequent in neonates and children, often on daily basis. It is important to note that affected children tend to have more seizures with concurrent fever or illness, and they can experience prolonged bouts of status epilepticus. Therefore, a seizure rescue plan is warranted for patients with SLC13A5 epilepsy.

Almost complete control of seizures is achieved in at least half of the patients with the use of antiseizure medications as there appears to be an age-related improvement in seizure control during adolescence although it is not present in all individuals, nor it is clear why older patients are more likely to be seizure free. Regardless of achieving seizure freedom, almost all patients remain on anti-seizure medications.

Several families report siblings with different seizure control suggesting that the symptoms and experience can vary even within the same family. Importantly, seizure control seems attainable in the majority of patients though trials with different antiseizure medications and their doses.

What other problems apart from epilepsy, affect people with SLC13A5?

In addition to epilepsy, the following symptoms are commonly associated with SLC13A5 epilepsy:

Movement Disorders

- Low muscle tone (hypotonia). Infants and young children experiencing this symptom are often described as “floppy.” Parents/caregivers often notice their child feels limp when they hold them and children are showing less control of their neck muscles, causing their head to drop. It may also be difficult for them to place weight on their leg or shoulder muscles.
- Lack of muscle control and/or coordination of voluntary movements, such as walking or picking up an object (ataxia)
- Episodes of body stiffening or weakness lasting a few minutes to a few hours

Developmental Delay

- Severe difficulty with speech production (expressive language delay), with better ability to understand language (receptive language)
- Motor delay
- Cognitive delay

Other characteristics of SLC13A5 epilepsy include poor development of teeth (hypodontia) or weakness of teeth enamel, and excessive drooling.

The disease phenotype (the observable characteristics of the disease) is variable so that even siblings with the same genetic mutation can show variabilities in the severity of symptoms, including differences in the seizure type and frequency, as well as differences in their developmental milestone timeline.

What are the treatment options?

Vagal Nerve Stimulation or Deep Brain Stimulation may be surgical treatment options for epilepsy in general. We do not have data specific to SLC13A5 Epilepsy on these devices.

Currently there are no specific treatments that cure the disease. Treatment options are focused on treating the symptoms and include antiseizure medications. There are no treatment guidelines yet nor the treatment is universal in every individual, but some antiseizure medications like phenobarbital, valproic acid, acetazolamide and topiramate may be more successful than other drugs. Antiseizure medication is usually prescribed based on the seizure types present. In some cases, Vagal Nerve Stimulation (VNS), Deep Brain Stimulation (DBS) or ketogenic dietary treatment might be helpful when satisfying seizure control is not achieved with antiseizure medication, but there are no specific data on SLC13A5 epilepsy and these devices.

Other therapies individuals require include: physical therapy, occupational therapy, speech therapy, and sometimes placement of feeding tubes. Many patients seem to benefit from augmentative communication devices.

What is the emergency protocol for seizures?

A seizure rescue plan with emergency medications is warranted for patients with SLC13A5 epilepsy. It is important to note that patients tend to have more seizures with illness, and they can experience prolonged bouts of status epilepticus.

Hence it is important to share information about illness management in order to try to minimize the impact on seizure frequency.

What could I ask my doctor or specialist epilepsy nurse about?

- Genetic testing and counselling
- Family planning options
- Seizure action plan/emergency protocol
- Fever/illness management
- Current antiseizure medication options, and their side-effects
- Ongoing clinical trials and/or new treatment options
- Patient, carer and employer support requirements including neuropsychological evaluation, guidance, potential psychiatric support
- An individualized rehabilitative program (occupational, physical and speech therapy, and schooling)
- Sudden Unexpected Death in Epilepsy (SUDEP) risk management
- Transition management

Who should be a part of the medical team?

Healthcare professionals involved in the multidisciplinary team may include: paediatrician (focuses on children), primary care physician, epileptologist (neurologist who specializes in epilepsy), neurologist (physician who specializes in brain disorders), neuropsychologist (to evaluate cognitive or learning issues), psychiatrist and psychologist (to help with mood and learning disorders), physiatrist, social worker, geneticist and genetic counsellors, and other therapists (physical, occupational, and speech and language therapist).

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