NEUROLOGICAL EMERGENCIES

Hemiplegic migraine attack

May result in brain atrophy; prophylactic treatment of these attacks might be needed in early stages of the disease to prevent permanent brain damage.[10]

Stroke

It has been reported that ischemic strokes can occur, secondary to minor head trauma and should be considered in a diagnostic evaluation of childhood stroke.[9]

Coma

Attacks of familial hemiplegic migraine (FHM) can be triggered by minor head trauma and are sometimes accompanied by coma.[10]

Cerebral edema

Trivial head trauma may be accompanied by severe, sometimes fatal, cerebral edema and coma after a lucid interval (delayed cerebral edema).[11]

Seizure emergencies

Some CACNA1A variants are prone to status epilepticus with apnea. Those patients may benefit from emergency medications, at home oxygen and an Ambu bag, along with appropriate training on the medications and equipment.

PATIENT REGISTRY

A Patient Registry, an organized collection of data about CACNA1A, is being developed by the CACNA1A Foundation in coordination with the Chung Lab at Columbia University Medical Center. As a natural history study, the registry aims to thoroughly describe all aspects of the disease. Understanding the full spectrum of CACNA1A as a disease is necessary for clinical trials. Sharing information is one of the most important things one can do as it provides data for future generations. Please support this initiative and advance research by asking all of your CACNA1A patients to enroll. Contact **info@cacnala.org** for more information.

- The CACNA1A Foundation is an all-volunteer, parent-led 501(c)(3) non-profit organization.
- We are a global community dedicated to creating awareness, supporting families and finding a cure for CACNA1A genetic variants.
- Our website contains resources for families and professionals who want to learn more about CACNA1A variants.
- Please visit our website for more information on how one can join our Patient Registry and make a difference. **https://www.cacna1a.org/**

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CACNA1A FOUNDATION

WHAT DOES IT MEAN TO HAVE A DIAGNOSIS OF CACNA1A?

INFORMATION FOR MEDICAL PROVIDERS

WWW.CACNA1A.ORG

WHAT IS CACNA1A?

CACNA1A-related syndrome is a rare genetic condition that is caused by changes to the CACNA1A gene. It results in various neurological symptoms and health concerns, including seizures, ataxia and tremors, nystagmus, hemiplegic migraine, cerebellar atrophy, intellectual disability and autism. There is no cure for CACNA1A and currently, it is only possible to treat individual symptoms. CACNA1A codes for the alpha-1A subunit of the P/Q-type voltage-gated calcium channel called Cav2.1 and is located on the short arm of chromosome 19 at position 13.13. Channel dysfunction can be categorized as gain of function (GOF) or loss of function (LOF), which can have implications for treatment.[1,2] Periodic literature reviews of published variants should be used to inform treatment recommendations.

Congenital ataxia, eye movement disorders, developmental delay and early onset epilepsy are some of the earliest presentations of a CACNA1A mutation.[3] Clinicians should seek genetic testing if CACNA1A is suspected. Currently, CACNA1A is included on gene panels for ataxia, autism/ID, epilepsy, dystonia, hemiplegic migraine, nystagmus and retinol dystrophy **(www.genedx.com).**

AFTER DIAGNOSIS

Patients/parents should receive

- Genetic counseling
- Referral to early intervention services/evaluation for special education
- GOF or LOF treatment implications (if published)
- Information on specific variant (if published)
- Epilepsy patients: Risk & management of prolonged seizures, risk of SUDEP & seizure related accidents
- Information on head trauma and cerebral edema risk
- Referral to support resources such as the CACNA1A Foundation & social services

Effective multidisciplinary care coordination is important and may include:

- Neurology/Epileptology
- Developmental Pediatrics
- Genetics
- Ophthalmology/Neuro-ophthalmology
- Physical Therapy/Occupational Therapy/Speech and Language Pathology
- Behavioral Therapy
- Neuropsychology/Educational Psychology
- Social work

HOW TO SUPPORT YOUR PATIENT

- Provide continuity of care
- Help adolescent patients transition to adult care
- Help with symptom management and offer practical support to address disabilities
- Coordinate and consult with specialists

MEDICAL CONCERNS

Epilepsy and seizures can occur shortly after birth and range from mild and easily managed to severe and refractory. Some individuals may be diagnosed with Lennox-Gastaut Syndrome or Dravet Syndrome.[1]

Ataxia presents in 3 forms

- **Congenital ataxia** Early onset (before age of 2) characterized by hypotonia, developmental delay; cerebellar atrophy may be present
- **Episodic Ataxia Type 2 (EA2)** Consists of episodes of poor balance and unsteadiness of movement, vertigo, nausea and headaches. Episodes can last from hours to days and are triggered by emotional stress, physical exercise, fever, alcohol and caffeine.[4]
- **Spinocerebellar Ataxia Type 6 (SCA6)** Degenerative neurological disorder which includes progressive ataxia, tremors, dysarthria and nystagmus with onset typically between ages 40-50. Caused by unique genetic difference within CACNA1A of an increase of CAG repeats in the tail end of the gene.

Hemiplegic migraine is a rare and severe form of migraine with aura associated with weakness and/or temporary paralysis on one side of the body. Due to minor head trauma it is possible to lose consciousness or enter a state of coma.[9] These attacks are often mistaken for stroke because of the severity and symptom overlap, but they are not strokes.

Eye movement disorders include nystagmus and paroxysmal tonic upgaze (PTU).[5] Nystagmus is an uncontrolled movement of the eyes from side to side or up and down. PTU entails periods where one's eyes uncontrollably stare upwards. These are not seizures. It can occur during episodes of ataxia or migraine.

Cerebellar atrophy can be related to CACNA1A and can be progressive. The pattern and rate of progression of atrophy varies.[2,5] The most common characteristic is a wide based, unsteady lurching walk, often accompanied by a back and forth tremor in the trunk of the body. Other symptoms include slow, unsteady and jerky movements of the arms and legs, slowed or slurred speech, and nystagmus.[6] Patients with cerebellar atrophy at a higher risk of cognitive impairment.[7]

Neurodevelopmental differences can include global developmental delays, cognitive impairment, intellectual disability, autism spectrum disorder and learning differences. Children can have difficulty with language and motor impairment due to hypotonia, making it difficult to meet their milestones. Intellectual disability can range from mild to severe.[1,8]

TREATMENTS

There currently is no cure for CACNA1A gene variants. Symptoms may be managed by medications and diet.

Ataxia Medications include acetazolamide and 4 aminopyridine (contraindicated if there is a diagnosis of epilepsy). Caffeine and alcohol can trigger ataxia attacks.

HM Acetazolamide and calcium channel blockers such as verapamil have shown positive responses in preventing the occurrence of acute phenotype (migraine, S/FHM or acute coma), however, there are no clinical trials evidencing this benefit.[9]

Epilepsy Clarifying the mechanisms by which specific mutations affect the function and localization of CACNA1A channels may improve therapeutic interventions for patients with CACNA1A-associated DEEs.[1]