EpiCARE

Alternating Hemiplegia of Childhood (AHC)

Also known as: AHC or Alternating Hemiplegia

Overview

Alternating Hemiplegia of Childhood (AHC) is an ultra rare neurodevelopmental life-long disease. For the majority of patients, it is due to a ***de novo*** mutation in the ATP1A3 gene, which codes for a critical sodium/potassium ATPase pump.

Whilst plegia is the hallmark of the disease, AHC encompasses a vast and wide-ranging complex constellation of neurological symptoms, both paroxysmal and non-paroxysmal. Non-paroxysmal manifestations include mild to severe motor, cognitive and language impairment and sometimes regression.

Paroxysmal symptoms include: dystonic attacks; plegic attacks (hemiplegia/quadriplegia/single limb/two limbs different side); abnormal eye movements; epileptic seizures; episodes of autonomic dysfunction; episodes of reduced awareness and rarely headaches.

Common triggers, especially for plegic and dystonic episodes, include excitement, fatigue, temperature change, immersion in water, pain, constipation, fever/illness, exercise, or exposure to sunlight or bright lights. However, many episodes have no clear triggers and are totally unpredictable.

Sleep is critical in AHC and plegic episodes usually resolve upon sleep.

AHC patients may also manifest paroxysmal or permanent symptoms as dystonia, chorea, ataxia, tremor, or other complex movement disorders.

Incidence and prevalence

Prevalence was initially believed to be 1 in a million, but novel observations show that it probably is at least 10 times higher (1/100 000).

Diagnosis

The association of the presence of a mutation in the ATP1A3 gene (often part of the rare epilepsy gene panels) along with clinical symptoms of AHC confirm the diagnosis (revised 2021 criteria, by Mikati, Panagiotakaki, and Arzimanoglou1). It is of notice, that not all patients have a mutation in this gene and other genes can provoke the disease in a minority of patients. Certain ATP1A3 mutations are more frequent (D801N and E815K) and have been linked to different clinical presentations. Up to some degree there is a genotype- phenotype correlation, but the type of mutation is not the only factor that determines clinical picture. Clinical picture can vary a lot even in patients with the same mutation. In addition, there is recognition of other ATP1A3- related diseases with overlapping phenotypes to AHC.

For patients without an identifiable ATP1A3 mutation, the diagnosis is given clinically according to the classical Aicardi's criteria or their revised version. Careful medical workup is required to ensure other diseases with similar symptoms are excluded.

Age of onset

Symptoms first occur before 18 months of age. There is a wide variation in age of onset. Some will be affected severely from birth and others have subtle, easily missed symptoms initially.

Epileptic seizure types at presentation

Seizures are not always present at onset of AHC symptoms. But many AHC episodes can be interpreted as epileptic seizures at onset. A prolonged video - EEG recording helps in clarifying their epileptic or non-epileptic nature, but its realization and interpretation are challenging. Around 60% will develop epilepsy at some point in time. A normal EEG is not always reassuring in AHC. There can be a lag of 3-4 years between symptom onset and abnormal EEG activity.

Seizures in AHC can be focal (frontal, temporal and posterior) or generalized (tonic, tonic-clonic, myoclonic, or absences). Some patients experience prolonged epileptic seizures (status epilepticus), after which a neurological regression may be reported.

Clinical assessment, patient's event diaries and home video recordings of the episodes (even without an EEG) play an important role in the management of this complex disorder. Several EEGs may be required to differentiate a seizure from an AHC 'typical' episode, especially if there has been a non-resolving regression following the latter.

In some other extreme cases prolonged AHC episodes may cause wide-spread depolarization leading to seizures. It can be difficult to establish the underlying precipitant in an emergency situation when access to EEG is limited.

How do seizure types change over time?

Epileptic seizure types and semiology vary significantly between individuals and over time. Some will have epilepsy confirmed early in their patient journey and others may present seizures many years after first AHC symptoms.

EEG & MRI features/other diagnostic testing

EEGs can be normal during an AHC episode and/or show epileptiform activity later.

Many EEG abnormalities have been reported but a consistent pattern is not known.

MRIs are typically normal. However, some recent reports have suggested possible cerebellar atrophy in a few cases that is often missed on routine neuro-imaging examination.

Lumbar puncture CSF is traditionally normal.

Neurological examination may be near normal early in the course of the disease if there is no concurrent AHC episode. Hypotonia is a nearly constant feature, for most of patients and is present very early. Movement disorder and other neurological symptoms are extremely frequent.

Treatment

There is no specific treatment for AHC.

Management involves minimizing triggers, reducing episodes and careful monitoring of co-morbidities. A holistic multi-disciplinary team approach for AHC is essential.

- Plegic episodes: Flunarizine (treatment originally used for migraine prophylaxis) has some effect in AHC (reduction in frequency and severity of plegic episodes) for some patients. Other drugs used include benzodiazepines, acetazolamide and topiramate or other antiseizure medications.
- Dystonic episodes: trihexyphenidyl, gabapentin, clonidine, benzodiazepines, baclofen.
- Seizures: Anti-seizure treatment choice is taken upon consideration of the types of epileptic seizures and ictal/interictal abnormal activity if present. Patients with AHC may be offered treatment following assessment of risk and discussion with the patient/family.
- Others: There is limited evidence to date concerning the efficacy of the ketogenic diet and only anecdotal reports concerning the use of cannabinoids in AHC. Some case studies have investigated oral ATP, memantine, and intravenous immunoglobulins without conclusive data.

An emergency rescue plan should be available for all patients and can involve relaxation methods and rescue treatments, usually benzodiazepines, chloral hydrate, and other drugs to induce sleep (melatonin). Occasionally oxygen and rarely, in severe cases, non-invasive/invasive ventilation is needed.

Consideration of drug interactions is also important to ensure avoidance of triggers (e.g., constipation, pain, irritability) that may exacerbate episodes.

Co- morbidities

- An annual cardiological examination is recommended (the ATP1A3 gene is expressed in the cardiac cells) given the risk of arrythmias and possible sudden death.
- A sleep study is recommended in view of sleep apnoea risk. Some patients with AHC also have complex breathing involvement requiring close monitoring. More research is required to understand this.
- Swallowing difficulties, need for supplementary nutrition, feeding tubes and gastrointestinal symptoms are common.
- Autism Spectrum and other behavioral disorders may be encountered in AHC patients.

Review the impact of seizures, drugs & co-morbidities on:

- Day-to-day activities; nutrition and fluid intake; overall well-being and quality of life; mental and physical health; cognition and development; behavior; sleep; autonomy/independence.

Individualized emergency protocols

Clinicians must be aware that AHC can be life-threatening. All protocols must therefore be individualized and person-centered.

Emergency protocols should cover severe AHC episodes/seizures/breathing difficulties and other possible manifestations necessitating acute intervention.

Provide patient and/or carer with information on:

- Avoidance of known triggers; safe fluid/food intake; drug side effects
- Discuss sleep hygiene and consider sleep study for sleep apnoea
- Discuss annual cardiology review
- Basic life support training
- SUDEP risk management
- Holistic input including liaison with physiotherapy, occupational therapy and speech and language therapists
- Genetic counselling
- Referral to behavioural and neuro-psychiatry services where appropriate
- Patient, carer & employer support (referral to appropriate social/psychological/benefit services)

EpiCARE Information Leaflet regarding Alternating Hemiplegia in Childhood (AHC), by Katherine Behl, AHC-UK; Rosaria Vavassori, IAHCRC Consortium, AHC18+ e.V.. Reviewed and validated by Drs. E. Panagiotakaki & M. Papadopoulou (HCL, France). The European Commission support for the production of this publication does not constitute endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

1 Mikati MA, Panagiotakaki E, Arzimanoglou A. Revision of the diagnostic criteria of alternating hemiplegia of childhood. Eur J Paediatr Neurol. 2021;32:A4-A5. doi:10.1016/j.ejpn.2021.05.004

EpiCARE

Alternating Hemiplegia of Childhood (AHC)

Also known as: AHC or Alternating Hemiplegia

Overview

Alternating Hemiplegia of Childhood (AHC) is an ultra-rare neurodevelopmental life-long disease. For the majority of patients, it is due to a ***de novo*** mutation (i.e. not inherited from parents) in the ATP1A3 gene, which codes for a critical sodium/potassium ATPase (energy) pump. Patients that have no mutation in the ATP1A3 gene can also receive the clinical diagnosis, based on the fulfilment of all or most of the clinical diagnostic criteria defined in scientific literature.

Whilst the name of the disease highlights a key component in the condition, AHC encompasses a vast and wide-ranging complex constellation of neurological symptoms, both paroxysmal (i.e. having a sudden onset, a duration and a conclusion, either spontaneous or induced by drugs) and permanent.

Paroxysmal symptoms include:

1. Epileptic seizures, in about 60% cases
2. Dystonic attacks (painful muscle rigidity), which can include full body dystonia,
3. Plegic attacks, i.e floppy/flaccid paralysis involving either side (half) of the body (hemiplegic attacks) or individual limbs and alternating in laterality. Quadriplegic/full body attacks can occur in isolation or as a generalization of a hemiplegic attack.
4. Reduced awareness spells (RAS)
5. Episodes of nystagmus (repetitive eye jerking) and other abnormal eye movements (one or both eyes)
6. Episodes of tremor, chorea (uncontrolled jerky movements), and rarely headaches (migrainous or not)
7. Changes in the rhythm of breathing and autonomic nervous system disorders (flushed skin, paleness, fast heartbeat, vomiting)

AHC paroxysmal symptoms may appear isolated or as a combination of several types of symptoms during the same episode. Common triggers include excitement, fatigue, temperature change, water, pain, constipation, fever/illness, exercise, or sunlight. However, many episodes have no clear triggers and are unpredictable.

Sleep is critical in AHC and inducing it can resolve plegic episodes. However, it is described that on waking the attacks can re-occur within the first hour.

How common is AHC?

Prevalence was initially believed to be 1 in a million, but novel observations show that it probably is at least 10 times higher (1/100 000). .

When do symptoms first appear?

The first paroxysmal symptoms usually appear within 18 months of age. However, there is a wide variation in the age of onset. Seizures are not always present at onset of AHC and can appear at any age, even in late adulthood.

What are the types of seizure(s) seen in AHC?

About 60% cases have epilepsy. Epileptic seizures in AHC can be focal (starting in one part of the brain) or generalized (widespread onset).

Some patients have also more prolonged severe epileptic seizures (status epilepticus), in some cases leading to a regression in what they can do.

In some extreme cases, prolonged dystonic and plegic episodes may cause wide-spread changes leading to epileptic seizures.

In many patients with suspected epileptic seizures, EEGs are normal, particularly at onset. It may take 3-4 years to develop an abnormal EEG, thus regular follow-up and monitoring may be needed to confirm epilepsy.

Most patients with AHC also have episodes that can be misinterpreted as epileptic seizures. They manifest as staring and decreased responsiveness without any concurrent epileptic EEG change. Such episodes might be Reduced Awareness Spells (RAS). Careful assessment by an experienced AHC neurologist is indicated, before treatment is prescribed.

Is AHC linked to any other epilepsy syndromes?

AHC is considered a rare disorder, whose patients' can frequently have epileptic seizures. As such AHC is considered an etiology specific type of epilepsy. However, not everyone with AHC will have epilepsy.

How frequent are seizures typically in AHC?

Epileptic seizures, as well as any other type of paroxysmal symptoms, vary greatly in their frequency, severity and duration between individuals as well as with age and with different seasons, without a specific pattern. Some episodes can last for minutes or hours, others for days or even weeks.

Seizure of an epileptic nature are usually short in duration, with the exception of episodes of status epilepticus. Some can occur up to several times a day. In a patient who presents with new or modified symptoms in the course of the disease or concerning paroxysmal manifestations, medical advice must be sought.

How may seizures change over time?

Epileptic seizures, as well as any other type of paroxysmal episodes, can change significantly over time, also regarding the combination of different types of symptoms during one single episode. Epilepsy can manifest at any age, even in late adulthood. Triggers for paroxysmal episodes can also change over time.

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

AHC is a neurodevelopmental condition. As such, in addition to the paroxysmal symptoms, it is characterized by other manifestations, ranging from mild to severe motor and cognitive disabilities. Autism spectrum disorder (ASD) and other behavioral disorders may also be diagnosed.

Additionally, the ATP1A3 gene is expressed in the heart, linked to a risk of abnormal heart rhythms and possible sudden death.

Gastrointestinal disorders, breathing complications and sleep apnoea have also been shown in AHC.

What are the treatment options for AHC?

Epilepsy in AHC is often drug- resistant. The choice of the appropriate anti-seizure medication (ASM) depends upon the specific types of seizures a patient presents with and is not specific to AHC.

In some cases, vagal nerve stimulation (VNS) may be effective in reducing seizures. There have been reports of some limited benefits of ketogenic diet. Anecdotal reports suggest a benefit from the cannabinoids, both for epileptic seizures and/or for dystonic/plegic episodes, but we still lack controlled studies.

Reduced Awareness Spells should not be misdiagnosed as epileptic seizures as this would lead to needless use of ASMs.

Flunarizine is the current medication of choice for the treatment of non-epileptic episodes (predominantly plegia episodes), but with limited effect on reducing their frequency, duration and severity. Other drugs used for prophylaxis are topiramate and acetazolamide.

Treatment for dystonia can include medications such as benzodiazepines, trihexyphenidyl, gabapentin, clonidine or baclofen.

Benzodiazepines and chloral hydrate are used for emergency rescue treatment, i.e. to interrupt ongoing plegic, dystonic and seizure-like episodes. Ensuring a dark, calm environment to induce sleep is essential.

A preventive measure for all types of episodes can be also to limit the exposure to the most known individual triggering factors.

Cardiac abnormalities should be properly treated and monitored. Sleep apnoea should be properly investigated and managed. Irregular sleeping patterns should be avoided as much as possible.

What is the emergency protocol for seizures and other AHC episodes?

Patients with AHC must be offered from onset an individualized emergency treatment plan, regularly updated. The disease can be life-threatening for some individuals. Most patients' protocols include effective relaxation techniques for dystonic/plegic attacks, along with minimising triggers and favouring sleep. For prolonged dystonic/plegic episodes and epileptic seizures rescue medications are to be prescribed by a child or adult neurologist. This is especially important if those manifestations are accompanied by alterations of the autonomic system.

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

- A personalized rescue medication plan for prolonged seizures and dystonic/plegic episodes.
- The side effects of medication particularly when changing treatment
- Genetic counselling
- Management of triggers
- Management and monitoring of associated disorders (heart, gut, breathing, sleep problems, behavioral/psychiatric problems)
- Basic life support training
- Rehabilitation and occupational therapy (physiotherapist, occupational therapist, speech and language therapist)
- Input from a specialist epilepsy nurse
- Liaison with school or college for support
- Patient, career & employer support requirements including support/benefits, neuropsychological evaluation, guidance, potential psychiatric or psychological support including counselling
- Sudden Unexpected Death in Epilepsy (SUDEP) risk management if confirmed epilepsy

Patient and scientific groups

Alternating Hemiplegia of Childhood UK (AHC-UK)
www.ahcuk.org | support@ahcuk.org

International Consortium for the Research on Alternating Hemiplegia of Childhood - IAHCRC
www.iahcrc.net | info@iahcrc.net

EpiCARE Information Leaflet regarding Alternating Hemiplegia in Childhood (AHC), by Katherine Behl, AHC-UK; Rosaria Vavassori, IAHCRC Consortium, AHC18+ e.V.. Reviewed and validated by Drs. E. Panagiotakaki & M. Papadopoulou (HCL, France). The European Commission support for the production of this publication does not constitute endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.