Alternating Hemiplegia of Childhood - AHC Patient Journey

European Reference Network | Neurological Diseases (ERN-RND)

EpiCARE

STAGE OF JOURNEY

1. PRE-NATAL DIAGNOSIS

In general, not possible. Almost all ATP1A3 mutations are de novo, 25% cases have no ATP1A3 mutations, and there are no known risk factors (environment, family).

CLINICAL PRESENTATION SYMPTOMS

A *de novo* mutation in the **ATP1A3** gene is the cause of AHC in 75-80% of people. In some people of the remaining 25%, other genes have been reported as involved (**RHOBTB2**, **ATP1A2** and **SCN2A**) but most of them remain genetically unexplained and in such case only a clinical diagnosis is possible. In the future, there may be further genes discovered.

A de novo mutation means neither parent carry the mutation. Therefore, discovery of a child with AHC is normally after birth during the first 18 months of life when symptoms develop.

There is no regular screening for AHC in the pre-natal period. For parents who conceive a child after they have had a child with AHC, there is a 1% chance of having another child with AHC. This is due to small possibility that the AT1A3 mutation is a germline mutation (a mutation found only in the reproductive organs e.g., the egg or sperm).

IDENTIFY PATIENT NEEDS

Parents who have not completed their family and wish to have more children should be counselled about the possibility of a 1% risk of AHC in future pregnancies.

For those who wish it, genetic counselling should be offered.

IDEAL OUTCOME AND SUPPORT

Genetic counselling is important for all families.
For those who wish to have future pregnancies, it is important that further discussion with a geneticist takes place. This should ideally occur prior to subsequent pregnancies to allow parents to have all available information to make their informed decisions, If not prior, then it must be offered early in the pregnancy.
Pre-natal diagnostic testing for subsequent pregnancies is possible and it is important that families are given this information to make their own informed decision.

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2. FIRST SYMPTOMS

Timeline
Within 18 months

First Symptoms
First neurological symptoms within 18 months, non AHC specific.

CLINICAL PRESENTATION SYMPTOMS

The first symptom is always neurological but non AHC specific. It can be only one or a combination of any of the following manifestations: seizures, dystonic / tonic episodes, episodes of altered awareness, abnormal eye movements, autonomic dysfunctions or other neurological symptoms.

The hallmark of AHC, i.e. the recurrent episodes of hemiplegia alternating in either side of the body and occasionally also spreading to the whole body, usually appears later, in addition to the previous symptoms.

Such episodes are usually interrupted by sleep, natural or induced with drugs; when patients awake after even only a short nap, they are completely recovered, but another episode may arise after few minutes. Parents usually take the opportunity of these short intervals of relief, to feed and hydrate their children after a prolonged episode.

IDENTIFY PATIENT NEEDS

Family needs information and reassurance during all the long and complex diagnostic process. They also **need to be actively involved in this process and their report about the episodes occurring at home should be taken into valuable consideration**, especially the hemiplegic episodes shifting from one side of the body to the other, which are very difficult to conceptualize even for expert paediatric neurologists.

It is important that clinicians acknowledge that they will often see only a fraction of what the families manage in the community at home.

IDEAL OUTCOME AND SUPPORT

Correct diagnosis as early as possible, preventing the start of ineffective and potentially dangerous treatment and a late handling at the onset of any other co-morbidity.

Increased awareness and ability of the family to accept the diagnosis of AHC, its rarity and complexity, and to face the burden of the many neuro co-morbidities.

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3. DIAGNOSIS

Timeline
As soon as the characteristic clinical diagnostic criteria for AHC are assessed, possibly confirmed by the genetic test.

Diagnosis
Clinical diagnosis confirmed as soon as the characteristic plegic episodes appear, affecting either side of the body alternatively.

May be confirmed by the genetic test.
Need for a clinical and genetic counselling about the outcomes and possible evolution of the disease.

CLINICAL PRESENTATION SYMPTOMS

An early diagnosis can be based on the assessment of the paroxysmal manifestations, possibly confirmed by the ATP1A3 gene test which is also a gene within the epilepsy gene panels.

In case of no mutation in ATP1A3, the clinical diagnosis can be confirmed based on the clinical manifestations if it fulfills the diagnostic criteria, and after excluding other differential diagnoses with a complete battery of examinations (instrumental, biochemical, imaging, genetic).

IDENTIFY PATIENT NEEDS

Family needs a clinical and genetic counselling on the prognosis and possible evolution of the disease.

A multispecialty reference centre, with the availability of various specialists with considerable experience in AHC, should take in charge the patient directly, if close to the patient's residence.

Otherwise, in order to avoid long journeys for follow up visits, and to provide a correct and quick intervention also in emergency situations, the local hospital and neurology services should liaise with such a reference centre, through a shared healthcare agreement.

In particular, the emergency services should be informed and trained about the specific assistance required, especially for those patients that have also respiratory crises, that may be associated to hemiplegic, quadriplegic, dystonic, or autonomic dysfunction episodes; or seizures and episodes of status epilepticus.

IDEAL OUTCOME AND SUPPORT

Family should remain in close contact with the expert reference centre, in order to receive advice about the management of the disease in all its coexisting neurologic issues, paroxysmal (episodes of all types: seizures, dystonic, oculomotor, respiratory, others) and non- paroxysmal (motor delay and complex movement disorder, development delay, cognitive impairment, behavioural problems, others) as they appear at different stages in the patient's life.
A rehabilitation plan (physiotherapy, speech and occupational therapy) must be defined as soon as possible and carried out by a rehabilitation centre expert in AHC or in a local hospital in coordination with a reference centre for AHC. Assessment for specific aids for mobility and education, adapted for AHC, should also be provided.

Family should also be put in contact with the local social services (or equivalent), in order to activate all the necessary assistance services (home assistance, mobility, indemnities for disability, and other assistance/benefits).
It could be also beneficial for parents to get in contact with the national patient association, charity or family group, if any. They could share their everyday experience with the disease and search for a mutual support, with the aim to prevent feelings of isolation, and anxiety about the future.

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4. TREATMENT

Timeline
As soon as seizures are confirmed and at the confirmation of the diagnosis of AHC, for the treatment of hemiplegic, quadriplegic, and dystonic episodes.

Diagnosis
Antiepileptic drugs specifically for epilepsy and additional drugs for prophylaxis and acute treatment of plegic and dystonic episodes.

Need to avoid triggering factors.

CLINICAL PRESENTATION SYMPTOMS

Antiepileptic drugs are used for those patients with confirmed seizures and episodes of status epilepticus. For some patients, where the diagnosis of epilepsy is unclear, anti-epileptic drugs are occasionally used after balancing risk versus benefits.
As for AHC-specific episodes, plegic and dystonic, several drugs are used both as prophylaxis, to reduce the frequency, duration and severity of the episodes, and as acute treatment, to interrupt an ongoing episode.
As for prophylaxis, Flunarizine is the only drug effective for most patients, albeit in open label experience. Other drugs are used for prophylaxis (topiramate or other antiepileptic drugs, acetazolamide, memantine, aripiprazole, and more recently, medical ketogenic diet and CBD), but most of these other drugs' reports of efficacy are from case series of only a handful of patients. Other treatments that have been tried have included oral ATP and other cannabinoids, but again without any clear evidence and with a single case report or anecdotal reports only. Treatment for dystonia can sometimes include medications such as benzodiazepines, trihexyphenidyl, gabapentin, clonidine, or baclofen.
For acute treatment, the most effective reported drugs are benzodiazepines or chloral hydrate. Recently, oxygen therapy has been reported as effective for dystonic and plegic attacks, even if in a limited group of patients.
In addition to pharmacological treatment, with the aim to reduce their frequency, a preventive measure can be to limit the exposure to the most known triggering factors for AHC episodes. This includes triggers such as: intense physical and emotional stress, sudden exposure to bright lights and loud noises, pain, constipation, abrupt changes in temperature, bathing.
For severe and long-lasting plegic and dystonic episodes, and for seizures or status epilepticus, hospitalization may be necessary, and a more specific treatment may be adopted with an individualized emergency treatment protocol for the patient.

IDENTIFY PATIENT NEEDS

Family needs to receive accurate information about all the therapeutic options, specific for epilepsy and for the prophylaxis and acute treatment of AHC episodes. They should also be made aware of their possible ineffectiveness, and side-effects.

The introduction of any new drug, especially in case Flunarizine is not effective, should be discussed in detail and decided in full collaboration with the AHC reference neurologist. Monitoring of blood pressure on starting Flunarizine initially is important. If newly started, doses should be increased slowly as it can take some weeks for Flunarizine to reach its steady state.

For any new drug, the family should be trained to detect and report any changes in the types of episodes, in their frequency, duration and severity and any possible side-effects or interference with other administered drugs. There should also be a plan from the clinician, when necessary, to modify the dosage accordingly with clear instructions and monitoring.

Family should also be informed about the most known triggers for the AHC-episodes, and about the importance to identify the specific triggers for their children and determine the best way to avoid them.

IDEAL OUTCOME AND SUPPORT

A comprehensive treatment plan including maintenance of a diary about all different types of episodes is helpful.

Especially in case of the initiation of a new drug, the diary should be started some months in advance and continued some months after, and, where appropriate, with a continued monitoring and support by the AHC reference centre.

Any changes in the daily routine and in the pattern of the exposure to the main triggers for the patient should also be recorded and correlated to the frequency, severity and duration of the episodes, in order to determine the efficacy of a drug correctly.

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5. SURGERY

Timeline

At any age after the diagnosis if clinical indication.

Surgery

A **VNS implantation** may be needed for patients with severe, drug-resistant epilepsy.

A **defibrillator** or **pacemaker** may be needed in case of associated cardiac disturbances.

A **Gastrostomy** may be required in some cases.

CLINICAL PRESENTATION SYMPTOMS

There's no type of surgery specific for AHC.

Only in case of severe, drug-resistant epilepsy, the AHC reference neurologist may recommend a VNS implantation.

Where cardiac abnormalities associated with AHC are present, the cardiologist, in collaboration with the neurologist and expert in AHC, may decide for the implantation of a defibrillator or pacemaker.

A gastrostomy may be required for some people with AHC. This is particularly for those who have frequent very prolonged paralysis severely affecting nutritional intake, or a permanent impaired swallow.

IDENTIFY PATIENT NEEDS

Family and patients must be informed in detail about any possible risks for a surgery, in particular if they may be in some way related to AHC, compared with the potential benefits, so that they can take a fully aware decision.

Careful planning by a multi-disciplinary team is required particularly for surgery requiring a general anaesthetic to minimize the complications secondary to AHC.

They also need to be monitored and assisted after the surgery, also for some time at home, after the hospitalization.

IDEAL OUTCOME AND SUPPORT

Even if there are no reported problems with anaesthesia specific for any AHC patients, the anaesthesiologist must be well informed about AHC and involved in the surgery planning as early as possible as part of a multi-disciplinary team.

Patients should be strictly monitored for all the follow-up after surgery. This includes determining any changes in the pattern of the episodes or any complications that may be secondary to AHC.

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6. FOLLOW UP

Timeline

Childhood and Adolescence

Follow Up

Paroxysmal events of many types: epilepsy, frequent and long-lasting plegic and dystonic episodes, affecting only one side alternatively or the whole body, respiratory crises, abnormal eye movements.
In addition, complex motor and cognitive disorders.

Need for regular follow-up visits by a multi-disciplinary team of experts in AHC.

Need for adapted rehabilitation and education plans.

Need for coordination with the social services

CLINICAL PRESENTATION SYMPTOMS

Severity of the disease varies greatly amongst every patient and can vary between mutations in the ATP1A3 genes.
The most severe cases have frequent episodes of seizures, status epilepticus, respiratory crisis, as well as severe motor and intellectual deficits.
Even the moderate and mild cases that develop from early childhood have motor and cognitive impairment, in addition to all the different types of AHC episodes. Epilepsy may appear at any age, since childhood, without any evident reason.

The frequency and duration of AHC episodes is generally very high throughout adolescence, although with significant and sudden variations even within a few days (from one in a week or two, to an episode each day, lasting from few minutes to many hours), without any identifiable pattern. Usually, there are no consequences for each single AHC episode, but many cases are reported of inexplainable regression, with only partial recovery or no recovery at all, after an AHC episode, even if identical to any other previous episode.
As patients grow up, they can become more and more aware of their condition and anxious about the possibility of having an episode at any moment. They may develop behavioural problems (aggressivity, hyperactivity, depression, others/etc.). It is important that a holistic assessment is made of any behaviour problem as this might be communication of an unmet need (e.g., pain or other modifiable factors) in a person who is non-verbal.

In summary, **AHC is a combination of many major neurological symptoms (epilepsy, movement disorders, and cognition) and other associated symptoms. Each of these symptoms may be considered as a disease per se, but their co- existence contributes to the severity of AHC as an entity.**

IDENTIFY PATIENT NEEDS

Parents need to create a close, peer collaboration with their children's AHC reference neurologists, based on mutual trust and acknowledgment of respective roles and expertise of the disease. Any new information about new therapeutic options and interventions, the progress of research, new rehabilitation or assistance plans, should be evaluated together and any decisions on any new actions should be taken jointly.

There is a need for major coordination of all the multidisciplinary medical, rehabilitation and social interventions and services that an AHC patient may require in everyday life.
There is a need for the parents to receive psychological support/counselling, to help following diagnosis as well as help them in the management of all the concurrent types of episodes, and with the other non- paroxysmal manifestations.

Additional support is beneficial to help families balance the necessity to avoid all possible triggering factors (especially changing their daily routine and emotional and physical stress), and the necessity for their children to have as many normal experiences, stimuli and relationships as possible (rehabilitation sessions, school attendance, birthday parties with their schoolmates, etc.) to acquire development skills and autonomy which are appropriate for them.
Patients themselves may need psychological support, especially when in adolescence, to cope with their anxiety, and tendency to avoid emotionally stressing situations, which could lead to isolation, social exclusion and depression.

IDEAL OUTCOME AND SUPPORT

Regular follow-up visits should be provided by a multidisciplinary team of experts in AHC, including a neurologist, a neuropsychologist, an ophthalmologist, a cardiologist, and where appropriate a pain consultant, psychiatrist, gastroenterologist, and respiratory consultant.
During the visits, any possible adjustment in the therapeutical plan and the inclusion of any new therapeutical option should be evaluated. Extemporary visits and counselling should also be offered to the family at the onset of any new concerning symptoms or for the sudden worsening of any other manifestation.
Members of the team should remain coordinated in their specific actions and coordinate and support the action of any other professionals involved in the daily care, at the local level: rehabilitation therapists, teaching staff, home assistants, psychologists, others.

In case of frequent, prolonged and painful episodes, the activation of a service for pain therapy might be recommended.

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7. FOLLOW UP

Timeline

Adulthood

Follow Up

All symptoms persisting to adulthood with possible sudden worsening with no evident reasons.

Need for a proper transition from pediatric to neurology for adults

CLINICAL PRESENTATION SYMPTOMS

Moderate and mild affected patients may experience long periods of stability, with a certain decrease in the frequency, duration and severity of the episodes. However, there are some patients who deteriorate or have a progressive course that is not yet explained.

In the long-term, the continuous exposure to the episodes since childhood usually results in a worsening of the non-paroxysmal manifestations, in terms of motor and cognitive deficits, further limiting the autonomy and often preventing the possibility of independent life and social inclusion. Behavioral problems and psychological issues usually can become more prominent.

In all situations, **the sudden onset of new paroxysmal manifestations, especially seizures, or the sudden worsening of any other symptom, with a consequent regression, can always occur, even in the mildest of cases of adult patients.**

Many sudden deaths are also reported, at different ages, usually in connection to severe seizures or prolonged AHC episodes. In many cases the ultimate cause of the death is a cardiac abnormality, but for others it is uncertain.

IDENTIFY PATIENT NEEDS

Adult patients and their families need to be supported in the transition from the pediatric neurology to the adult neurology care, with all the related services.

Many adult services have even less experience of AHC than pediatric neurology services. Therefore, it is essential that local teams link with the national AHC reference centre for guidance.

Patients should be encouraged and supported in their desire for an independent life, for positive relationships outside the family and of social inclusion. Parents should also be motivated and supported in the gradual detachment from their adult children.

IDEAL OUTCOME AND SUPPORT

An adult neurologist should be included in the multi-disciplinary team and be properly informed by the pediatric neurologist about how to continue the follow up care. A cardiologist should also be definitively included in the team, as the cardiac disturbances associated to AHC tend to be more frequent in adulthood.
The Multi-disciplinary team should work closely with the AHC reference centre as well as the local pediatric neurological team to aid transition and ensure safe patient care.

An individualized plan for autonomy and independent life should be defined in collaboration with the social services for adult patients, including a home separated from their parents (where appropriate/desired), by themselves or with a small group of co-tenants, a work employment or a work-like occupation, sport and leisure activities possibly in normal contexts, travels for tourism and cultural events. An adequate level of personal assistance must always be provided, part-time or even full-time, depending on the specific severity or combination of symptoms.

Appropriate management of medications and safety issues must be addressed holistically for those patients with significant cognitive impairments.

A tele surveillance service, for a prompt intervention in case of seizures or other AHC manifestations, might also be activated.

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Full text and Infographics

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Co-funded by the European Union