orphanaesthesia

Anaesthesia recommendations for

Alternating Hemiplegia of Childhood syndrome

Disease name: Alternating hemiplegia of childhood syndrome (AHC)

ICD 10: G98

Synonyms: AHC syndrome (An ATP1A3-related neurologic disorder). AHC was named for its most striking and diagnostic motor symptom; however, the range of manifestations show it to be a CNS disorder affecting function broadly in various brain circuits, heart and the disease evolves with age.

Disease summary: AHC is a very rare neurological disorder first described in 1971 which has received increasing interest recently [1]. It is characterized by hemiplegia of either side of the body, paroxysmal tonic or dystonic spells, oculomotor abnormalities and developmental delay.2-4 Onset occurs before 18 months of age. This condition is diagnosed based on the occurrence of the above combination of symptoms, is usually due to de novo pathogenic variant in ATP1A3 and has also been reported in a few families [2-3]. Onset and progression of neurological symptoms have been well characterized. While the course and severity of deficits can vary considerably, there appears to be progression over time, at least in some patients. The differential diagnosis of AHC includes familial hemiplegic migraine (FHM) syndromes (e.g. FHM1-CACNA1A; FHM2-ATP1A2), episodic ataxia type 6, glutamate transporter disorders (SLC1A3), glucose transporter defects, GLUT1 deficiency (SLC2A1), infantile onset epileptic encephalopathies, severe myoclonic epilepsy of infancy (Dravet syndrome), SCN1A mutations, mitochondrial disorders, and disorders of dopamine biosynthesis/ neurotransmitter disorders. The prevalence has been estimated at 1:1,000,000 with most cases being due to de novo mutations [4-6]. Triggers in AHC and other ATP1A3 related diseases that can induce paroxysmal episodes in AHC are frequent. They include the psychological stress, emotional excitement, environmental stressors (bright light; sunlight or fluorescent lighting), excessive heat or cold, situations associated with excessive noise, crowds, water exposure in the form of bathing, swimming, shampooing, certain foods or odours, missed meals, excessive or atypically strenuous exercise, illness, irregular sleep, missing a nap, and delayed bedtime [5-7]. Flunarizine has remained the most commonly prescribed therapy for prophylaxis of episodic neurologic dysfunction in AHC for more than two decades. However, the response of the paroxysmal hemiplegia and dystonia is usually only partial and patients continue to have significant developmental and neurological impairments despite this therapy [6-13].

Figure 1. Clinical features which when occurring in combination should raise the suspicion of AHC and or of ATP1A3 mutation related disorders [7,9].

Current research is emphasising developing a better understanding of the various clinical characteristics of the disease including, but not limited to, cardiac, radiological, developmental, and paroxysmal manifestations [5]. Natural history documentation in database registries at a national and international level is a prelude to novel therapy trials. Open-label clinical trials are also going on. The IAHCRC International Consortium (https://

www.iahcrc.net) is a collaborative research initiative established in 2015 whose goal is to unite clinicians, geneticists, and researchers at research centres in Europe, USA, Australia, Asia and other countries to work towards a better understanding of the manifestations and natural history of AHC and related disorders and to eventually develop more effective therapies [4,5].

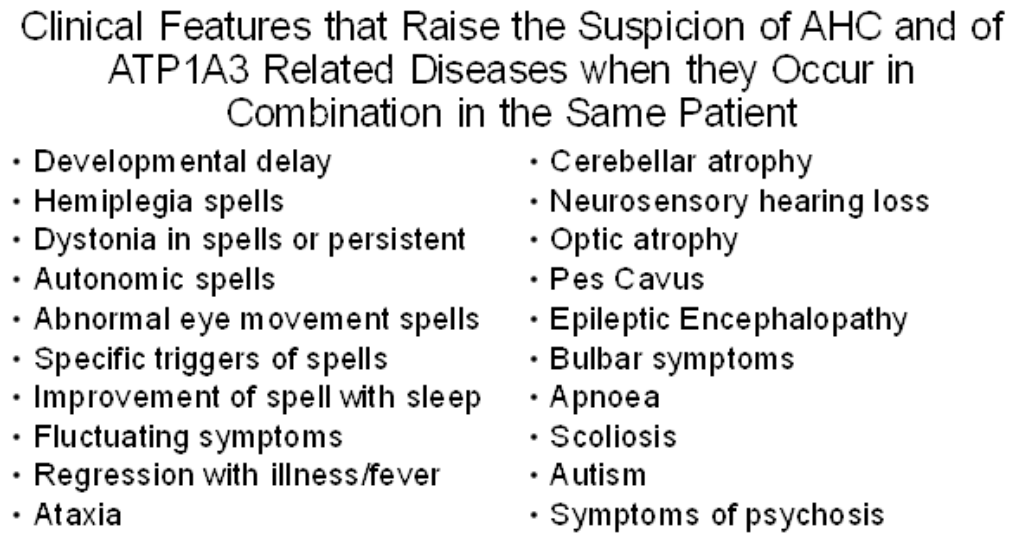

Figure 1

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgery

Typical surgeries are gastrostomy, orthopaedic surgery, tendon releases, tendon transfers, correction of scoliosis, dental procedures, ophthalmic explorations, tonsillectomy and adenoidectomy, and caesarean section [14-19]. Anaesthesia and or sedation may also be needed for certain procedures like MRI [17,18,20].

Type of anaesthesia

There is no definite recommendation for either general or regional anaesthesia. Given the low prevalence of the disease, the experience of anaesthetic management is limited.

In addition to episode prophylaxis, acute management focuses on removing known triggers and facilitating early sleep. The use of oral midazolam or rectal diazepam has been advocated by some authors to provide rapid sedation [10]. However, sedation should be done after carefully calculating the individual risks, especially concerning respiratory failure and risk of aspiration. Other benzodiazepines, like clonazepam, are also often used in AHC patients on an as needed base as abortive medications after the onset of acute AHC spells.

Regional anaesthesia may, theoretically, trigger an attack due to the stress involved, but since there are no reports in literature about that, it remains a potential and not a definite contraindication.

Necessary additional pre-operative testing (beside standard care)

Careful preoperative assessment is necessary to avoid precipitation of spells or seizures with potential related complications in patients with AHC. The severity of a patient´s deficits can vary considerably and must be evaluated.

Since AHC patients can be predisposed to cardiac arrhythmias, the evaluation by cardiology before administration of anaesthesia is advisable. In addition, since about half of the AHC patients have epilepsy, is should be ensured that the patients have taken their anti-seizure medications, and reviewing and taking into consideration the epilepsy history are also advisable.

Since AHC patients can have obstructive and/or sleep apnoea, the team administering sedation or anaesthesia should be aware of that and should have expertise in managing patients with a predisposition to apnoea [11]. As sleep dysfunction is common among children with AHC, physicians should routinely screen for sleep pathology, with a low threshhold to obtain a nocturnal polysomnography [11].

Particular preparation for airway management

Most AHC patients will have a difficult airway. They also are affected by sleep-apnoea and SAOS [11]. They also have particular problems with swallowing and oropharyngeal control since the ATP1A3 has high expression in brain stem nuclei [10]. This may account for the increased risk of obstructive sleep apnoea in these patients.

Particular preparation for transfusion or administration of blood products

Maintaining intraoperative normothermia is important, avoid transfusion of cold blood products and if it is necessary, it is better to have a slow infusion and a warming system. This is important in anyone undergoing anaesthesia and likely even more important in patients with AHC since they can be sensitive to temperature changes.

Particular preparation for anticoagulation

It is not known.

Particular precautions for positioning, transportation and mobilisation

The positioning of these patients must be careful to avoid injuries in areas where there is no sensitivity or there are sequelae derived from residual neurological deficits.

Interactions of chronic disease and anaesthesia medications

Patients with AHC usually receive several chronic medications. The most common is flunarizine, a selective calcium channel blocker appears to have some success in reducing duration and frequency of attacks. Flunarizine can cause an increase in extrapyramidal and depressive symptoms, and develop Parkinsonism. This generally occurs in elderly patients and with higher doses [6,21]. The use of antiemetic drugs may interact with flunarizine. Cardiac ECG abnormalities reported in AHC are with T-wave abnormalities, short QT interval, J-wave changes, and intraventricular conduction delay. Some drugs that may be used during or around anaesthesia may, at least theoretically, exacerbate these complications [13]. There are currently reports of only two AHC cases undergoing anaesthesia, one reported twice after undergoing multiple sequential anaesthesia procedures [14-16]. The following discussion will centre not only on those but also on the underlying potential complications from anaesthesia and sedation given our current understanding of the known manifestations and underlying pathophysiology of AHC.

Patients with AHC are predisposed to catastrophic regression in association with prolonged spells particularly in association with prolonged seizures and after discontinuation of flunarizine resulting in permanent loss of milestones and MRI changes [17-19]. Thus, it is important for the sedating/anaesthesia team to make sure that flunarizine is not stopped and to treat any seizures that may occur around the time of the procedure. Flunarizine has a long half-life [21] and thus a few hours of inability to take the medication by mouth should not affect the level significantly. However, in patients on the medication one should avoid longer periods during which the medication is withheld. The reason is that in some patients with AHC, particularly those with the E815K mutation, such suspension of flunarizine intake has been followed by severe spells with regression in development [16-17].

Other proposed treatments include beta blockers, anticonvulsants, methysergide, amantadine, aripiprazole, and haloperidol [5,21]. Antiepileptic drugs are effective in treating seizures only [8].

Anaesthetic procedure

Mitochondrial dysfunction and disorder of calcium channels present the possibility of atypical anaesthetic reactions, similar to Malignant Hyperthermia (Malignant Hyperthermia-like reactions). These reactions are potentially serious due to hyperkalaemia. However, even though mitochondrial dysfunction has been suspected in AHC [6], we are not aware of Malignant Hyperthermia occurring in AHC.

Anaesthesia can impact postoperative muscle weakness in this population. In one case report were mentioned potential risks of general anaesthesia related to the use of volatile agents and suxamethonium as the patient experienced extreme limb weakness, difficulty in swallowing and hemiplegia in the postoperative period after two episodes of inhalational general anaesthesia. When the patient subsequently presented for caesarean section, Rocuronium was chosen as a suitable alternative to suxamethonium for rapid sequence induction and it was used in combination with intravenous anaesthetics [14]. After induction, general anesthesisa using propofol as target controlled infusion (TCI) with rocuronium and alfentanil was uneventful. Several years later, the patient presented for termination of another pregnancy at 13 weeks gestation. Anaesthesia with premedication with ranitidine, metoclopramide and sodium citrate, induction with midazolam and fentanyl followed by a propofol TCI (Malignant Hyperthermia protocol) was again successful without complications [16].

Rubio et al reported a case of outpatient surgery in an 18-year-old male AHC patient. The patient was pre-medicated with oral midazolam and EMLA cream (eutectic mixture of 2.5% lidocaine and 2.5% cream prilocaine) in the venipuncture areas. A venous catheter was obtained and administered ranitidine, ondasetrone and midazolam. Induction was performed with propofol, lidocaine, fentanyl and rocuronium. The maintenance was performed with propofol by controlled target infusion. He was extubated in the operating room. The patient remained in the recovery unit for 5 hours without reporting any episodes of dystonia or other postoperative complications such as pain, nausea or vomiting [14]. That same patient had had extreme but transient limb weakness and swallowing difficulty after inhalational anaesthetics on two occasions.

Regional anaesthesia may cause stress that could trigger an attack, but that may not necessarily be an absolute contraindication.

Particular or additional monitoring

Monitoring should be targeted at patient-specific pre-existing organ dysfunction. It also should include monitoring functions corresponding to surgical intervention. Monitoring of temperature and neuromuscular function is always desirable.

Possible complications

In epilepsy of any cause in general, increased risk of Sudden Unexpected Death in Epilepsy (SUDEP) has been observed in association with seizure activity and is hypothesised to be related to cardiac arrhythmias and to autonomic dysfunction resulting from brainstem spreading depolarisation which are part of the manifestations of AHC [5,22-25]. AHC patients carrying pathogenic AHC causing mutations have increased risk of early death, SUDEP, cardiac rhythm problems, T-wave abnormalities, short QT interval, J-wave changes, and

intraventricular conduction delay [13,24-28]. Many patients report sleep difficulties and may have sleep apnoea which can be either central or obstructive [11]. Additionally, most patients have behavioural problems, usually consistent with ADHD superimposed on cognitive impairment and at times extreme aggressive behaviour, rarely psychotic episodes which can occur spontaneously or may be triggered by medications [9,29-32]. Awareness of all these potential complications that can occur around the time of anaesthesia is important for the managing team to recognise any such complications promptly and to administer the right management.

Post-operative care

From the anaesthetic point of view, known triggers for seizures should be minimised perioperatively. Shivering, pain, extreme temperatures, and other stimuli should be promptly treated. This should take into consideration all the above mentioned potential AHC complications.

Disease-related acute problems and effect on anaesthesia and recovery

As AHC is a rare condition described only relatively recently, its underlying pathophysiology is only partially understood [24,26,27]. There are no controlled studies of anaesthesia or sedation, only rare case reports, reported above, on anaesthesia and recovery in AHC.

Ambulatory anaesthesia

Ambulatory anaesthesia in general allows patients to be accompanied by their relatives until their transfer to the operating room. It is demonstrated that it significantly reduces the degree of perioperative anxiety. When surgery is minimally invasive and allows early home discharge, the patients' benefit from immediate reincorporation to their usual routine [14]. These are general principles that also likely apply to AHC.

Obstetrical anaesthesia

In literature, one AHC patient was reported twice, once for undergoing a caesarian section and once for termination of pregnancy [14,16]. On both occasions, total intravenous anaesthesia (target-controlled propofol infusion, opioid and rocuronium) was successfully performed. The patient had reported extreme limb weakness, difficulty in swallowing and hemiplegia in the postoperative period of two previous anaesthesias with inhaled anaesthetic [14,16].

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