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Alternating hemiplegia of childhood syndrome

Williams syndrome

orphanaesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 15 | 2021

OrphanAnesthesia –

ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

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OrphanAnesthesia –

a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

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Anaesthesia recommendations for

Alternating hemiplegia of childhood syndrome

Disease name: Alternating hemiplegia of childhood syndrome (AHC)

ICD 10: G98

Synonyms: AHC syndrome (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 and in the 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 characterised by hemiplegia of either side of the body, paroxysmal tonic or dystonic spells, oculomotor abnormalities and developmental delay [2-4]. Its 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 characterised. While the course and severity of deficits may 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 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, not all patients respond to flunarizine, 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 the need for developing a better understanding of the various clinical characteristics of the disease including, but not limited to, cardiac, radiological, developmental, and paroxysmal manifestations [5]. A 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

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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 the natural history of AHC and related disorders and to eventually develop more effective therapies [4,5].

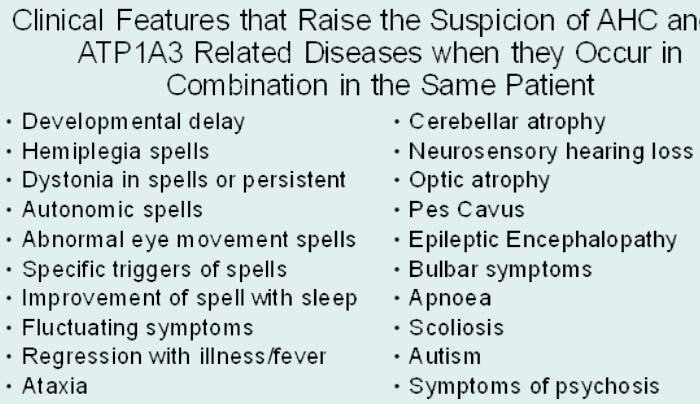

Figure 1

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

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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, e.g. 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, experience in 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 the risk of aspiration. Other benzodiazepines, like clonazepam, are also often used in AHC patients on an as needed basis as abortive medication after the onset of acute AHC spells.

Regional anaesthesia may theoretically trigger an attack due to the stress involved, however, there are no reports in the literature about the experience with regional anesthesia in AHC patients. Consequently, deciding to use or not to use regional anesthesia remains a judgement call in need of further investigations.

Necessary additional pre-operative testing (beside standard care)

Careful pre-operative 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 a cardiologist before administration of anaesthesia is advisable. In addition, since about half of the AHC patients have epilepsy, it should be ensured that the patients have taken their anti-seizure medications. It is also advisable to review and consider the patient's epilepsy history.

Since AHC patients may have an obstructive and/or sleep apnoea, the team administering sedation or anaesthesia should be aware of that and 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 threshold including 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 ATP1A3 has high expression in brain stem nuclei [10]. This may account for the increased risk of obstructive sleep apnoea in these patients.

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Particular preparation for transfusion or administration of blood products

Maintaining intraoperative normothermia is important, avoid transfusion of cold blood products and, if 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 might be sensitive to temperature changes.

Particular preparation for anticoagulation

Unknown.

Particular precautions for positioning, transportation and mobilisation

Positioning of these patients must be done carefully to avoid injuries in areas where sensitivity is lacking or sequelae derived from residual neurological deficits exist.

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 which 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 doses [6,21]. The use of anti-emetic drugs may interact with flunarizine. Cardiac ECG abnormalities reported in AHC are 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 patients underwent multiple sequential anaesthesia procedures [14-16]. The following discussion will centre not only on those, but also on the underlying potential complications resulting 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 associated with prolonged spells, particularly occurring in association with prolonged seizures and after discontinuation of flunarizine and resulting in a 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 any seizures that may occur around the time of the procedure are treated. Flunarizine has a long half-life [21]. Hence a few hours of inability to take the medication by mouth should not affect the level significantly. However, longer periods during which the medication is withheld should be avoided in patients who were on the medication. The reason is that in some patients with AHC, particularly those with the E815K mutation, such suspension of flunarizine intake has been seen to be followed by severe spells with regression in development [16-17].

Other reported, but not proven treatments used for AHC spells include beta blockers, anticonvulsants, methysergide, amantadine, aripiprazole, and haloperidol [5,21]. Antiepileptic drugs are effective in treating seizures only [8].

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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 post-operative muscle weakness in this population. There are two patients with AHC in the literature, one reported twice, describing experience during anaesthesia. The first case report 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 post-operative 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 was used in combination with intravenous anaesthetics [14]. After induction, general anaesthesia using propofol as a 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 a premedication consisting of ranitidine, metoclopramide and sodium citrate, induction with midazolam and fentanyl followed by a propofol TCI (malignant hyperthermia protocol) was again successful and without complications [16].

Rubio et al. reported a case of outpatient surgery in an 18-year-old male AHC patient. This is the second patient reported in the literature. The patient was premedicated 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 inserted and the patient was administered ranitidine, ondansetron and midazolam. Induction was performed with propofol, lidocaine, fentanyl and rocuronium. The maintenance was performed with propofol by controlled target infusion. The patient was extubated in the operating room. He remained in the recovery unit for 5 hours without reporting any episodes of dystonia or other post-operative complications such as pain, nausea or vomiting [15]. The 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 administer the right management.

Recently it was found that patients with AHC, specifically those with the most common D801N mutation, are more likely to have short QT syndrome on their ECG [33]. So it is recommended that not only all patients with AHC be cleared by a paediatric cardiologist before sedation or anaesthesia procedures, but also for the cardiologist and/or physician in charge of sedation/anaesthesia of the patient to review the current prescribing information of any medication the patient will be taking for any potential adverse effects on the QTc interval to avoid unfavorable reactions.

Post-operative care

From the anaesthetic point of view, known triggers for seizures should be minimised peri-operatively. 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 peri-operative 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 post-operative period of two previous anaesthesias with an inhaled anaesthetic [14,16].

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