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Perioperative management of patients with genetic multisystem diseases associated with pre-excitation

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Abstract

Pre-excitation is associated with life-threatening arrhythmias. Apart from the well-known Wolff-Parkinson-White syndrome, a number of rare diseases are associated with pre-excitation due to the existence of accessory pathways. The present review aims to focus on anaesthesia and perioperative care of patients with rare genetic diseases associated with pre-excitation due to the existence of a bundle of Kent or other accessory pathways. The Danon disease, Fabry disease and Pompe disease, tuberous sclerosis, Leber hereditary optic neuropathy (LHON), and mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome are genetic multisystem disorders which may involve pre-excitation, usually combined with cardiomyopathy. The anaesthetic management of the above syndromes may become quite challenging. We conducted a PubMed and manual literature search for all types of relevant publications; we identified 58 articles suitable to be included in the present review. According to the literature, a high index of suspicion for the possibility of pre-excitation is required, and anaesthetic drugs and adjuvants should be chosen carefully, in order to prevent or at least not facilitate arrhythmias associated with accessory pathways. The perioperative management should be further tailored to the specific abnormalities of each condition. Multidisciplinary consultation and care, according to the affected organs, are mandatory for a safe outcome. The anaesthetic plan should be focused on preoperative clinical optimization and on case-specific management, tailored to the various systems involved.

Key words: perioperative management, anaesthesia, arrhythmias, pre-excitation, multisystem diseases, Danon disease, Fabry disease, Pompe disease, tuberous sclerosis, MELAS syndrome.

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The cardiac electrical stimuli are generated in the sino-atrial node, reach the atrio-ventricular (AV) node and the His bundle/Purkinje fibers, and finally spread to the left and right ventricular myocardium. In the AV node, the action potential relies on a slow calcium current, which delays the conduction of incoming electrical impulses, thus preventing the development of ventricular tachycardias. However, abnormal fibro-muscular anatomic tracts – with action potentials depending upon rapid sodium currents – may connect the atria with the ventricles. Through these alternative pathways, the cardiac impulses can bypass the AV node and travel very fast towards the ventricular myocardium, causing its activation (depolarization) earlier than if the impulses travelled through the normal conduction system. The extra electrical conduction tracts are called "accessory pathways" and the electrophysiological phenomenon of the earlier than normal ventricular excitation is named "pre-excitation" [1]. This mechanism may precipitate serious, even lethal arrhythmias, such as ventricular tachycardia and ventricular fibrillation [2-4].

An accessory pathway (AP) may be located anywhere along the AV ring, while up to 10% of patients may have more than one accessory bundle [1]. An AP may be capable of conducting impulses anterogradely (towards the ventricle) or retrogradely (from ventricles to atria) or in both directions [1]. Based on electrocardiographic (ECG) findings, anterograde conduction may be overt or latent; in patients with overt conduction, the ventricular pre-excitation is manifested on surface ECG as an upstroke at the beginning of QRS, known as a "delta wave". The delta wave indicates that the part of the ventricle which is directly connected to the AP is depolarized first. In patients with latent AP conduction, the delta wave may be absent on the resting surface ECG or may present intermittently. However, pre-excitation may become apparent in specific conditions (i.e. an episode of atrial fibrillation or flutter or atrio-ventricular node block). The prevalence of arrhythmia and the risk of malignancy in overt and latent pre-excitation are similar. In APs with retrograde conduction, pre-excitation is concealed during sinus rhythm (absence of ECG

signs) but may be revealed during atrio-ventricular re-entrant tachycardia (AVRT) [1, 3, 5].

The AVRTs, orthodromic or antidromic, are the commonest arrhythmias that may develop in patients with APs [3, 5, 6]. Atrial or ventricular premature beats may trigger an AVRT, which usually presents on the ECG as a regular, narrow- or wide-complex tachycardia, with very high ventricular rates (i.e. 150-250 bpm). The orthodromic AVRTs are characterized by narrow QRS complexes, because the impulses travel to the ventricle through the AV node and return via the AP, while the antidromic AVRTs have wide QRS complexes, because the impulses travel down through the AP and return via the AV node [5, 6]. If atrial fibrillation or flutter develops, the conduction of stimuli towards the ventricle may occur via the AP, which usually has a shorter refractory period than the AV node; in this case, very fast anterograde conduction of atrial impulses may cause extremely high ventricular rates, even ventricular fibrillation [3, 5, 6].

The most well known AP is named the "bundle of Kent", and is found in the Wolff-Parkinson-White (WPW) syndrome [5, 6]. Other, less common APs have also been identified, and rarer pre-excitation conditions have been described, such as the Mahaim fibers and the Lown-Ganong-Levine syndrome. The Mahaim fibers are APs that may arise from the AV node or the His bundle or most likely from the right atrium and terminate in the right ventricular myocardium or close/into the right bundle branch (nodo-ventricular or fasciculo-ventricular or atrio-ventricular or atrio-fascicular fibers) [3]. They are characterized by anterograde transmission only, and longer conduction times than the bundle of Kent [3]. In the Lown-Ganong-Levine syndrome, possible mechanisms of pre-excitation include the fast conduction of atrial stimuli through a defective AV node or their transmission via an AP (i.e. James fibers or Brechenmacher fibers) which bypass – completely or partly – a normal AV node [3].

Diagnosis of pre-excitation is based on the combination of ECG findings and development of symptoms, usually palpitations, or more rarely syncope or even cardiac arrest [6]. The pre-excitation pattern on surface ECG is characterized by a shortened PQ (PR) interval (< 120 ms in adults), a prolonged QRS complex (> 120 ms) and a delta wave, with secondary ST-T changes directed opposite to the major delta wave and QRS vector [5-6]. This characteristic pattern, usually called the "WPW pattern", may not be present in all pre-excitation conditions, depending on the type of the AP and its specific characteristics. For example, the ECG pattern in the Lown-Ganong-Levine syndrome, which may represent a perinodal AP, is characterized by a short PQ (PR) interval and a normal QRS complex, without a delta wave [3].

Electrophysiology testing is the gold standard for certain diagnosis of pre-excitation and identification of the AP. The procedure can be combined with ablation of the pathway, which represents the definite treatment in cases with recurrent episodes or life-threatening arrhythmias [6]. Finally, congenital heart defects associated with pre-excitation abnormalities may co-exist in these patients and should be sought (i.e. Ebstein's anomaly in WPW syndrome) [6].

The most widely known pre-excitation condition, almost synonymous with the term "pre-excitation", is the WPW syndrome. Nevertheless, there are a few familial forms of pre-excitation found in rare multisystem diseases [7], namely γ-2 regulatory subunit of AMP-activated protein kinase gene (PRKAG2) mutation, Danon, Fabry and Pompe disease, tuberous sclerosis, Leber hereditary optic neuropathy (LHON) and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome (MELAS) [7]. Patients with the above syndromes and diseases may present at some time in their lives for elective or emergency surgery. The perioperative management of such cases may be quite complex and difficult due to the several co-existing abnormalities. Especially in case of emergency, the challenge is greater due to the lack of time for extensive investigation and adequate preparation of the patients. Moreover, anaesthesia may unmask an undiagnosed pre-excitation abnormality and facilitate the development of life-threatening arrhythmias. The present review aims to focus on the anaesthetic management and perioperative care of patients with rare genetic diseases associated with pre-excitation, due to the existence of a bundle of Kent or other APs.

We conducted a PubMed literature search for all types of publications – up to January 2018 – combining the terms: "preexcitation", "pre-excitation", "PRKAG2", "Danon disease", "Fabry disease", "Pompe disease", "tuberous sclerosis", "Leber hereditary optic neuropathy", "LHON", "mitochondrial encephalopathy", "mitochondrial encephalopathy, lactic acidosis and stroke-like episodes syndrome", "MELAS syndrome" and "anaesthesia" or "perioperative management " or "perioperative care". Articles in languages other than English were used only if they had an informative English abstract. We found 56 articles suitable for inclusion in this review. Additionally, two published papers were found by manual searching of the references in the electronically retrieved articles. The articles we identified were mostly case series and reports, and a few retrospective studies. We also used articles that provided information on genetics, clinical presentation, diagnosis and treatment of the diseases. In total 82 articles were included in the present review.

METABOLIC DISORDERS ASSOCIATED WITH PRE-EXCITATION

There are a number of genetic metabolic diseases associated with pre-excitation, combined with structural cardiac and other organ abnormalities [7, 8]. The most well known are the Danon, Fabry and Pompe disease, which are lysosomal storage disorders due to enzymatic deficiency. They are characterized by accumulation and deposition of substrates in various organs, including the cardiovascular system. PRKAG2 deficiency is a more heart-specific, non-lysosomal metabolic disease, involving glycogen accumulation [7, 8].

The above disorders share similar cardiac manifestations, namely hypertrophic cardiomyopathy, short PQ (PR) interval and AV blocks [7, 8]. An electrophysiological study is required to confirm the presence of an AP, since pseudo-pre-excitation has been described in patients with Fabry disease and PRKAG2 mutation [7, 9, 10]. In these cases, fast AV node transmission, combined with His-Purkinje conduction abnormalities, may result in short PQ (PR) intervals, giving the false impression of existence of an accessory pathway [7, 9, 10]. Compared to the classic WPW syndrome, the prognosis is much poorer, since these diseases include major structural and functional cardiac abnormalities [7]. Not rarely, the gradual deterioration of myocardial function finally necessitates heart transplantation [11]. Also, the perioperative management of these rare syndromes is probably more challenging, since it should be tailored to the various systems involved. Publications on the perioperative management of patients with rare metabolic disorders associated with pre-excitation are presented in Table 1.

Danon disease

Danon disease is typically characterized by cardiomyopathy, proximal skeletal myopathy and cognitive dysfunction [12, 13]. Pre-excitation, other cardiac conduction abnormalities, hepatic, pulmonary and ophthalmic pathology may also co-exist [12, 13].

An X-linked dominant pattern of inheritance and mutations in the gene encoding the lysosome-associated membrane protein 2 (LAMP2) have been identified [14]. Deficiency of the LAMP-2B isoform causes lysosomal dysfunction with accumulation of autophagic material in the cardiac and skeletal muscles [13, 14]. Hypertrophic cardiomyopathy – obstructive or not – is a prominent feature of Danon disease; it usually progresses to dilated cardiomyopathy and congestive heart failure [7, 13, 15]. Men are mostly affected and usually live only until early adulthood [12, 13, 16].

The co-existing electrophysiological abnormalities, especially ventricular pre-excitation, differentiate the disease from other forms of hypertrophic cardiomyopathy [17]. The mechanism of pre-excitation may be inherent, due to the abnormal autophagy per se, or mechanical, due to myocardial hypertrophy [13]. While conduction abnormalities are encountered in both genders (> 80%), an electrocardiographic WPW pattern is mostly found in men (70% of males versus 27% of females) [13]. Thus, the combination of hypertrophic cardiomyopathy, WPW pattern and male gender raises strong suspicion for Danon disease and should be investigated by genetic testing.

Atrial and ventricular arrhythmias develop in about 50% of patients and implantable cardioverter defibrillators are used for their treatment [13]. Nevertheless, DC shocks are not always effective [16], and lethal dysrhythmias occur in about 30% of high risk patients [13]. Also, over 1/3 of patients undergo ablation for pre-excitation; notably, multiple attempts may be required due to the development of diffuse fibrosis [13].

The literature on anaesthesia for patients with Danon disease is poor. In a child who received general anaesthesia for dental procedures, the management mainly focused on the existing hypertrophic cardiomyopathy with outflow obstruction [15]. Inhalational anaesthesia with N_2O and sevoflurane was safe and no arrhythmias or other cardiovascular complications occurred [15].

Fabry disease

Fabry or Anderson-Fabry disease is another lysosomal storage abnormality with an X-linked recessive inheritance. It is characterized by deficiency of α-galactosidase A and accumulation of the glycolipid globotriaosylceramide (Gb3) in various organs [8]. The heart is always affected, while cutaneous, renal, respiratory and nervous system involvement is also quite common [8]. Enzyme replacement therapy seems to reduce the Gb3 deposits [8].

Cardiac involvement includes lesions in the myocardium, in the valves and conduction pathways; left ventricular hypertrophy and valvular regurgitation are common echocardiography findings, while supraventricular tachycardias, atrial fibrillation or flutter, bundle branch blocks, AV conduction delay and nodal dysfunction may also be encountered [7, 8, 10]. Ventricular tachycardias – occasionally resistant or even fatal – occur in more than 8% of patients [10].

The ECG findings include a short PQ (PR) interval which is not followed by the classic delta wave of the WPW syndrome, features of left ventricular hypertrophy, pathological Q waves and ST interval changes [8, 10, 18, 19]. Accessory pathways connecting the atria and His bundle or ventricular tissue have been suggested as possible causes of pre-

TABLE 1. Publications on perioperative management, complications and outcome of patients with rare metabolic disorders associated with pre-excitation

First author (publication year)	Syndrome – clinical description	No. of pts – Sex/ Age	Type of surgery	Type of anesthesia/Drugs used	Complications/ *Management	Outcome/ Points of interest
August [15] (2009)	Danon disease	1 M/5 y	Multiple dental procedures	GA/premed: midazolam, acetaminophen IN: sevoflurane, N_2O MNT: sevoflurane, N_2O, fentanyl Other drugs: local anaesthetic infiltration	Brief ↑ HR during induction and emergence/no dysrhythmias or hypotension *None	• Hypertrophic cardiomyopathy is main feature: request recent full cardiac evaluation • Anaesthesia tailored to pt needs
Watanabe [18] (1995)	Fabry disease/ Renal failure/ ECG ischaemic changes	1 F/45 y	Cholecystectomy	GA IN: thiopental, vecuronium MNT: isoflurane, N_2O, vecuronium RV: atropine avoided	None reported	• Atropine avoided due to common symptom of reduced sweating, tears and saliva production in pts with Fabry disease
Krüger [21] (2017)	Fabry disease $n = 2$	2 F • 23 y • 67 y	• 2 laparoscopic gynecological surgeries • 2 orthopedic surgeries	GA in all cases 1st case: IN: fentanyl, propofol, rocuronium MNT: propofol, remifentanil/lidocaine RV: glycopyrollate/neostigmine 2nd case: IN: fentanyl, propofol, rocuronium MNT: desflurane or propofol, remifentanil	None	• Uneventful anaesthetics • Monitoring according to severity of disease • ERT should be continued periop
Woolley [22] (2008)	Fabry disease/ Renal failure/ LV hypertrophy	1 M/NA	Non-heart beating renal transplantation	GA IN: propofol, fentanyl, atracurium MNT: sevoflurane	Intraop bronchospasm/fiberoptic bronchoscopy *No specific measures/ spontaneous resolution	• Temporary dialysis/Good outcome • Lung involvement is common • Careful preop assessment of end-organ damage
Desena [24] (2011)	Pompe disease	1 F/3 m	Central vascular line	GA: sevoflurane, vecuronium	VF *DC shock/Propranolol for LV outflow obstruction	• High risk for fatal arrhythmias during GA
Wang [25] (2007)	Pompe disease (9 cases/1†)	$n = 9$; 5 F, 4 M 14 d – 2 y	Central line, biopsies, respiratory distress, hernia repair, gastrotomy, bronchoscopy, stomaplasty	GA in all cases • Anaesthetics: propofol, sevoflurane, etomidate, thiopental, ketamine, N_2O, midazolam • Opioids: fentanyl, morphine • NMBs: succinylcholine, vecuronium, rocuronium	• VF, VT, TdP in 7 pts receiving propofol or sevoflurane *Resuscitation (DC shocks, drugs, CPR) according to algorithm • Bradycardia (5 pts) *Atropine/epinephrine	• 3 deaths • LV mass correlates with mortality risk • Adequate preload in hypertrophic cardiomyopathy • Be prepared for resuscitation • Caution with propofol/sevoflurane • Ketamine may be preferable
Al Atassi [26] (2015)	Pompe disease	1 M/2 m	Central vascular line	GA IN: ketamine, fentanyl MNT: sevoflurane, N_2O	Severe hypotension *Fluids	• ICU/Good outcome • Extensive preop investigation/Assessment of LV mass index
Kim [27] (2010)	Pompe disease	1 F/56 y	Open right hemicolectomy	• GA & EA IN: sevoflurane, propofol, rocuronium (20 mg) MNT: sevoflurane • EA/Postop PCEA: ropivacaine, fentanyl	↑ HR, ↓ BP after induction *Dopamine, fluid loading	• ICU/Good outcome • RA strongly recommended • Avoid NMBs if possible
Kumbar [28] (2016)	Pompe disease	1 F/13 y	Orthopedic (kyphoscoliosis)	GA IN: dexmedetomidine, ketamine, morphine MNT: dexmedetomidine, sevoflurane	2nd postop day: mild pleural effusion *Diuretics/antibiotics	• IPPV for 5 d/Good outcome • Avoid NMBs if possible • Careful fluid management

TABLE 1. Cont.

First author (publication year)	Syndrome – clinical description	No. of pts – Sex/ Age	Type of surgery	Type of anesthesia/Drugs used	Complications/ *Management	Outcome/ Points of interest
Cilliers [29] (2007)	Pompe disease	1 F/31 y	Urgent CD (37 w) for preeclampsia	RA • CSE: hyperbaric bupivacaine 0.5%, fentanyl (spinally) • Bupivacaine 0.5% (epidurally) • Other drugs: labetalol, hydralazine, oxytocin	• ↓ BP after block established *Hydralazine infusion stopped • Recovery ward: frontal headache with photophobia *Fentanyl IV	• HDU/Good outcome • Suggestion to avoid succinylcholine (muscle damage and risk of hyperkalaemia)
McFarlane [30] (1986)	Pompe disease	1 F/5 m	Hickman line insertion, marrow aspiration, liver/muscle biopsy	• GA/premed: atropine IM/halothane, N_2O (surgery cancelled) • GA/premed: atropine IM/ketamine, vecuronium, N_2O RV: atropine/neostigmine	• After halothane induction: bradycardia, VF *Atropine, succinylcholine-intubation, CPR, epinephrine, DC shocks/Transfer to ICU	• Cancelled surgery was rescheduled and performed with ketamine (uneventfully) • Succinylcholine may cause hyperkalaemia
Ing [31] (2004)	Pompe disease	*n* = 5 5–12 m	13 procedures • Central vascular lines • Muscle biopsies	GA in all cases • Anaesthetics: ketamine, propofol, sevoflurane, thiopental, N_2O, midazolam • Opioid: fentanyl • NMB: rocuronium, RV: glycopyrrolate/neostigmine	• VF after sevoflurane/Propofol *DC shock/Epinephrine – surgery cancelled • ST depression on ECG (*n* = 2) *Phenylephrine (normalization)	• Cancelled surgery was rescheduled and performed with ketamine (uneventfully) • Caution with propofol/Not suitable • Ketamine may be preferable
Sato [32] (2007)	Pompe disease	1 M/4 y	Orthopedic operation for clubbed foot	GA & Caudal block • GA: sevoflurane, N_2O • Intubation without NMB • Caudal block (ropivacaine 0.375%)	None	Uneventful course
Sakakibara [33] (2009)	Pompe disease	1 F/6 m	• Central vascular line • Tracheotomy	• GA: ketamine, midazolam, N_2O • GA: sevoflurane Other drugs: dopamine, olprinone	NA	NA
Walker [34] (2007)	Pompe disease	*n* = 5 2 m – 2 y	11 procedures • Muscle biopsies • Vascular access devices	RA (caudal or peripheral block) • Femoral nerve block (levobupivacaine 0.25%) • Caudal block: levobupivacaine 0.125–0.25% Sedation: ketamine/midazolam, propofol (boluses 1 mg kg^{-1} in 1 case)	↑ HR, ↓ SpO_2, hypotension after propofol bolus *CPAP and O_2 100%	• Uneventful recovery • Caution with propofol: not suitable • Preserve preload and afterload in hypertrophic cardiomyopathy
Weida [35] (2012)	Pompe disease	1 F/23 y	CD	CSE (no further information)	None reported	• ICU/BiPAP • GA avoided because of impaired respiratory muscle strength
Dons-Sinke [36] (2014)	Pompe disease *n* = 2	2 F/41 y, 30 y	CD	• CSE: bupivacaine 0.5% + sufentanil (spinally)/ 2.5 ml ropivacaine 1% (epidural boluses) • Other drugs: phenylephrine infusion, oxytocin • Postop EA: ropivacaine 0.2% + sufentanil (infs)	None	HDU/Good outcome
Perniconi [37] (2016)	Pompe disease (ERT during pregnancy)	1 F/28 y	VD	Labor EA	None	• Uneventful VD • Non-invasive/Assisted ventilation peripartum • Multidisciplinary care is required
Rosen [38] (1986)	Pompe disease suspected	1 F/5 m	Muscle biopsy	• Femoral nerve block (lidocaine + epinephrine) • Sedation: glycopyrrolate, ketamine	None	Uneventful course

no. of pts – number of patients, † – disease undiagnosed, * – management of complication, BP – blood pressure, BiPAP – bilevel positive airway pressure, CD – Cesarean delivery, CPAP – continuous positive airway pressure, CPR – cardiopulmonary resuscitation, CSE – combined spinal-epidural anaesthesia, d – days, DC shock – direct current shock (defibrillation), EA – epidural anaesthesia/analgesia, ECG – electrocardiogram, EEG – electroencephalogram, ERT – enzyme replacement therapy, F – female, GA – general anaesthesia, HR – heart rate, HDU – high dependency unit, ICU – intensive care unit, IM – intramuscularly, IPPV – intermittent positive-pressure ventilation, IN – induction, Intraop – intraoperatively, IV – intravenously, LV – left ventricle, M – male, m – months, MNT – maintenance, NA – information not available, NMB – neuromuscular blockade/blocker, PC(E)A – patient controlled (epidural) analgesia, Premed – Premedication, Preop – preoperatively, Postop – postoperatively, Pts – patients, RA – regional anaesthesia, RV – reversal of neuromuscular blockade, SpO_2 – peripheral oxygen saturation, TdP – torsades de pointes, VD – vaginal delivery, VF – ventricular fibrillation, VT – ventricular tachycardia, y – years

excitation and AVRTs [20], while Gb3 deposits on AV junction can also cause accelerated AV nodal and subsequently AV conduction [9, 10].

Commonly used general anaesthetics, such as propofol, thiopental, isoflurane, sevoflurane and desflurane, combined with fentanyl or remifentanil, have been described as safe [18, 21, 22]. Intraoperative lidocaine IV infusion has also been used without problems [21]. Enzyme replacement therapy should be continued perioperatively, as no interaction with anaesthetics has been reported [21]. There are no data about regional anaesthesia in patients with Fabry disease.

Pompe disease

Pompe disease is a glycogen storage disorder characterized by musculature damage due to acid α-glucosidase deficiency [8]. It follows an autosomal recessive pattern of inheritance, and may present at any time of life, mainly as skeletal muscle weakness and hypotonia [8]. Glycogen deposition on cardiac muscle, nodes and conduction pathways causes left ventricular hypertrophy – with or without outflow obstruction – and serious arrhythmias [8, 23–25]. Specifically, the infantile Pompe disease has been strongly associated with pre-excitation [23]. Enzyme replacement therapy has a positive effect on cardiac hypertrophy, but seems less beneficial for arrhythmias [8].

Characteristic ECG findings include a short PQ (PR) interval and high QRS voltages due to the hypertrophic cardiomyopathy [8, 24]. Also, ST-segment depression and T-wave inversion may be seen [24, 26]. Echocardiography can reveal possible dynamic obstruction and assess the ventricular cavity volume; left ventricular mass index values higher than 350 g m^{-2} seem to correlate with the development of lethal arrhythmias [25-27].

There is no evidenced relation between a specific anaesthetic drug and cardiovascular complications [25]. Nevertheless, haemodynamic instability, especially after anaesthesia induction, has been reported in patients with Pompe disease, who seem to be extremely sensitive to the negative inotropic and vasodilating actions of general anaesthetics [24–27]. The use of dexmedetomidine (1 μg kg^{-1} in 10 min, followed by 0.5 μg kg^{-1} h^{-1} infusion) has been recently described as useful and haemodynamically stable [28]; it should be noted, though, that this particular patient had no signs suggesting serious cardiac involvement, according to preoperative ECG and echocardiography. Among neuromuscular blockers, succinylcholine should probably be avoided due to the risk of hyperkalaemia from the damaged muscular tissue [29, 30].

Most patients with Pompe disease requiring anaesthesia are infants undergoing muscle biopsy or placement of central venous catheters [24–26, 30–33]. Wang *et al.* described the anaesthetic management and complications in 9 patients with infantile Pompe disease: seven patients developed ventricular tachycardia, ventricular fibrillation or torsades de pointes, and three of them died [25]. Notably, all arrhythmias occurred under propofol or sevoflurane anaesthesia [25]. Based on complications they encountered, other authors also suggest that propofol should be used with caution or avoided [31, 34], while ketamine exhibits a more favorable profile [25, 30, 31, 34].

Regional anaesthetic techniques have been advocated [27, 32], especially in parturients undergoing caesarean delivery [35, 36]. Successful labour epidural analgesia [37], peripheral nerve blocks for muscle biopsies [34, 38], and patient-controlled epidural analgesia [27] have also been reported. Caution is needed, especially with spinal local anaesthetics and subsequent intense sympathetic block; a phenylephrine infusion for maintenance of systemic vascular resistance, and consequently blood pressure, seems useful [36].

OTHER RARE SYNDROMES ASSOCIATED WITH PRE-EXCITATION

Tuberous sclerosis

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by benign growths, mainly in the skin, heart, brain, kidneys and lungs [39-41]. It has an autosomal dominant inheritance, with mutations in TSC1 and TSC2 genes, which are responsible for the proteins hamartin and tuberin [41]. The characteristic triad of facial angiofibromas, mental retardation and seizures is found in 30% of patients [39, 40]. Cardiac rhabdomyomas are found in about 80% of patients, causing blood flow obstruction, cardiac failure or life-threatening arrhythmias, such as blocks, supraventricular tachycardias, ventricular tachycardia or ventricular fibrillation [40]. Pre-excitation is encountered in about 10% of patients, especially in those with cardiac tumors [40].

Surgical procedures may be performed for tumor excision due to the disease per se or for unrelated reasons. Rhabdomyomas, causing severe arrhythmias or heart failure, may require cardiac surgery [39, 40]. Sedation [42, 43], general anaesthesia [39, 40, 44–50] and regional anaesthesia [40, 44, 51, 52] have all been used in patients with TSC. Shenkman *et al*. studied retrospectively 24 paediatric patients who received 52 general anaesthetics, while epidural anaesthesia was performed in two cases [40]. Both inhalational and intravenous agents were used for induction of general anaesthesia. The authors suggest that an anticholinergic agent,

such as glycopyrrolate, should be readily available, since pre-existing conduction defects (i.e. sinus node dysfunction) render these patients prone to bradyarrhythmias [40]. This should be taken into account when drugs reducing the sympathetic outflow, such as central alpha-2 agonists (i.e. clonidine, dexmedetomidine), are used [42]. Publications on the perioperative management, complications and outcome of patients with TSC are presented in Table 2.

MELAS and LHON syndrome

The MELAS and LHON syndromes are rare genetic diseases with mutations in the mitochondrial DNA [7, 53]. The LHON syndrome is characterized by bilateral loss of central vision, while the MELAS syndrome involves mainly the musculoskeletal system and brain, manifested as muscle weakness, seizures and progressive dementia [7, 53]. Cardiovascular abnormalities may exist in both diseases, namely cardiomyopathy, conduction abnormalities (i.e. AV blocks) and pre-excitation [7, 53–56]. Specifically, about 13% of MELAS patients have pre-excitation ECG abnormalities of the WPW type; in some cases, ablation of the accessory pathway is required, because pre-excitation is symptomatic, causing recurrent episodes of supraventricular tachycardia [53–55, 57].

While information about the anaesthetic management of patients with LHON syndrome is lacking, there are several case reports describing the anaesthetic implications for MELAS syndrome. Unfortunately, most of them focus on the musculoskeletal abnormalities. Regarding their cardiovascular responses, patients with MELAS syndrome generally exhibit good tolerance to common anaesthetics, neuromuscular blockers and their standard reversals (i.e. anticholinergic/neostigmine) [54, 58–60]. Due to possible susceptibility to malignant hyperthermia, caution is needed with potentially triggering agents, such as succinylcholine and volatiles [54, 61–63], although no complications have been reported in published cases where these agents were used [54, 64, 65]. Drug interactions, especially between anticonvulsants and general anaesthetics/adjuvants, should also be taken into account [66]. Monitoring of the anaesthetic depth and neuromuscular transmission should be considered, since the patients may exhibit excessive sensitivity to sedatives and hypnotics [58, 67], and also an unpredictable response to NMBs [67]. The latter ones should better be omitted, if possible [55, 62].

Gurrieri *et al*. described 20 anaesthetics for 9 patients with MELAS syndrome; three of the patients had significant cardiac pathology, such as AV blocks, cardiomyopathy, WPW, and valvulopathy [54]. Propofol, etomidate and thiopental were given for induction, while desflurane, isoflurane or halothane were used in the majority of cases for maintenance of anaesthesia, without complications [54]. Total intravenous anaesthesia with propofol – with or without remifentanil – seems advantageous in terms of minimizing the risk of MH [61], and is preferred by many authors [58–61, 67–70]. Notably, although propofol infusion has been used uneventfully for a few hours [54, 58–60, 71], caution is needed in case of prolonged administration – i.e. for sedation in intensive care units – because it may further decrease the mitochondrial ATP production and cause severe acidosis [72]. Actually, mitochondrial dysfunction is considered to be involved in the pathophysiology of propofol infusion syndrome, and the death of a patient with LHON, who developed the syndrome after five days of propofol infusion, has been reported [73].

Regional anaesthesia may be preferred in order to avoid the risk of malignant hyperthermia or drug interactions [64, 66, 74]. Spinal anaesthesia has been used without complications [64, 66, 74, 75], but caution is needed to definitely exclude any pre-existing neurological problems [75]. Light sedation may be added to reduce patients' anxiety [66]. Surgical, postoperative and labour epidural anaesthesia/analgesia have also been used uneventfully [57, 58, 60, 66, 70, 72], and may effectively reduce the metabolic demands associated with pain and perioperative stress [72].

Hyponatraemia and hyperkalaemia are often encountered in these patients, and may increase the risk of arrhythmias [54, 65]. In this regard, succinylcholine should be avoided due to possible induction of hyperkalaemia [60]. Echocardiography should be performed, especially in patients with severe muscle weakness possibly masking their limited cardiovascular reserves [65].

Regarding the relation between other mitochondrial diseases and pre-excitation, little is known. Driessen *et al*. analyzed retrospectively the records of 122 children diagnosed with mitochondrial defects; cardiomyopathy or conduction defects were found in 10 patients (8.2%) [76]. Relative anaesthetic data are lacking [77–80]. Publications on the perioperative management of patients with rare mitochondrial diseases associated with pre-excitation are presented in Table 3.

GENERAL PRINCIPLES OF THE PERIOPERATIVE CARE IN PATIENTS WITH RARE MULTISYSTEM SYNDROMES ASSOCIATED WITH PRE-EXCITATION

Multidisciplinary perioperative care should be provided to patients with the abovementioned multisystem syndromes, according to the affected organs [37]. Pre-anaesthetic assessment should focus on end-organ damage, starting with a detailed

TABLE 2. Publications on perioperative management, complications and outcome of patients with tuberous sclerosis complex

First author (publication year)	Syndrome – clinical description	No. of pts Sex/Age	Type of surgery	Type of anesthesia/Drugs used	Complications/ *Management	Outcome/ Points of interest
Lee [39] (1994)	TSC	1 F/13 y	Surgery for scoliosis in two stages (in 2 w interval)	GA (same in both surgeries)/premed: temazepam IN: thiopentone, vecuronium MNT: isoflurane, N_2O Other drugs: hydralazine, labetalol, morphine	Postop • Pleural effusion, fever *Cefuroxime, chest drain tube • Seizures	• HDU recovery • Seizure risk should be considered when choosing anesthetics/RA may be good alternative to GA
Shenkman [40] (2002) Retrospective study	TSC: $n = 24$ Cardiac involvement: $n = 17$	14 M 10 F/ Mean age: 11 ± 8 y	52 various procedures in 36 years	GA in 47 cases, sedation in 4, combined GA/EA in 1 case, 1 EA for postop analgesia IN: various inhalational or IV anesthetics	• ↓ HR with ↓ BP/Junctional ↓ HR, ($n = 2$, with preexisting SN dysfunction) *Glycopyrrolate • Postop haemodynamic instability/death ($n = 1$, after cardiac tumor resection) • Postop seizures ($n = 3$)	• Cardiac involvement is very common • Caution with cases having preexisting SN dysfunction
Mason [42] (2009)	TSC	1 M/12 y	Brain MRI	Sedation with dexmedetomidine	Bradycardia *Glycopyrrolate: good response	• Association of bradycardia with the disease not certain
Sugi [43] (1996)	TSC	1/22 y	NA	N_2O 67% in O_2, fentanyl, midazolam	None	• Uneventful course
Causse-Mariscal [44] (2006)	TSC: $n = 2$ 1) Cardiac involvement 2) Renal involvement	2 F • 21 y • 34 y	1) Pregnancy termination (27 w) 2) Elective CD	1) EA: ropivacaine 0.08%, sufentanil, clonidine 2) GA IN: thiopental, succinylcholine MNT: sevoflurane, N_2O, sufentanil Postop analgesia: paracetamol, morphine Other drugs: oxytocin (10 U), continuation of antiepileptic therapy (valproate)	None	• Uneventful course • Preop testing: echocardiography, evaluation of renal function and lung involvement, brain and spinal cord MRI before neuraxial blockade for presence of tubers and intracranial hypertension
Cho [45] (2009)	TSC†/Lung involvement	1 F/33 y	Elective CD (placenta praevia)	GA/tracheal intubation/IPPV • N_2O (early discontinuation because of hypoxaemia) • No further details about anesthesia	Hypoxaemia (SpO_2: 70–90%)/ pulmonary hemorrhage *FiO_2: 1/Tracheal suctioning/Investigation/ Tansfer to ICU after extubation	• Good outcome • A detailed history and physical examination might have revealed the disease preop and RA could be preferred
Papaioannou [46] (2003)	TSC/Renal, lung and skin involvement	1 F/ 36 y	Renal transplantation	GA/premed: diazepam IN: midazolam, fentanyl, thiopental, succinylcholine MNT: isoflurane, fentanyl, atracurium Other drugs: furosemide, methylprednisolone, paracetamol, morphine	None	• Good outcome • Preop ECG and echocardiography necessary to exclude cardiac involvement
Nott [47] (1996)	TSC/Mental retardation, seizures	1 M/27 y	Dental conservation	GA with atropine, thiopental, fentanyl, vecuronium, isoflurane, N_2O	None	• Uneventful/No seizure worsening • Continuation of anti-convulsants
Tsukui [48] (1995)	TSC/Mental retardation, seizures	1 F/4 y	Graft operation of abdominal aortic aneurysm	GA and EA/premed: atropine, thiopental IN: sevoflurane, N_2O, vecuronium MNT: isoflurane, N_2O, epidural morphine Postop analgesia: bupivacaine epidurally	↑ EEG spikes after surgery *Diphenylhydantoin	• ICU • Uneventful course discharge on 32nd day

TABLE 2. Cont.

First author (publication year)	Syndrome – clinical description	No. of pts Sex/Age	Type of surgery	Type of anesthesia/Drugs used	Complications/ *Management	Outcome/ Points of interest
Ong [49] (2000)	TSC	1 F/30 y	Laparotomy for hemorrhage	GA/premed: fentanyl, midazolam IN: thiopental, succinylcholine MNT: desflurane, N_2O, vecuronium Postop: morphine, phenytoin, carbamazepine	None	• ICU/sporadic seizures/otherwise uneventful recovery • Avoid agents with proconvulsant properties
Bowditch [50] (2017)	TSC/Neurological abnormalities	1 F/32 y	CD (39 w)	GA IN: thiopental, fentanyl, succinylcholine MNT: isoflurane, N_2O Other drugs: oxytocin, ergometrine, misoprostol	None	• Caution with neuraxial techniques (request CNS imaging/consultation) • Cardiovascular investigation preop
Takahashi [51] (2009)	TSC	1 F/55 y	Hysterectomy	CSE (no further details)	None	Detailed preop assessment is suggested
McLoughlin [52] (2003)	TSC/Lung involvement	1 F/29 y	VD (ventouse assisted)	EA for labor Bupivacaine 0.1% + fentanyl	None	Preop assessment of respiratory system is mandatory

No. of pts – number of patients, † – disease undiagnosed, * – management of complication, BP – blood pressure, CD – Cesarean delivery, CNS – central nervous system, CSE – combined spinal–epidural anaesthesia, EA – epidural anesthesia/analgesia, ECG – electrocardiogram, EEG – electroencephalogram, F – female, GA – general anesthesia, HR – heart rate, HDU – high dependency unit, ICU – intensive care unit, IM – intramuscularly, IN – induction, Inf – infusion, Intraop – intraoperatively, IV – intravenously, M – male, m – months, MNT – maintenance, MRI – magnetic resonance imaging, NA – information not available, NMB – neuromuscular blockade/blocker, Premed – premedication, Preop – preoperatively, Postop – postoperatively, Pts – patients, RA – regional anaesthesia, RV – reversal of neuromuscular blockade, SR – sinus rhythm, SN – sinus node, SpO_2 – peripheral oxygen saturation, TSC – tuberous sclerosis complex, VD – vaginal delivery, w – weeks, y – years

history about the age of presentation, symptomatology, course and treatment of the disease [21]. The patients should undergo careful and extensive cardiological evaluation, regarding history of arrhythmias or syncopal episodes, symptoms of heart failure, detailed physical examination with vital signs and auscultation, and an X-ray for revealing possible cardiomegaly [40]. An ECG is mandatory, since it may show features of cardiac hypertrophy, arrhythmias, conduction abnormalities and patterns of pre-excitation [40, 60, 65, 68, 70]. A 24h-Holter may also be considered, according to cardiologic consultation [13]. Echocardiography is indicated in the majority of cases to exclude cardiomyopathy, to assess the cardiac function accurately [22, 60, 65, 68], and guide cardiovascular monitoring, anaesthesia and perioperative management. Non-invasive cardiac stress testing may also be required in selected cases [22]. In the case of cardiomyopathy, it should be kept in mind that the cardiac function may significantly deteriorate over a short period of time (i.e. over 3-6 months in Danon disease) [13, 15]. Regarding the preparation and optimization of patients who are scheduled for elective surgery, specialized consultation – including cardiological – and improvement of the function of all affected systems are mandatory, by the use of drugs or invasive methods, if required. Arrhythmias should be adequately suppressed and cardiac function should be optimized. Antiarrhythmics should be continued perioperatively, while implantable cardioverter defibrillators should be temporarily inactivated for the operation in order to avoid the risks of electromagnetic and electrocautery interference. Nevertheless, a back-up source for external defibrillation should be available. In the presence of conduction abnormalities, an external pacemaker should also be prepared before anaesthesia induction. Intravenous antiarrhythmic agents should be available for treatment of arrhythmias in haemodynamically stable patients [70], while a defibrillator should also be ready for use in case of hemodynamic compromise.

Intraoperative cardiovascular monitoring should include a five-lead ECG and invasive arterial pressure measurement, while cardiac output monitoring is also indicated in cases with significant cardiac function impairment. Arrhythmias associated with pre-excitation should be managed according to their type and hemodynamic consequences. In the algorithm of arrhythmia management, emphasis should be given to the first step, which is the prompt assessment of patient's hemodynamic status [81, 82]. In case of hemodynamic instability, the patient should undergo urgent electrical synchronized cardioversion [82]. Synchronized cardioversion is also indicated for supraventricular

TABLE 3. Publications on perioperative management, complications and outcome of patients with mitochondrial diseases

First author (publication year)	Syndrome – clinical description	No. of pts Sex/Age	Type of surgery	Type of anesthesia/Drugs used	Complications/ *Management	Outcome/ Points of interest
Gurrieri [54] (2011) Retrospective study	MELAS syndrome $n = 9$ (12 out of 20 anesthetics†)	4 M, 5 F/ 10–65 y	20 diagnostic or surgical procedures	GA in all cases IN: propofol, etomidate, thiopental (+ midazolam, fentanyl)/Non-depolarizing NMBAs ($n = 14$), succinylcholine ($n = 4$)†/RV: neostigmine ($n = 6$) MNT: volatiles (desflurane, isoflurane, halothane) ($n = 14$), propofol ($n = 3$)	• Non-sustained VT and ↓ BP *Vasopressin, fluids • Post-op renal failure ($n = 2$) • Periop ↓ Na and ↑ K ($n = 7$)	Transfer to ICU ($n = 7$) for monitoring, or anticonvulsant therapy titration or due to severity of condition
Uchida [55] (2010)	Mitochondrial encephalo-myopathy and WPW, and cardiomyopathy	1 F/39 y	Radical operation for proctoptosis	GA with laryngeal mask without NMB (no further information)	None	• Early postop course uneventful • Death due to cardiogenic shock (4th post-op day) unrelated to anaesthesia
Lee [56] (2011)	MELAS syndrome – preexcitation†	1 F/21 y	Dental procedures	Local anaesthesia with lidocaine	SVT/Change of consciousness *Amiodarone	• Good outcome • Pre-excitation found on follow-up ECG (propafenone started)
Okajima [57] (1998)	MELAS syndrome	1F/ 31 y	VD	Labor epidural analgesia with bupivacaine + fentanyl + epinephrine	None	Good outcome for both mother and fetus
Gentili [58] (2013)	MELAS syndrome	1 F/71 y	Laparotomy for colectomy and ovariectomy	GA and EA GA: TIVA with propofol, remifentanil, cisatracurium RV: glycopyrrolate/neostigmine Postop EA: levobupivacaine 0.125%, morphine	None	BIS recommended due to increased sensitivity to sedatives and anesthetics
Pedroviejo [59] (2010)	MELAS syndrome	1 M/38 y	Laparoscopic cholecystectomy	GA: premed: midazolam and TIVA with propofol, fentanyl/remifentanil, rocuronium Other drugs: metamizole, paracetamol, ondansetron	None	Uneventful course
Sasano [60] (2007)	MELAS syndrome	1 M/53 y	Gastrectomy	GA and EA IN: fentanyl, propofol, vecuronium MNT: propofol and EA (ropivacaine 0.375%) RV: atropine/neostigmine	None significant	• ICU transfer • Preop ECG/Echocardiography are mandatory • Maintain periop normothermia • Avoid succinylcholine (↑ K^+/MH)
Imai [61] (2010)	MELAS syndrome	1 F/58 y	Emergency total gastrectomy	GA with midazolam, propofol, ketamine, fentanyl and vecuronium (TIVA)	None	• ICU transfer/Good outcome • MH risk (caution with volatiles, succinylcholine)
Singh [62] (2004)	MELAS syndrome	1 M/6 y	Dental surgery	GA with propofol, alfentanil (no further information)	None	• Uneventful course • Postop monitoring • Avoid volatiles and NMBs for MH risk and myopathy
Itaya [63] (1995)	MELAS syndrome ($n = 2$)	2 F/11 y	Surgical treatment of hydrocephalus	GA IN: fentanyl, midazolam, rocuronium MNT: fentanyl, midazolam, N_2O	None	• Uncomplicated anaesthetic • Avoid volatiles and succinylcholine for MH risk
Maslow [64] (1993)	MELAS syndrome	1 M/40 y	Ankle fracture fixation	RA SA with hyperbaric tetracaine	None	• Uneventful course/3 y before: GA without problems under thiopental, succinylcholine, curare, isoflurane

TABLE 3. Cont.

First author (publication year)	Syndrome – clinical description	No. of pts Sex/Age	Type of surgery	Type of anesthesia/Drugs used	Complications/ *Management	Outcome/ Points of interest
Humeidan [65] (2016)	MELAS syndrome	1 F/33 y	Renal transplantation	GA/Premed: midazolam IN: propofol, cis-atracurium MNT: sevoflurane, fentanyl	None	Suggestions: • Preop echocardiography • Close electrolyte monitoring • Postop monitoring
Blair [66] (2011)	MELAS syndrome	1 M/33 y	Surgical fixation of femur fracture	RA • SA with bupivacaine 0.5% • Sedation: midazolam, fentanyl, ketamine	None	• Good outcome • RA solved the problem of GA with possible drug interactions
Aouad [67] (2005)	MELAS syndrome	1 F/13 y	Nissen fundoplication and gastro-jejunostomy	GA with propofol, remifentanil, cis-atracurium Postop analgesia: morphine, paracetamol	Initial cis-atracurium dose had no effect on TOF response *Two more doses were given without any effect (No clinical problem/Surgery completed)	• Successful extubation/Transfer to ICU/Uneventful course • Unpredictable response to NMBs • High sensitivity to anesthetics
Park [68] (2010)	MELAS syndrome	1 F/23 y	Laparoscopic appendectomy	GA: propofol, remifentanil, atracurium (TIVA) RV: glycopyrrolate/pyridostigmine Other drugs: ondansetron	None	Uneventful course
Thiel [69] (2001)	MELAS syndrome	1 M/6 y	Adenoidectomy – paracentesis	GA with propofol, fentanyl, N_2O	None	• Good outcome • Transient ↑ lactate post-op
Bolton [70] (2003)	MELAS syndrome	1 M/17 y	Fundoplication and insertion of feeding tube	GA and EA GA with midazolam, propofol, remifentanil, rocuronium (TIVA) Thoracic EA with bupivacaine	None	• Postop transfer to ICU • Preop ECG mandatory (in present case: Q waves in lateral leads) • RSI for the risk of aspiration
Thompson [71] (1997)	MELAS syndrome	1 M/20 y	Right cochlear implant	GA with midazolam (premed), propofol, fentanyl, cis-atracurium RV: glycopyrrolate/neostigmine Other drugs: droperidol 0.625 mg	None	• Uncomplicated recovery • Antiarrhythmics and a pacemaker should be available
Maurtua [72] (2009)	MELAS syndrome	1 F/31 y	Labor	Labor EA with bupivacaine + fentanyl + epinephrine	None	Uncomplicated course
Bell [74] (2017)	MELAS syndrome	1 F/36 y	Delivery of stillborn fetus	• PCA with fentanyl (IV) for labor • SA (bupivacaine 10 mg) for placenta removal	↑ K^+, metabolic acidosis, stroke-like episode, pulmonary edema *Standard appropriate measures	• CT for a stroke-like episode without findings • ICU transfer for further management
Hsiao [75] (2000)	MELAS syndrome	1/NA	Appendectomy	RA SA (no further information)	None	• Uncomplicated recovery • Attempt RA only if neurological abnormalities are excluded
Rosaeg [77] (1996)	Mitochondrial myopathy and WPW	1F/ 33y	CD	RA EA with lidocaine (+ epinephrine), opioid	None	• Uncomplicated course for both • Avoid shivering (risk of acidosis) • Avoid MH triggering agents • Monitoring of blood gasses/ lactate

TABLE 3. Cont.

First author (publication year)	Syndrome – clinical description	No. of pts Sex/Age	Type of surgery	Type of anesthesia/Drugs used	Complications/ *Management	Outcome/ Points of interest
Kelly[78] (1990)	Mitochondrial myopathy & WPW	1M/ 26y	Intranasal antrostomies/ turbinectomy	GA / premed: temazepam, verapamil IN: propofol, atracurium MNT: propofol, N_2O RV: glycopyrrolate/neostigmine	None	• Preop ECG revealed WPW previously undiagnosed
Fritz[79] (1988)	Mitochondrial encephalo-myopathy (Kearns-Sayre & MERRF)	1M/ 20y	Cataract extraction	Local anesthesia and sedation (no further information)	None	• Risk of cardiac arrest • Pacemaker availability • If serious AV block possible need for preop placement of pacemaker
Klockgether-Radke[80] (1993)	Mitochondrial myopathy: Kearns – Sayre	2/NA	NA	• GA with propofol, alfentanil, vecuronium • GA with propofol, fentanyl, vecuronium	↓HR in both cases (< 50 bpm) *atropine (successful)	• Often conduction abnormalities • Risk of MH

no. of pts – number of patients, † – disease undiagnosed, * – management of complication, AV – atrio-ventricular, BIS – bispectral index monitoring, BP – blood pressure, bpm – beats per minute, CD – Caesarean delivery, CPR – cardiopulmonary resuscitation, CSE – combined spinal-epidural anaesthesia, CT: computed tomography, d – days, EA – epidural anaesthesia/analgesia, ECG – electrocardiogram, EEG – electroencephalogram, F: female, GA: general anaesthesia, HR – heart rate, HDU – high dependency unit, ICU – intensive care unit, IM – intramuscularly, IN – induction, Inf – infusion, Intraop: intraoperatively, IV – intravenously, M – male, m – months, MELAS – mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome, MERRF – myoclonus epilepsy with ragged red fibers, MH – malignant hyperthermia, MNT – maintenance, NA – information not available, NMB – neuromuscular blockade/blocker, P(E)A – patient controlled (epidural) analgesia, Premed – premedication, Preop – preoperatively, Postop – postoperatively, Pts – patients, RA – regional anaesthesia, RSI: rapid sequence induction, RV: reversal of neuromuscular blockade, SA – spinal anaesthesia, SVT – supraventricular tachycardia, TIVA – total intravenous anaesthesia, TOF – train of four, VD – vaginal delivery, w – weeks, WPW – Wolff-Parkinson-White, y – years

tachycardia and atrial fibrillation resistant to drugs [82]. Immediate defibrillation, combined with cardiopulmonary resuscitation and drugs (adrenaline, amiodarone), is indicated in ventricular fibrillation or pulseless ventricular tachycardia, according to the Advanced Life Support algorithm [82].

Patients who are haemodynamically stable can be evaluated and treated according to the type of arrhythmia with appropriate maneuvers and/or drugs. Regular supraventricular (narrow-complex) tachycardia should be terminated by the use of vagal maneuvers, and IV adenosine [81]. Beta blockers (esmolol and propranolol) can also be helpful. Irregular wide complex tachycardia may indicate pre-excited atrial fibrillation; amiodarone can be given, while digoxin, verapamil, adenosine and diltiazem should be avoided, because they facilitate the conduction via the AP and may increase the risk of ventricular fibrillation [82].

Preload, afterload, inotropy and anaesthetics should be titrated according to the cardiac disease [15]. Adequate hydration to ensure optimal ventricular filling and maintenance of peripheral vascular resistance are mandatory for avoiding hypotension and coronary hypoperfusion in patients with hypertrophic cardiomyopathy [25, 28, 34]. Arrhythmogenic or triggering factors such as stress, fever, pain, intravascular volume depletion/haemorrhage, light anaesthesia and hypercarbia should be avoided [24, 27, 31]. Electrolyte and acid-base monitoring, with prompt correction of any abnormality, is also required to reduce the risk of arrhythmias [54, 65]. Careful selection of agents – regarding their chronotropic, dromotropic and inotropic action – and titration of doses is required, especially during anaesthesia induction [24–26]. Also, smooth recovery from anaesthesia, adequate postoperative analgesia, prevention of nausea/vomiting that may cause stress and tachycardia, should be taken care of. Finally, close postoperative follow-up and cardiovascular monitoring in a high dependency unit are usually required for early diagnosis and prompt treatment of arrhythmias and other cardiovascular complications [26, 27, 35, 36, 40, 65, 68].

LIMITATIONS

In the present review, we used information from a few retrospective studies, and mainly from case series and reports. For some conditions the data were limited, since only a small number of case reports were identified. Nevertheless, we believe that the present review may help to achieve a better understanding of rare genetic multisystem diseases associated with pre-excitation and provide some useful information on their perioperative management.

CONCLUSIONS

The anaesthetic management of patients with rare genetic multisystem diseases associated with pre-excitation may be quite challenging, especially in case of emergencies, when there is not adequate time for thorough investigation and clinical optimization. In these patients pre-excitation usually co-exists with structural cardiac abnormalities, thus increasing the risk of serious perioperative arrhythmias and other life-threatening cardiovascular complications. A multidisciplinary approach and perioperative care are required, according to the affected organs. Also, close observation, invasive cardiovascular monitoring and a high level of alertness are mandatory for prevention and prompt treatment of arrhythmias.

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