Anesthesia for patients with *PTRF* mutations

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Background

What is *PTRF* (polymerase I and transcript release factor)?

- *PTRF* is a caveolar-associated protein.
- *PTRF* is suggested to play an essential role in the formation of caveolae and the stabilization of caveolins.¹⁾

What are caveolae?

- Caveolae are invaginations of the plasma membrane.
- They are involved in many cellular processes, including clathrin-independent endocytosis, cholesterol transport, and signal transduction.¹⁾

Kagawa et al.,
Glia, 2015

What is caveolin?

- Caveolin is a membrane protein that characterizes caveolae.
- There are 3 subtypes of caveolin: Cav-1, Cav-2, and Cav-3
- Cav-1 and Cav-2 are present in most cell types.
- Cav-1 plays an important role in cholesterol trafficking and homeostasis.²⁾
- Cav-3 is specific to skeletal, smooth, and cardiac muscles.
- Genetic aberrations in Cav-3 are reported to cause muscular disorders.³⁾
- An interaction between the ryanodine receptor and Cav-3 is known.

What are the symptoms of *PTRF* mutation?

- Congenital generalized lipodystrophy (CGL) developed from infancy.
 - Abnormal metabolism of lipids and glucose.
 - Muscular disease (muscular hypertrophy, atrophy and mounding).
 - Cardiomyopathy, long QT syndrome.
 - Renal impairment, IgA nephrosis.
 - Immunodeficiency.
 - Disturbance of growth.
- Few *PTRF* mutations have been reported,
but there are no reports regarding anesthesia.

Case report

A 29-year-old man (height, 126 cm; weight, 22 kg) harboring *PTRF* mutations was scheduled for a mandibular dentigerous cystectomy.

His profile

- Neonatal period: Patient was born with neonatal asphyxia (full term birth, 3720 g), had cerebral hemorrhage, and was a ‘floppy’ infant.
- 4 months of age: Patient underwent muscle biopsy and was diagnosed as having non-Fukuyama dystrophy.
- 3 years of age : Patient began treatment for nephrosis
- 19 years of age: Patient fainted twice. He underwent a Holter ECG exam and was diagnosed as having long QT syndrome (LQTS). He began to receive medication.
- 22 years of age: Patient was diagnosed, by genetic analysis, with a metabolic disorder related to caveolin owing to *PTRF* mutations.
- 29 years of age: Patient developed cholecystitis and came to our hospital. The cholecystitis was not clinically urgent, but the purulent cyst needed to be treated.

Primary symptoms

CGL associated with myopathy
Long QT syndrome
Refractory nephrosis
Abnormal lipid metabolism
Skeletal dysplasia

Preoperative examination

Blood exam: TP 6.6 g/dl, Alb 3.7 g/dl,
UN 9 mg/dl, Cre 0.2 mg/dl, eGFR 429, CK 282 U/l, T-cho 243 mg/dl
ECG: 66 bpm QT/QTc 370/383z

Medication

methylprednisolone 4 mg, mexiletine 100 mg, propranolol 10 mg,
levocarnitine, alfacalcidol, cyclosporin A, pravastatin

Three important patient concerns

- ① Avoiding malignant hyperthermia
- ② Concerns about abnormal lipid metabolism
- ③ Counterplan for arrhythmia including Torsade de Pointes

Our plan

- ① Avoid exposure to inhalation agents
- ② Avoid using lipid-soluble agents, such as Propofol
- ③ Use defibrillation pads and prepare medications for treatment

References

- 1)Hayashi YK, Matsuda C, Ogawa M, et al. J. Clin. Invest. 2009; 119(9):2623-33.
- 2)Shi Y, Tan SH, Ng S, et al. Autophagy. 2015,11(5):769-784
- 3)Song DW, Lee KE, Ryu JY, et al. BBRC. 2015, 463: 975-981

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Oxygen (l/min)	6	1	2	5	3				
Air (l/min)	2		0.5						
Remifentanyl (μg/kg/hr)		100μg	0.1	0.15	0.25	0.15	0.1		
Dexmedetomidine(μg/kg/hr)	4	0.7	0.5	0.7	0.4				
Midazolam (mg)	1	1	1	2	2				
Rocuronium (mg)		5	5						
Atropine (mg)	0.2								
Hydrocortisone (mg)	50								
Sugamadex (mg)						50			
Ephedrine (mg)	25								
Flumazenil (mg)							0.2	0.1	0.2
Lidocaine (mg)			9						

Preparation

- Wash out inhalational anesthetics (flushing oxygen at 10 L/min for 30 min)
- Prepare intubation tubes of several sizes (#5-7)
- Ready the airway management system, including a pediatric Airway scope®, a McGrath®, Defibrillator, a Bispectral Index Score (BIS) monitor, and a TOF monitor

Induction of anesthesia

- Load dexmedetomidine (DEX) 4μg/kg/hr for 15 min
- Spray lidocaine around the larynx
- Add up to 7 mg midazolam (MDZ)
- Administer 100 μg remifentanyl and 10 mg rocuronium prior to intubation
- Intubate using a McGrath (tube size #6)

Maintenance of anesthesia

- Use local anesthesia for the surgical field
- Continuously administer DEX and remifentanyl

Extubation

- Administer sugammadex and flumazenil before extubation
- Continuously administer flumazenil after extubation

Postoperative management

- One-day (20 hr) stay in the ICU
- Titrate flumazenil according to the BIS score.
- Apply defibrillator pads until the next day.
- Check intraoperative or unpleasant memories during the postoperative visit.

Our observations in this case

- Contrary to expectation, the susceptibility to treatment was normal.
- BIS score was high during the operation.
- The patient took longer than normal to regain a conscious state.

Discussion

- Despite the high BIS score, the patient had no intraoperative memory, suggesting the unreliability of the BIS score or existence of anterograde amnesia owing to MDZ.
- Drug used for sedation was excessive for smooth and clear awakening. Shorter-acting, non lipid-soluble agents might be better, but these are not routinely available.

Learning points

~ regarding anesthesia in patients with *PTRF* mutations ~

- Local anesthesia is recommended, if possible.
- Avoid using inhalation or lipid-soluble agents.
- Counterplan for long QT syndrome.
- Be aware of various complications of the disorder.