Acta Anaesth. Bel., 2024, 75 | Suppl. 1: 183-193

Masterthesis / Review

Safe anesthesia practice in patients with lipin-1 deficiency: a case report and narrative review

C. Royon[1,2], A. Parashchanka[1]

[1]*Department of Anesthesia, Ghent University Hospital, Belgium;* [2]*Military Hospital Queen Astrid, Brussels, Belgium.*

Corresponding author: Royon C., Department of anesthesia; C. Heymanslaan 10, 9000 Gent, Belgium.

Abstract

Lipin-1 deficiency is a rare recessive autosomal disorder which causes recurrent episodes of rhabdomyolysis. These episodes are frequently initiated by a triggering event such as febrile illness, exercise or fasting. Anesthesia has also been claimed to provoke rhabdomyolysis in these patients. These episodes start in early childhood and often require intensive treatment which is complicated by a high morbidity and mortality.

We present a review of the available literature and analyzed the data of 80 lipin-1 deficient patients. We found 79 cases published in 24 articles. We also report our own patient.

Analysis of this data could not provide documentation proving a causal relationship between anesthesia and a rhabdomyolysis episode. We found four case reports of anesthetic procedures in lipin-1 deficient patients. These patients had been given an intravenous glucose infusion to avoid the induction of a catabolic state. The procedures were uncomplicated and did not provoke rhabdomyolysis.

We present the case of a 14 year old boy requiring several surgical and anesthetic procedures. Administration of intravenous glucose was part of our strategy to prevent the perioperative occurrence of rhabdomyolysis. We provide detailed information about the agents we used for the anesthetic management of this patient.

We hypothesize that not the anesthetic exposure but other factors might cause rhabdomyolysis in the perioperative period. These factors include fasting, inflammation, the surgical stress response and a mismatch in metabolic supply and demand. We provide recommendations for anesthetic procedures in lipin-1 deficient patients.

Keywords: **Rhabdomyolysis, anesthesia, lipid metabolism, fasting.**

Introduction

Lipin-1 deficiency has only recently been described in humans. The first case series was published in 2008. It was reported as a cause for recurrent rhabdomyolysis and myoglobinuria[1]. Rhabdomyolysis is an acute syndrome due to extensive skeletal muscle breakdown. This results in the release of cellular metabolites and proteins from muscular origin into the systemic circulation. These include, amongst others, creatine kinase (CK) and myoglobin. Rhabdomyolysis can result in serious morbidity and mortality[2].

Lipin-1 deficiency (OMIM 68200) is a recessive disorder, requiring biallelic pathogenic mutations of the LPIN1 gene to provoke the clinical picture of recurrent myoglobinuria[1,4]. Prevalence of the deficiency is not precisely known. We found only 79 unique patients that have been described in literature. A study by michot et al. retrospectively analyzed 171 patients from an international recruitment. Their study revealed lipin-1 deficiency in 18 patients, a prevalence of 10.5%. The recruited patients experienced unexplained muscular symptoms such as rhabdomyolysis and exercise-induced myalgia. The patients previously had negative metabolic work-up which included plasma amino acids, acylcarnitine profile, lactate, glucose and screening for urinary organic acids[9].

Lipin-1 deficiency causes early onset recurrent episodes of life threatening rhabdomyolysis. The rhabdomyolysis episodes is believed to be due

The abstract has been presented at the BeSARPP graduation day 01/06/2024.
The scription has not been submitted for publication elsewhere.

to loss of the enzymatic phosphatidate phosphatase 1 (PAP1) activity. These episodes requiring hospitalization, intensive treatment and have a high mortality rate. Bouts of rhabdomyolysis were preceded by a provoking factor such as fasting, intense exercise, fever or (viral) illness. Three publications linked anesthetic exposure to the occurrence of rhabdomyolysis in patients with lipin-1 deficiency[4,9,12].

In order to avoid peri-operative rhabdomyolysis in a lipin-1 deficient patient, we performed a literature search, in which we wanted to investigate the physiopathology of lipin-1 deficiency and find evidence about anesthetic exposure and the occurrence of rhabdomyolysis.

Second, by presenting our own case, we want to contribute to the available knowledge about patients with lipin-1 deficiency undergoing anesthetic procedures.

Methods

This narrative review consist of a literature review analyzing most published cases of lipin-1 deficiency. The articles were selected by two researchers. The search strategy was not predetermined and consisted of the keywords lipin-1 deficiency and Lpin-1 deficiency in the PubMed database and google. The latest literature update was in December 2022. The references of the included articles were checked to ensure no published cases have been missed.

We found a total of 31 articles eligible after a first screening based on title and abstract.

Inlcusion criteria consists of humans with biallelic LPIN1 mutations. One article was excluded due to rhabdomyolysis in a patient with monoallic LPIN1 mutation.

Due to differences in clinical presentation and phenotype between lipin-1 deficiency in mice and humans[7], experimental data from mice was excluded. One article described the physiopathology in mice and was excluded for this reason. Articles about normal lipin-1 function were excluded as well.

In the second part of this paper we also present retrospective data about our patient with lipin-1 related acute recurrent myoglobinuria. The data consists of a summary of the clinical picture of an acute rhabdomyolysis episode and the details of six anesthetic procedures. The patient underwent four anesthetics before he was diagnosed with lipin-1 deficiency. The patient and his parents consented to the publication of this data.

Results

Our literature study managed to identify a total of 79 unique lipin-1 deficient patients, published in 24 publications. Patient data and clinical characteristics found in the publications and supplementary materials were encoded in a database. We added our case to the database, identifying a total of 80 lipin-1 deficient cases. This data is presented in the results section.

Physiopathology of lipin-1 deficiency

The LPIN1 gene (OMIM #605518), located on chromosome 2p25.1 translates into the lipin-1 protein. Lipin-1 is predominantly expressed in skeletal muscle and adipose tissue. Lipin-1 is a magnesium dependent enzyme, which has two functions.

First, it has an enzymatic function. PAP1 is involved in the synthesis of triacylglycerides and phospholipids. Triglycerides are the most important molecule for energy storage in the human body[8]. The impairment of the glyceride metabolism leads to accumulation of lipid droplets[4,7,9]. Free fatty acid content is also increased in lipin-1 deficient patients[7]. In vitro studies of resting myoblasts of lipin-1 deficient patients, showed that they had lower ATP stores compared to controls[7].

Second, it acts as a transcriptional co-activator. This system is involved in the expression of genes encoding fatty acid β-oxidation and mitochondrial respiratory chain enzymes[3-5].

Lipin-1 expression is increased by fasting, diabetes and in response to endogenic and exogenic glucocorticoids, such as dexamethasone[3].

Inflammation and abnormal lipid metabolism have been identified to play an important role in the pathophysiology. Proinflammatory cytokines, lipopolysaccharides and zymosan are known inflammatory inducers which suppress LPIN1 expression[4]. Catabolic stress leads to the production of these inflammatory inducers and the subsequent reduction in lipin-1 activity is hypothesized to cause rhabdomyolysis[6]. This has been demonstrated in vitro, where myoblasts from lipin-1 deficient patients were exposed to tumor necrosis factor α and interleukin-1β. The effect this had on the myoblasts, consists of a massive increased accumulation of lipid droplets and triacylglycerol content, compared to basal circumstances. Another effect of pro-inflammatory stimulation was a further decrease in ATP content[7].

Experimental measurements of fatty acid oxidation (FAO) was found to be normal at rest, but was not able to increase during exercise[11].

The net effect of lipin-1 deficiency results in an energy deficiency in catabolic conditions. The myoblasts are unable to use the stored fatty acids and lipid droplets as an energy source, which leads to lysis of skeletal muscle[12].

Phenotype

Patients affected by lipin-1 deficiency have normal height, weight, fat distribution and cognitive abilities. Cardiac abnormalities, however, have been described in 17 patients[9,16,17,19,22,27]. Nine patients with cardiomyopathies were reported[9,17,19]. Cardiomyopathies included dilated cardiomyopathy, hypertrophic cardiomyopathy and infiltration of adipocytes with fibrosis of the myocardium[9,19]. Prospective screening of four lipin-1 deficient patients with cardiac 1H-magnetic resonance spectroscopy showed significant myocardial steatosis in all patients[17]. These lipid accumulations exert a toxic, arrhythmogenic effect on the myocardium[17,19]. Ten patients with cardiac involvement or cardiac complications died. Due to incomplete reporting we cannot determine if cardiac arrythmias were secondary to underlying cardiomyopathy or to rhabdomyolysis induced hyperkalemia. The details about cardiac involvement in lipin-1 deficiency can be found in Table I.

LPIN1-related acute recurrent rhabdomyolysis

Triggers

We have data about triggering events of 57 patients. Due to incomplete reporting, we identified 23 missing values about triggering events in our literature study.

Infection has been observed to be the most common trigger for rhabdomyolysis and was reported in at least 48 patients (84.2%)[1,2,4–6,8-10,12,15,16,18,20–28]. Febrile illness, gastro-intestinal infections, respiratory infections and subclinical viral infections all have been mentioned in publication to have triggered rhabdomyolysis.

Fasting was the second most common trigger, as this has been reported to have triggered rhabdomyolysis in at least 11 patients (19.3%)[4,9,14,18,20,22,25].

Intense or prolonged exercise has been reported to have caused rhabdomyolysis in nine patients (15.8%)[2,5,11,12,14–16,18,21].

"Fasting with local anesthetic" has been noted to have caused rhabdomyolysis in three patients (5.3%)[4]. General anesthesia was reported to cause rhabdomyolysis in two patients (3.5%)[4,12]. In at least one patient (1.8%) "anesthesia and/ or fasting" triggered a bout of rhabdomyolysis[9].

In our literature review, we found two case reports and one abstract describing an anesthetic procedure for a patient with LPIN1 deficiency. Burstal described a volatile anesthetic and Kaur et al. and Dutoit et al. described a total intravenous anesthesia (TIVA) technique[25,26,28]. All anesthetics

Table I. — Cardiac involvement in lipin-1 deficiency.

Reference	Number	Presence and and type of arrythmia	Myocardium	Hyperkalemia	Status
Michot 2012 [9]	1	Probable, unspecified	CMP	Probable	Deceased
	2	Probable, unspecified	Dilated CMP	Probable	Deceased
	3	Probable, unspecified	Dilated CMP	Probable	Deceased
	4	Probable, unspecified	NM	Probable	Deceased
	5	Probable, unspecified	NM	Probable	Deceased
	6	Probable, unspecified	NM	Probable	Deceased
Bergounioux 2012 [19]	7	VT	Normal	Suggestive ECG changes	Deceased
	8	Asystole	Hypertrophic CMP	Suggestive ECG changes	Deceased
Jaradat 2016 [22]	9	"Cardiac complications"	NM	NM	Deceased
Legendre 2018 [17]	10	NM	LV dysfunction	Not present	Alive
	11	Not present	Myocardial steatosis	Not present	Alive
	12	Not present	Myocardial steatosis	Not present	Alive
	13	Not present	Myocardial steatosis	Not present	Alive
	14	Not present	Myocardial steatosis	Not present	Alive
Kanderi 2022 [27]	15	Arrythmia	NM	Present	Alive
Kahraman 2022 [16]	16	VT	NM	Present	Deceased
	17	SVT	NM	NM	Alive

In patients 1 and 8, autopsy revealed infiltration of adipocytes and fibrosis of the myocardium, these are signs of arrhythmogenic ventricular dysplasia. Patient 7 had LV dysfunction on echocardiography. Unspecified: type of arrythmia is not mentioned in the publication. Abbreviations: CMP: cardiomyopathy; VT: ventricular tachycardia; ECG: electrocardiogram; NM: not mentioned in the publication; LV: left ventricle; SVT: supraventricular tachycardia.

were uncomplicated and did not provoke rhabdomyolysis. Table II summarizes the data from these three case reports. All patients were provided with an intravenous glucose infusion to provide caloric input during preoperative fasting.

One patient (1.8%) experienced two episodes of rhabdomyolysis after a stressful event. The proposed mechanism of this trigger is hypothesized to be due to stress induced increase in sympathetic tone. This leads to release of catecholamines into the circulation. These catecholamines influence metabolism by stimulating lipolysis and releasing fatty acids. In lipin-1 deficiency the muscle cells cannot process these increased levels of fatty acids which is thought to lead to rhabdomyolysis[8].

Clinical picture of acute rhabdomyolysis

The clinical picture is highly variable and varies from a subclinical elevation in plasma CK levels to life threatening rhabdomyolysis with multisystem involvement. There are more than 20 LPIN1 mutations described. A clear genotype-phenotype relationship has not yet been determined[10].

The overwhelming clinical presentation necessitated intensive care admission in at least 15 patients[5 8,10,16,18-21,26,27]. Hyperkaliemia has been observed in six patients[16,19,27]. With measured levels as high as 8.3 mmol L-1[27].

Mortality of rhabdomyolysis episodes in patients with lipin-1 deficient is high. Out of the 80 patients we analyzed, 17 were recorded to have died, accounting to 21.3% overall mortality. Of these 17 patients, cardiac involvement such as cardiomyopathy or arrythmias were reported in 10 cases, or 58.8% of the deceased patients.

Treatment of rhabdomyolysis usually consists of hyperhydration and supporting normal organ function[29]. Early detection and treatment of the life threatening complications are extremely important. These complications include hyperkalemia, renal failure and cardiac arrythmias.

Kandari et al. also promotes the use of 10% dextrose infusion. Their suggestion however, is to use a 10% dextrose with 0.9% NaCl infusion. They recommended an infusion rate at 1.5 times the maintenance rate. This should correspond to a glucose delivery of 6-10 mg Kg-1 min-1[27].

The use of an intravenous 10% dextrose infusion has shown to significantly increase the exercise tolerance in experimental conditions[11].

Insulin was used to treat hyperglycemia, and prevent hyperkalemia. Its use allows for

Table II. — Anesthetic procedures in literature.

Reference	Type of surgery	Age (years)	Weight (Kg)	Type of anesthesia	Medications	Dose	IV infusion
Burstal 2018 [25]	Adenotonsillectomy	7	NM	Volatile	Dexamethasone	0,16 mg Kg-1	Glucose 10%/NaCl 0,9%, rate not mentioned
					Morphine	0,1 mg Kg-1	
					Ondansetron	0,16 mg Kg-1	
					Paracetamol	NM	
					Parecoxib	1 mg Kg-1	
					Remifentanil	1 mcg Kg-1 bolus	
					Sevoflurane	NM	
					Thiopentone	5 mg Kg-1	
Kaur et al. 2020 [26]	Catheter placement	3	NM	TIVA	Clonidine	1 mcg Kg-1	Glucose 10%/NaCl 0,9% at 60 mL hr-1
					Midazolam	premedication 0,5 mg Kg-1	
					Propofol	10 - 15 mg Kg-1 hr-1	
					Remifentanil	0,1 - 0,15 mcg Kg-1 min-1	
Dutoit et al. 2012 [28]	Adenoidectomy	5	7,5	TIVA	Fentanyl	20 mcg	Glucose 5%/NaCl 0,45% at 54 ml hr-1
					Midazolam	1 mg	
					Parecoxib	NM	
					Propofol	40 mg bolus 12mg Kg-1 hr-1 infusion	
					Remifentanil	0,2 mcg Kg-1 min-1	

Table II summarizes the data about three anesthetic case reports in lipin-1 deficient patients. These three patients did not experience rhabdomyolysis in the perioperative period. A glucose infusion was provided in all patients as a preventive measure to avoid the induction of rhabdomyolysis due to preoperative fasting. Abbreviations: TIVA total intravenous anesthesia; NM not mentioned.

the infusion of high concentration glucose to be continued without the adverse effect of hyperglycemia. The insulin is believed to help terminate rhabdomyolysis due to its anabolic effect[12,27].

Prevention of rhabdomyolysis

Pichler et al. formulated a preventive strategy to prevent rhabdomyolysis. They recommend a high caloric diet in situations at risk of catabolism, e.g. viral infections or excessive physical activity. A glucose 10% infusion should be initiated in situations when patients need to be fasted, including for anesthetic procedures[12].

Lipin-1 deficient patients have been instructed to avoid strenuous physical activity[5,15,21].

Avoidance of the fasting state has been recommended by several authors[8,17,19,21]. One publication specifies that fasting should not exceed eight hours[5]. General guidelines in metabolic disease recommend that fasting should not exceed six hours[35].

Case report

We present the case report of a 14-year old boy with a homozygote LPIN1 deficiency. The patient underwent multiple surgical and anesthetic procedures.

The history of our patient starts at the age of 18 months when he developed life-threatening rhabdomyolysis after a mild gastroenteritis with vomiting, diarrhea and reduced oral intake. Due to signs of severe rhabdomyolysis, myoglobinuria and metabolic acidosis, he required emergency admission to the pediatric intensive care unit. Blood level of CK increased as high as 826.000 U L-1 (reference <219 U L-1). The patient had electrolyte disturbances due to the rhabdomyolysis, a hyperkalemia and a hypocalcemia. He was treated with mechanical ventilation, massive intravenous fluid repletion, hemodialysis and electrolytes were corrected.

During his hospitalization, he underwent five operative interventions under general anesthesia. The surgical procedures consisted of tissue debridement for extravasation injury, placement of a gastrostomy tube and a diagnostic muscle biopsy. At the time of the first four procedures, his underlying pathology was unknown and anesthesia was maintained with sevoflurane. After being diagnosed with lipin-1 deficiency, the anesthetic approach was adapted and the fifth intervention was performed using a TIVA technique with propofol. All five interventions proceeded uneventful intra- and postoperatively. More details about the administered products can be found in Table III.

Despite being asymptomatic between these episodes, his basal CK levels were supranormal with the highest reported value being 500 U L-1.

Acetabuloplasty

At the age of 12, the boy presented for right hip acetabuloplasty after developing avascular necrosis. His weight was 82 kg with a length of 164 cm. He was in a good general condition. His preoperative echocardiography and ECG were normal.

The patient was admitted to hospital the day before surgery. A preoperative blood sample was taken and analyzed. The results showed normal values, except for his CK levels, which were 570 U L-1. Avoidance of the fasting state was achieved by intravenous administration of a 10%-dextrose infusion at a rate of 1ml Kg-1 hr-1. He was allowed to ingest food until midnight and clear fluids until two hours preoperatively.

In the operation theatre, the intravenous dextrose infusion was continued throughout the complete process. Anesthesia was induced with propofol 1.5 mg Kg-1, sufentanil 0.1 µg Kg-1, and rocuronium 0.5 mg Kg-1. The patient was intubated and mechanically ventilated with oxygen enriched air achieving an inspired oxygen concentration of 30%. Capnography was used to measure end-tidal carbon dioxide (Et CO2). Ventilation was adjusted to ensure an Et CO2 concentration around 40 mmHg.

Anesthesia was maintained with sevoflurane at an end-expiratory concentration of 2.3%, corresponding to an age-adjusted minimum alveolar concentration of 1. Depth of anesthesia was monitored with bispectral index (BIS). BIS values fluctuated between 40 and 60. A central venous line was placed. Subsequently, an ultrasound guided right suprainguinal fascia iliaca compartment block was performed with 40 ml of levobupivacaine 0.25%. Next the patient was meticulously positioned, with attention to avoid compression injury. The body temperature remained around 36°C without active warming.

Table III provides a full list of medications given in the perioperative period. Fluid balance was maintained with crystalloids at 6 ml Kg-1 hr-1 along with the ongoing 10%-glucose infusion at a rate of 1 ml Kg-1 hr-1.

The patient remained hemodynamically stable throughout surgery and recovery. Postoperatively, the patient received patient controlled intravenous analgesia with morphine, which could be discontinued on the first postoperative day.

In the postoperative period, CK level analysis was performed every two hours in order to monitor

Table III. — Surgical and anesthetic procedures from our case.

Age (years)	weight (Kg)	Surgical procedure	Type of anesthesia	IV medication* (total dose or infusion rate)	Anesthetic duration (minutes)	Surgical duration (minutes)
1	13	debridement necrotic tissue	Sevoflurane inhalation	sufentanil 5 mcg cis-atracurium 2 mg ketamine infusion 12 mg hr-1 midazolam 1,5 mg hr-1 morphine 1 mg hr-1 clonidine infusion	65	30
1	13	muscle biopsy	Sevoflurane Inhalation	glucose 5% 20 ml hr-1 sufentanil 7,5 mcg clonidine infusion	65	45
1	13	debridement necrotic tissue	Sevoflurane inhalation	propofol 50 mg sufentanil 2 mcg	60	40
1	13	gastrostomy	TIVA	propofol 40 mg bolus propofol infusion 200 mg hr-1 cefazolin 500 mg	35	20
12	82,5	acetabuloplasty	Sevoflurane inhalation + LRA	glucose 10% 84 ml hr-1 propofol 100 mg sufentanil 20 mcg rocuronium 40 mg NaCl 0.9% 1500 ml dexamethasone 5 mg cefazolin 2 gram clonidine 150 mcg paracetamol 1 gram ondansetron 4 mg morphine 4 mg levobupivacaine 100 mg PN Diclofenac 75 mg	135	70
14	100	epiphysiodesis	Sevoflurane inhalation	glucose 10% 85 ml hr-1 propofol 200 mg sufentanil 15 mcg midazolam 2 mg ibuprofen 600 mg dexamethasone 5 mg cefazolin 2 gram clonidine 150 mcg paracetamol 1 gram piritramide 2 mg	65	30
*unless stated otherwise.						
Table summarizing the patient details, information about the type of surgery and type of anesthesia, the medications and dose administered during the operative intervention and the surgical and anesthetic duration. Abbreviations: IV: intravenous, TIVA: total intravenous anesthesia; LRA: loco-regional anesthesia, PN: peri-nervous.						

for rhabdomyolysis. The highest measured CK level occurred on the first day after surgery, reaching a value of 1.426 U L-1. The CK trend is visualized in figure 1.

Epiphysiodesis

At 14 years old, the patient underwent an epiphysiodesis of the right femur. Again the patient was admitted to hospital the night before surgery. He had a preoperative blood analysis and an intravenous infusion of glucose 10% was started at 85ml hr-1.

The glucose infusion was continued and anesthesia was induced using midazolam, propofol and sufentanil. Airway management was achieved by insertion of a supraglottic device. Anesthesia was maintained with sevoflurane. The patient received antibiotic and PONV prophylaxis. The full list with perioperative medications is summarized in Table 3. His core temperature was continuously monitored and remained stable. The vital signs remained stable and the procedure was uncomplicated. It can be noted that the CK levels even decreased during hospitalization, as pictured in Figure 1. The patient was discharged from hospital the day after surgery.

Discussion

In the previous section we reviewed the physiopathology and the triggers leading to

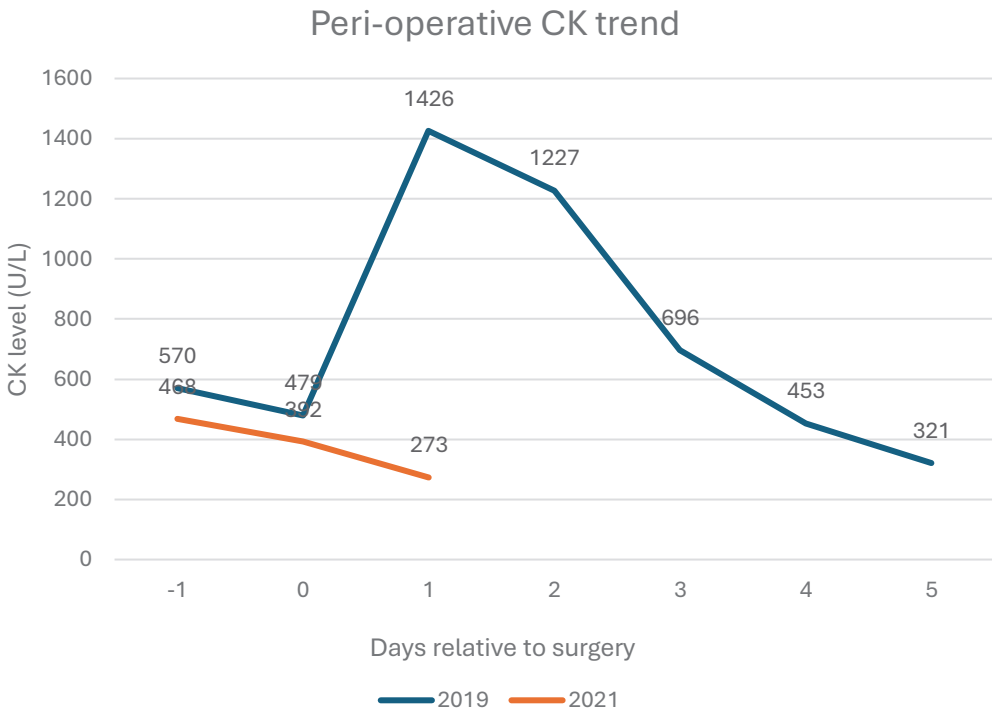

Fig. 1 — Peri-operative CK trend.
Graph showing the highest CK levels measured per day. The graph shows the data concerning the acetabuloplasty in 2019 and the epiphysiodesis in 2021. The graph shows the preoperative CK level, the level day before surgery is marked by the number -1, the day of the operation is marked by number 0 and the postoperative following days by the following numbers. In 2019 the patient was discharged on day one after surgery. CK reference: 36-219 U L-1.

rhabdomyolysis crisis in lipin-1 deficient patients. Next we described anesthetic management in four patients. In this section we provide alternative hypotheses which might explain the occurrence of rhabdomyolysis in the perioperative phase. We provide recommendations for anesthetic management.

The claim that anesthesia is a trigger for rhabdomyolysis in lipin-1 deficiency, is often mentioned in publications. Out of 29 of our referenced articles, 15 of them state that anesthesia provokes rhabdomyolysis[4-6,8-10,12,14-16,18,25,26,28,31]. However, only three articles provide original data on which this statement has been based[4,9,12]. The data that suggests a link between anesthesia as a trigger for rhabdomyolysis in these cases was analyzed retrospectively and seems to rely on anecdotal information. The publications do not provide any information to confirm a causal relationship between anesthetic exposure and the occurrence of rhabdomyolysis. All three of these publications do not share any details about the anesthetic and surgical procedure.

In contrast to the absence of evidence for anesthesia as a trigger, we have presented the experiences from three authors who reported safe anesthetic procedures. Our patient has had seven anesthetic and surgical procedures, with different anesthetic products and adjuncts. Both general anesthesia and loco-regional anesthesia did not provoke rhabdomyolysis. Both TIVA techniques with propofol and the use of sevoflurane to maintain anesthesia have been successfully used in the patients. Our report is the first to document the use of rocuronium and cis-atracurium muscle relaxants. Other authors have avoided the use of neuromuscular blocking due to the concern that these agents might provoke rhabdomyolysis[15,25,26,28].

Tables II and III summarize the anesthetic drugs and adjuncts which have been documented in safe anesthetic practice in lipin-1 deficient patients. It has to be noted that in all these cases the patient received either a 5% dextrose 28 or a 10% dextrose infusion 25, 26 to provide a source of caloric intake while the patient was kept nil by mouth.

Based on the pathophysiology of lipin-1 deficiency, laboratory information and clinical data we do not believe that the anesthetic causes rhabdomyolysis. We hypothesize that the following factors might play a role in provoking rhabdomyolysis in the peri-operative setting.

Hypothesis for peri-operative rhabdomyolysis

Fasting

It is common practice to deny oral intake to patients before anesthesia[37]. It has been established that fasting is a frequent trigger for rhabdomyolysis in lipin-1 deficiency and the molecular mechanism behind this phenomenon has been described[3,6]. The catabolic state leads to

production of proinflammatory cytokines, which have been shown to play an important role in the pathophysiology leading to rhabdomyolysis[7]. The FAO defects noticed by Raaschou-Pedersen confirms an impairment in fat metabolism in lipin-1 deficient patients[11]. This leads to an energy deficiency and subsequent rhabdomyolysis when body glucose stores are depleted, as is the case when patients are fasted for longer periods[12].

It is our hypothesis that the peri-operative fasting state provokes or greatly contributes to provoking rhabdomyolysis in the suspected anesthesia cases.

Inflammation

Surgery and the subsequent local tissue trauma leads to the release of pro-inflammatory substances[32]. These cytokines negatively affect the precarious cellular homeostasis in lipin-1 deficiency. We believe that the release of pro-inflammatory substances as a result from tissue trauma causes rhabdomyolysis via the same mechanism as observed with infections. It has been established that inflammation leads to down-regulation of residual lipin activity[6]. The effect of inflammatory cytokines on cultured myoblasts was an aggravation of the intracellular accumulation of lipid droplets and decrease in ATP stores[7]. It is believed that these mechanisms greatly contribute to the occurrence of rhabdomyolysis.

Stress response

Surgical trauma also leads to a central stress response via afferent nerves. It is comprised of endocrinological, metabolic, immunological changes via the activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. The release of hormones such as catecholamines, cortisol and glucagon leads to a catabolic state. It is characterized by glycogenolysis, gluconeogenesis and lipolysis. This leads to an increase in fatty acids. Fat metabolism is the primary energy source in the perioperative period[32].

Nociception plays an important role in the stress response. It has been determined that inadequate analgesia increases the stress response. This results into suboptimal postoperative recovery, due to increased metabolic demands, increased catabolism, impaired organ function and increased morbidity[33].

Pizzamiglio et al. hypothesized that the catecholamine-induced increase in fatty acids cannot be processed by the muscle cells which leads to the occurrence of rhabdomyolysis. This hypothesis was based on the observation that one patient had bouts of rhabdomyolysis after experiencing intense stress[8].

It has been established that attenuating the peri-operative stress response improves outcome[32]. This might be of extra importance in the case of lipin-1 deficiency.

Metabolic supply-demand mismatch

Another hypothesis is that a mismatch in metabolic supply and demand leads to an energy deficiency and subsequent rhabdomyolysis. Instances of increased metabolic demand, such as physical exercise and fever have been recorded to induce rhabdomyolysis.

Decreases in metabolic supply could provoke rhabdomyolysis. We found a case report of a patient suffering from bouts of rhabdomyolysis in the context of respiratory compromise. On one occasion due to asthma and on another due to a respiratory infection. The patient had clinical cyanosis, and thus low levels of oxygen within the blood[5]. Anaerobic metabolic conditions in this patient could have possibly attributed to the occurrence of rhabdomyolysis.

In the peri-operative setting a patients normal physiology is disturbed. Anesthesia induced alterations in cardiac output and systemic blood pressure might disturb metabolic supply to tissues. Use of a surgical tourniquet completely stops blood flow to tissues distal of the tourniquet. This completely abolishes metabolic supply. Direct local pressure due to patient positioning might cause a decrease in metabolic supply as well due to external compression of tissues and impairment of local tissue perfusion.

Use of active warming devices such as forced air heating systems, fluid warming systems, radiant heaters might lead to iatrogenic hyperthermia and thus an increase in metabolic demand. These peri-operative conditions of decreased supply or increased demand could potentially lead to rhabdomyolysis in lipin-1 deficiency.

Recommendations for peri-operative management

Preoperative phase

First, the patient should be scheduled in a center capable of dealing with the complications of a metabolic decompensation[35]. Prior to elective surgery, a preoperative evaluation by an anesthetist should be performed. The medical file should be examined and results of additional testing should be reviewed. A multidisciplinary treatment plan should be made in case of peri-operative occurrence of rhabdomyolysis. Intensivists, pediatricians, nephrologists and the treating surgeon should be involved.

Preoperative testing should include cardiac investigations with resting ECG and

echocardiography. This is especially important since we found that lipin-1 deficiency with cardiac involvement has a very high mortality. Even exercise echocardiography should be considered. This can be useful to detect subclinical cardiopathy[17]. Furthermore, blood should be taken and sent for analysis. Electrolytes, kidney and liver function, cell counts and coagulation testing should be included.

Anamnesis should provide information about general condition, comorbidities and pharmacological treatments. The patient should be informed about the procedure and regarding the increased anesthetic risk. Patient education and familiarization with the procedures should be initiated, aimed at reducing anxiety-induced peri-operative stress.

Next, the patient should be admitted the night before surgery and checked for absence of any signs of rhabdomyolysis and infection both clinically and biochemically.

Avoidance of the fasting state with initiation and maintenance of intravenous 10% dextrose infusion. This has been proven a successful strategy to avoid rhabdomyolysis in the peri-operative period[12,25]. The patient should ideally not be fasted for more than six hours[35].

We recommend the use of premedication in order to reduce anxiety and stress levels. Midazolam has been used for this purpose without complications[26,28].

Intraoperative phase

The glucose infusion should continue throughout the procedure, preferably on a separate lumen or canula to avoid boluses or inadvertent interruption of the infusion. Hypoglycemia should be avoided at all times[35].

Monitoring should include pulse oximetry, ECG, blood pressure, etCO2 and temperature. Vigilance for any signs of arrythmias, hyperkaliemia or rhabdomyolysis is imperative. We recommend frequent laboratory testing per- and postoperatively to identify electrolyte disturbances and monitor CK and blood glucose levels. An arterial line or central venous access can prove useful to regularly draw blood samples. Point-of-care blood gas analysis allows for a quick determination of electrolyte status and blood glucose levels.

Careful positioning with soft padding prior to applying surgical drapes to avoid pressure points. This should be done in order to avoid pressure-induced rhabdomyolysis.

Rigorous blood pressure management should be executed to keep the blood pressure within age-adjusted physiologic range in order to avoid rhabdomyolysis due to hypoperfusion. Beta-agonists should be avoided due to their stimulating effect on lipolysis[35].

Temperature should be kept within physiological range as well. Active warming and cooling devices should be made available to correct any change in body temperature. He hypothesize that hypothermia could lead to vasoconstriction and hypoperfusion, which has negative impact on metabolic supply. Hyperthermia could disrupt metabolic equilibrium due to an increase in metabolic demand.

Adequate depth of anesthesia should be provided in order to suppress the surgical stress response[32]. Both propofol and sevoflurane have been safely used to induce and maintain anesthesia in patients with lipin-1 deficiency.

Special attention to adequate analgesia should be made. However, the side effects of opioid analgesia negatively affect postoperative recovery due to respiratory depression, nausea and drowsiness. A multimodal analgesic approach should be considered. Loco-regional techniques have been shown to suppress the surgical stress responses by afferent and efferent sympathetic blockade[33]. This technique provides additional analgesia in a multimodal anesthesia technique.

We recommend the prophylactic use of dexamethasone. This drug has been proven to suppress the cellular mechanisms leading to rhabdomyolysis[7]. It has the additional benefits of anti-inflammatory and analgesic effects. Last, dexamethasone is an effective drug to prevent PONV[38]. Additional strategies to prevent PONV should be used, in order to get the patient to quickly resume oral intake.

The use of neuromuscular blocking agents provides better intubating and surgical conditions[36]. We safely used the non-depolarizing agents cis-atracurium and rocuronium. We recommend to avoid succinylcholine, it is a known trigger for drug induced rhabdomyolysis and malignant hyperthermia[30].

Tourniquet use should be avoided due to the risk of triggering rhabdomyolysis.

Tables II and III provide a full list of anesthetic products and adjuncts which have been documented to have been used without complications.

Postoperative phase

Continue the glucose infusion until the patient is able to resume adequate oral intake in the absence of vomiting[35]. We recommend prolonged monitoring to ensure the absence of arrhythmias and electrolyte disturbances. Oxygen saturation should be kept at preoperative levels by titrating oxygen supplementation.

Frequently reassess laboratory investigations to evaluate CK levels, electrolyte disturbances, kidney and liver function and hemoglobin. In our case a full lab was analyzed upon arrival in the post anesthesia care unit and a CK level analysis was performed every two hours during the first six hours after surgery, and every four hour hours for the following 12 hours. A CK level rise should promptly initiate a pre-defined treatment plan. Diagnosis of rhabdomyolysis should not be made on CK levels alone, as there is a lag in CK rise[27].

Continue to asses pain scores and analgesic requirements and multimodal analgesia should be titrated to meet the clinical need.

Postoperative infection should be treated with appropriate antibiotic treatment.

Conclusion

Lipin-1 deficiency, an autosomal recessive disorder, causes recurrent episodes of rhabdomyolysis. The probable mechanism is by a defect in the fat metabolism. The rhabdomyolysis can be life threatening. We calculated a mortality of 21.3%. The rhabdomyolysis is provoked by a triggering event. Infection, fasting and exercise most frequently cause rhabdomyolysis.

Patients experience good health between episodes but cardiac anomalies have been reported and patients should be screened to determine cardiac involvement.

Anesthesia has been claimed to cause rhabdomyolysis in these patients. We reviewed the evidence regarding this claim and conclude that the evidence to support this claim is extremely weak. We described evidence of uncomplicated anesthetic procedures in lipin-1 deficient patients, suggesting that anesthetic procedures can safely be performed in these patients. Alternative hypotheses to explain the occurrence of rhabdomyolysis in the peri-operative setting have been presented. This paper provides recommendations for anesthetic management for these patients.

Conflicts of interest: None to declare.

References

1. Zeharia A, Shaag A, Houtkooper RH, Hindi T, de Lonlay P, Erez G, et al. Mutations in LPIN1 cause recurrent acute myoglobinuria in childhood. Am J Hum Genet. 2008 Oct;83(4):489–94.
2. Schweitzer GG, Collier SL, Chen Z, Eaton JM, Connolly AM, Bucelli RC, et al. Rhabdomyolysis-Associated Mutations in Human LPIN1 Lead to Loss of Phosphatidic Acid Phosphohydrolase Activity. JIMD Rep. 2015;23:113–22.
3. Csaki LS, Reue K. Lipins: multifunctional lipid metabolism proteins. Annu Rev Nutr. 2010 Aug;30:257–72.
4. Michot C, Hubert L, Brivet M, De Meirleir L, Valayannopoulos V, Müller-Felber W, et al. LPIN1 gene mutations: a major cause of severe rhabdomyolysis in early childhood. Hum Mutat. 2010 Jul;31(7):E1564-73.
5. Indika NLR, Vidanapathirana DM, Jasinge E, Waduge R, Shyamali NLA, Perera PPR. Lipin-1 Deficiency-Associated Recurrent Rhabdomyolysis and Exercise-Induced Myalgia Persisting into Adulthood: A Case Report and Review of Literature. Vol. 2020, Case reports in medicine. United States; 2020. p. 7904190.
6. Yim SW, Chan TYC, Belaramani KM, Man SS, Wong FCK, Chen SPL, et al. Case Report: The first probable Hong Kong Chinese case of LPIN1-related acute recurrent rhabdomyolysis in a boy with two novel variants. F1000Research. 2019;8:1566.
7. Michot C, Mamoune A, Vamecq J, Viou MT, Hsieh L-S, Testet E, et al. Combination of lipid metabolism alterations and their sensitivity to inflammatory cytokines in human lipin-1-deficient myoblasts. Biochim Biophys Acta. 2013 Dec;1832(12):2103–14.
8. Pizzamiglio C, Lahiri N, Nirmalananthan N, Sood B, Somalanka S, Ostrowski P, et al. First presentation of LPIN1 acute rhabdomyolysis in adolescence and adulthood. Vol. 30, Neuromuscular disorders : NMD. England; 2020. p. 566–71.
9. Michot C, Hubert L, Romero NB, Gouda A, Mamoune A, Mathew S, et al. Study of LPIN1, LPIN2 and LPIN3 in rhabdomyolysis and exercise-induced myalgia. J Inherit Metab Dis. 2012 Nov;35(6):1119–28.
10. Meijer IA, Sasarman F, Maftei C, Rossignol E, Vanasse M, Major P, et al. LPIN1 deficiency with severe recurrent rhabdomyolysis and persistent elevation of creatine kinase levels due to chromosome 2 maternal isodisomy. Vol. 5, Molecular genetics and metabolism reports. United States; 2015. p. 85–8.
11. Raaschou-Pedersen D, Madsen KL, Stemmerik MG, Eisum A-S V, Straub V, Vissing J. Fat oxidation is impaired during exercise in lipin-1 deficiency. Neurology. 2019 Oct;93(15):e1433–8.
12. Pichler K, Scholl-Buergi S, Birnbacher R, Freilinger M, Straub S, Brunner J, et al. A novel therapeutic approach for LPIN1 mutation-associated rhabdomyolysis--The Austrian experience. Muscle Nerve. 2015 Sep;52(3):437–9.
13. Reue K. The lipin family: mutations and metabolism. Curr Opin Lipidol. 2009 Jun;20(3):165–70.
14. Minton T, Forrester N, Baba S Al, Urankar K, Brady S. A rare case of adult onset LPIN1 associated rhabdomyolysis. Vol. 30, Neuromuscular disorders : NMD. England; 2020. p. 241–5.
15. Tong K, Yu G-S. Acute recurrent rhabdomyolysis in a Chinese boy associated with a novel compound heterozygous LPIN1 variant: a case report. BMC Neurol. 2021 Jan;21(1):42.
16. Kahraman AB, Karakaya B, Yıldız Y, Kamaci S, Kesici S, Simsek-Kiper PO, et al. Two tales of LPIN1 deficiency: from fatal rhabdomyolysis to favorable outcome of acute compartment syndrome. Vol. 32, Neuromuscular disorders : NMD. England; 2022. p. 931–4.
17. Legendre A, Khraiche D, Ou P, Mauvais F-X, Madrange M, Guemann A-S, et al. Cardiac function and exercise adaptation in 8 children with LPIN1 mutations. Mol Genet Metab. 2018 Mar;123(3):375–81.
18. Stepien KM, Schmidt WM, Bittner RE, O'Toole O, McNamara B, Treacy EP. Long-term outcomes in a 25-year-old female affected with lipin-1 deficiency. Vol. 46, JIMD reports. United States; 2019. p. 4–10.
19. Bergounioux J, Brassier A, Rambaud C, Bustarret O, Michot C, Hubert L, et al. Fatal rhabdomyolysis in 2 children with LPIN1 mutations. J Pediatr. 2012 Jun;160(6):1052–4.
20. Topal S, Köse MD, Ağın H, Sarı F, Çolak M, Atakul G, et al. A neglected cause of recurrent rhabdomyolysis, LPIN1 gene defect: a rare case from Turkey. Vol. 62, The Turkish journal of pediatrics. Turkey; 2020. p. 647–51.

21. Che R, Wang C, Zheng B, Zhang X, Ding G, Zhao F, et al. A rare case of pediatric recurrent rhabdomyolysis with compound heterogenous variants in the LPIN1. BMC Pediatr. 2020 May;20(1):218.
22. Jaradat SA, Amayreh W, Al-Qa'qa' K, Krayyem J. Molecular analysis of LPIN1 in Jordanian patients with rhabdomyolysis. Meta gene. 2016 Feb;7:90–4.
23. Nunes D, Nogueira C, Lopes A, Chaves P, Rodrigues E, Cardoso T, et al. LPIN1 deficiency: A novel mutation associated with different phenotypes in the same family. Mol Genet Metab reports. 2016 Dec;9:29–30.
24. Yavuz L, Yavuz S, Alasrawi S. The Life-Threatening Case of Rhabdomyolysis Caused by A LIPIN1 Deficiency. BAOJ Pediatr. 2018 Apr 1;4:53.
25. Burstal RJ. Volatile anesthesia for a child with LPIN1 gene mutation and recurrent rhabdomyolysis. Paediatr Anaesth. 2018 Sep;28(9):813–4.
26. Kaur B, Rattalino M. Target-controlled infusion of Propofol and Remifentanil in a child with recurrent rhabdomyolysis secondary to LPIN1 deficiency. Vol. 30, Paediatric anesthesia. France; 2020. p. 726–7.
27. Kanderi N, Kirmse B, Regier DS, Chapman KA. LPIN1 rhabdomyolysis: A single site cohort description and treatment recommendations. Mol Genet Metab reports. 2022 Mar;30:100844.
28. Dutoit AP et al. Anesthesia for surgery in a pediatric patient with familial recurrent rhabdomyolysis secondary to LPIN1 gene mutation. http://www5.pedsanesthesia.org/meetings/2012ia/posters/uploads/30--GA4-65.pdf, 2012
29. Elsayed EF, Reilly RF. Rhabdomyolysis: a review, with emphasis on the pediatric population. Pediatr Nephrol. 2010 Jan;25(1):7–18.
30. Rüffert H, Bastian B, Bendixen D, Girard T, Heiderich S, Hellblom A, et al. Consensus guidelines on perioperative management of malignant hyperthermia suspected or susceptible patients from the European Malignant Hyperthermia Group. Br J Anaesth. 2021 Jan;126(1):120–30.
31. Scalco RS, Gardiner AR, Pitceathly RD, Zanoteli E, Becker J, Holton JL, et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015 May;10:51.
32. Yuki K, Matsunami E, Tazawa K, Wang W, DiNardo JA, Koutsogiannaki S. Pediatric Perioperative Stress Responses and Anesthesia. Transl Perioper pain Med. 2017;2(1):1–12.
33. Wolf AR. Effects of regional analgesia on stress responses to pediatric surgery. Paediatr Anaesth. 2012 Jan;22(1):19–24.
34. Shapiro F, Athiraman U, Clendenin DJ, Hoagland M, Sethna NF. Anesthetic management of 877 pediatric patients undergoing muscle biopsy for neuromuscular disorders: a 20-year review. Paediatr Anaesth. 2016 Jul;26(7):710–21.
35. Nyhan WL. Anesthesia in metabolic disease. In: Hoffmann GF, Zschocke J, editors. Inherited metabolic diseases. 2nd ed. Springer; 2017. p. 133–9.
36. Fuchs-Buder T, Romero CS, Lewald H, Lamperti M, Afshari A, Hristovska A-M, et al. Peri-operative management of neuromuscular blockade: A guideline from the European Society of Anaesthesiology and Intensive Care. Eur J Anaesthesiol. 2023 Feb;40(2):82–94.
37. Frykholm P, Schindler E, Sümpelmann R, Walker R, Weiss M. Preoperative fasting in children: review of existing guidelines and recent developments. Br J Anaesth. 2018 Mar;120(3):469–74.
38. Elvir-Lazo OL, White PF, Yumul R, Cruz Eng H. Management strategies for the treatment and prevention of postoperative/postdischarge nausea and vomiting: an updated review. F1000Research. 2020;9.

doi.org/10.56126/76.S1.15