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Review Article

Suspicion of a Case of Death Linked to Anesthetic Malignant Hyperthermia at Treichville University Hospital

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Abstract

Anesthetic malignant hyperthermia (HM) is a pharmacogenetic myopathy of anesthesia. It is induced by halogenated volatile anaesthetic agents and/or depolarizing curare (succinylcholine), in individuals with a familial muscle abnormality, transmitted in an autosomal dominant manner.

We report a probable case of fulminant HM linked to isoflurane.

The case was a 46-year-old patient with no particular medical history and had previously received uneventful general anaesthesia. Classified ASA 1 after a CPA, she was admitted to the operating room for a regulated thyroidectomy. General anaesthesia with intubation was performed with propofol and vecuronium during induction and anaesthetic maintenance with isoflurane. About 90 minutes after induction a symptomatological triad sets in: increased $ETCO_2$, generalized muscle rigidity and hyperthermia above 40°C. The probable hypothesis of a crisis of HM is then quickly evoked. In the absence of dantrolene as a specific treatment for HM, discontinuation of isoflurane and resuscitation measures were initiated. The consequences are marked by refractory metabolic acidosis and severe hypocalcaemia responsible for cardiac arrhythmia after several episodes of cardiac arrests resuscitated without success.

Due to a limited technical platform, confirmation of the diagnosis of anaesthetic HM in our patient could not be possible. Notamment the realization of a post-mortem muscle biopsy which would have allowed diagnostic tests of pathological contracture.

Nevertheless, the hypothesis of malignant hyperthermia of anesthesia seemed more than likely in our patient. Despite its rarity, the potentially lethal nature of this pharmacogenetic subclinical myopathy justifies that any anesthesiologist knows the elements of diagnosis and treatment of the crisis and knows how to recognize the subjects at risk to perform safe anesthesia in these patients.

Keywords: Malignant Hyperthermia of Anesthesia; Fulminant Crisis; Isoflurane

Introduction

Malignant hyperthermia (HM) is a rare but formidable and potentially fatal condition of general anesthesia related to an exaggerated patient response to volatile anesthetics (halogenes) and depolarizing curare [1]. It is a genetically transmitted myopathy in the dominant mode not related to sex and almost without clinical expression outside the onset of the seizure in the immediate intraoperative or postoperative period [2].

The rarity of the crisis encountered less than once during a working life and its occurrence in a context of countries with limited resources, justify the notification of this clinical case following exposure to isoflurane.

Observation

This was a patient of 46 years, 60 kg, 2 gestation Aries and 2 parities, without known medical history but who was operated in 1980 of an appendectomy performed under general anesthesia without reported incidents.

She had had a goiter for about a decade for which an indication for thyroidectomy was indicated. A preanesthetic consultation (CPA) was performed at 1 month of the procedure and had been classified ASA 1 with a strictly normal ECG tracing and euthyroidism. The pre-anesthetic visit (VPA) on the eve of the procedure had also not detected any particular abnormality.

The anesthetic technique chosen was a classic general anesthesia with intubation (AGI). It consists of: premedication (0.2 mg midazolam in IVD); pure O2 preoxygenation in spontaneous ventilation; anesthetic induction with 200 mg of propofol associated with 100 µg fentanyl IVD; curarization (vecuronium 4 mg IVD) followed by orotracheal intubation and then placed under mechanical ventilation in controlled volumetric mode (Vt: 420 ml, FR: 16 cycles/min, PEEP: 5 cm H_2O, Vm : 6.7 l/min). Anaesthetic maintenance was provided with isoflurane carried by fresh gases (oxygen and medical air with a ratio of 50/50 for an FIO_2 of about 40%) in a closed circuit.

The capnography then described a curve in phase with a successful tracheal intubation and the surgery was started. Intraoperative analgesia was provided by the administration of 60 µg of fentanyl every 30 min.

About 1h30 min after anaesthetic induction, a symptom of hypercapnia (and CO_2 > 55 mmHg) with arterial desaturation (SPO_2 < 90%) associated with ventricular tachycardia with wide QRS complexes and hyperthermia (T°: 41°C). After checking the permeability of the intubation tube, the symmetry of the vesicular murmur and a defect in analgesia (IVD injection of fentanyl), accidental extubation or selective intubation without facto. The hypothesis of malignant hyperthermia of anesthesia was quickly evoked in front of the triad hyperthermia, hypercapnia and muscle rigidity. Emergency therapy consisted essentially of symptomatic treatment: immediate discontinuation of isoflurane, hyperventilation in hyperoxia, vascular filling with a crystalloid (SSI) and use of physical and medicinal antipyretic means (paracetamol).

The immediate course was marked by persistent hypercapnia and hyperthermia with cardiac arrhythmia responsible for intraoperative cardiac arrest about one hour after the onset of symptomatology. After a successful basic and specialized cardio-circulatory resuscitation (MCE, adrenaline), she was admitted to the intensive care room after a correct surgical hemostasis.

The examination at admission mainly included:

- **General:** Arterial hypotension (PAM: 30 mmHg), Pulse: 120 bpm, T°: 39, 9°C, hypertonic urine;
- **Neurological:** A Glasgow score of 06 (Y:1; V: 1; M: 4) pupils in myosis, generalized muscle hypertonia;
- **Cardiovascular:** A cardiac arrhythmia without an organic murmur.
- **Biological:** Arterial gas and blood ionogram performed at H 3 post-crisis essentially found severe metabolic acidosis associated with severe hypocalcaemia and hyperkalaemia (Table 1).

GAZOMETRIE (FiO_2: 1)	Blood ionogram	Other reviews
pH: 6,94	Na+: 152 meq/l	CPK: 314 UI/L
PO2: 316 mmmHg	K+: 7 meq/l	
PCO2: 42,2 mmHg	Ca2+: 0.64 meq/l	
HCO3: 9.0 meq/l	Cl-: 124 meq/l	
BE: - 23 Lactatee: 2.8 mmol/l		

Table 1: Results of biological examinations carried out on the patient (H 3 post crise).

Treatment in the resuscitation room consisted of: mechanical ventilation, administration: vaso-active amines (noradrenaline), semimolar Bic arbonate, calcium gluconate. The continuation of vascular filling with crystalloids (SSI), physical and medicinal means (paracetamol) of fighting fever.

The aftermath in intensive care is marked by persistent hemodynamic instability (PAM < 60 mmHg), cardiac arrhythmia, hyperthermia and the occurrence of an externalized hemorrhagic syndrome: incoagulable bleeding at the various skin puncture sites. The death occurred in this context at about 9 hours after the onset of the crisis.

Discussion

We report a more than likely picture of a fulminant attack of malignant hyperthermia (HM) of anesthesia. Indeed, a whole range of arguments incriminated this hypothesis: ane former exposition to halogens; the context of general anesthesia with the use of isoflurane as a halogenated; hypercapnia, hyperthermia, cardiac arrhythmia, muscle hypertonia, metabolic acidosis, hyperkalemia and hypocalcaemia. However, in addition to these signs, the elevation of CO_2 excretion visualized on capnography ($ETCO_2$), the existence of muscle rigidity and hyperthermia above 40°C were the most suggestive of HM anesthesia [1,2].

The class fulminant form of isoflurane malignant hyperthermia is well known [3] (Table 2). The majority of these clinical and paraclinical signs were present in our patient. Seul spasme of the masseters was not observed certainly because of the use of a non-depolarizing curare in our case. Masseter spasm is more common with halothane/suxamethonium [4]. Also, the acute biological rhabdomyolysis usually typical of HM is not early onset but rather secondary [1].

Early signs Late signs
Spasm of masseters Generalized contracture
Unexplained tachycardia Hyperthermia (> 40°C)
Tachypnea Mixed acidosis
PETCO2 increase Major elevation PETCO2
Localized stiffness Rhythm disorders

Table 2: Clinical signs ofmalignant hyperthermia cry according to Dépret., *et al*. [4].

A review of the literature shows that all halogenated agents are HM triggers, namely halothane, enflurane, isoflurane, including the most recent agents, desflurane and sevoflurane. The rate of onset of seizure is slower with desflurane and sevoflurane, averaging 35 minutes on halothane, 140 minutes on isoflurane and 260 minutes on desflurane, in the absence of succinylcholine [5-8]. The delay between exposure to the agent and the declaration of the crisis was then in favour of a directly causal relationship.

In our case, the trigger for this probable HM crisis is undoubtedly isoflurane. To confirm this diagnostic approach, we would have had to carry out in vitro tests of halothane and caffeine contracture performed on a post-mortem muscle biopsy. Due to a limited technical platform in our context, confirmation of the diagnosis of anaesthetic HM in our patient could not be possible. However, a definitive diagnosis cannot be made urgently and an opinion in a specialized HM center is strongly recommended.

On the other hand, a diagnostic probability score has been proposed by Larach or «Clinical Grading Scale [CGS]» [9]. This score cannot be used to treat a suspected patient, but that it allows for scientific purposes to compare groups of patients. The scope of this score was therefore limited because it was retrospective and unusable for prospective diagnosis [2,3]. HM crisis or suspicion of HM crisis is a vital emergency. Early recognition of signs in favour of HM and initiation of treatment as soon as possible are essential for patient survival [1,2]. The diagnosis and its treatment with dantrolene do not suffer any delay to generally allow the resolution of the crisis.

Dantrolene is the only specific treatment for an HM attack [1,10]. Dantrolene is a direct muscle relaxant, derived from hydantoin. Physiologically, the dan-trolene molecule will bind to the R y R1 protein and decrease the activity of the R y R1 channel in skeletal striated muscles. Its muscle relaxant effect and antidote to HM crisis involves a return to normal intra-sarcoplasmic Ca^{2}+ concentration [1,11]. The recommended dose is 2.5 mg/kg, to be renewed by boluses of 1 mg.kg–1 to achieve regression of clinical signs (tachycardia, hypercapnia, hyperthermia, rigidity). A dose > 10 $mg.kg^{-1}$ is sometimes needed [1]. In France, a circular of 18 November 1999 requires the immediate availability of 18 vials of dantrolene per anaesthetic site associated with the establishment of a procedure to have quickly 36 vials to provide a dose of 10 mg/kg to a 70 kg adult with a HM crisis, as well as the poster of management recommendations [1,12].

Due to international recommendations, dantrolene was not available in our hospital. Our therapeutic strategy was then limited and focused on symptomatic and simultaneous measures as recommended [1]: discontinuation of halogen administration, pure oxygen ventilation and cooling by physical means. The correction of the various associated metabolic disorders was required (alkalizing, hypokalaemic) as well as hemodynamic support (norepinephrine).

This HM crisis was probably associated with haematological complications in this case DICD and as evidenced by the finding

of bleeding at the puncture sites. For technical reasons, biological samples could not be taken for the purpose of its confirmation. Similarly, Brossier., *et al*. reported a case of bleeding at puncture sites and surgical sutures that suggested the development of coagulation disorders despite normal haemostasis (platelets = 204 000 mm^{-3}, TP = 92%, TCA = 30s) [3].

In addition, systemic metabolic acidosis refractory to alkalosis was indisputably responsible for the ineffectiveness of high doses of vasoactive amines used to correct the cardiovascular collapse present. The collapse of serum calcium reflected the hyper-metabolic state and trouble of calcium homeostasis in the muscle fiber as described in the HM [13] and would explain this cardiac arrhythmia observed.

Despite the rarity of HM in our tropical and European context where the incidence of HM crisis is estimated at 1/250,000 anesthesia for the fulminant form and 1/62,000 anesthesia during halogen-succinylcholine combinations, and 1/85,000 anesthesia in the absence of succinylcholine [14,15], the suspicion of diagnosis of HM with isoflurane was early in our patient. It justified the immediate initiation of a non-specific therapy. The lack of administration of dantrolene in our context certainly explains the fatal outcome. Indeed, the early diagnosis of an HM attack of anesthesia and the early initiation of specific treatment, are the main prognostic factors of a HM attack [1].

The diagnosis of the HM crisis is under the control of the anesthetist in charge. This diagnosis, which involves the patient's vital prognosis if he is delayed, requires the start of the reference treatment, dantrolene, which then reduces mortality by 75% [2].

Thus, in an observation reported by Brossier., *et al*. [3], the rapid clinical suspicion of a fulminant attack of HM coupled with the instantaneous administration of dantrolene and specialized resuscitation allowed the resolution of a fulminant attack of HM with isoflurane despite the presence of multi-organ failure (CIVD, hepatic cytolysis, ARI...) with the only sequelae a muscle atrophy of the right calf [3].

Finally, the lack of general screening for HM of anaesthesia and the failure to perform reference tests for the diagnosis of HM anesthesia by in vitro tests of halothane and caffeine contracture performed a muscle biopsy at the level of the vast external quadriceps [16], were the main limitations of our observation. Nevertheless, these tests are difficult to carry out in an emergency and retain an interest in determining patients sensitive to HM [1]. In addition, the biological family was given the risk of HM and voluntary genetic testing was encouraged.

Conclusion

Anesthetic malignant hyperthermia despite its rarity seems to be a reality in our tropics as evidenced by our observation. Consequently, it must remain a haunt for the anesthetist who should take it into account during the preanesthetic consultation, in particular by means of a more targeted questionnaire.

The need for the creation in our country of a centre for the management of anaesthetic malignant hyperthermia, including genetic screening analysis, is more than necessary. In addition, the availability of a stock of dantrolene in each of the operating theatres in the country should be the norm in accordance with the recommendations.

Declaration Interest

The authors state that they have no conflicts of interest.

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