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# Anabolic androgenic steroids and illicit drugs as potential modulating factors in malignant hyperthermia: a case series

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Malignant hyperthermia (MH) is a life-threatening hypermetabolic pharmacogenetic disorder occurring in genetically predisposed individuals exposed to volatile halogenated anesthetics/succinylcholine [1]. MH involves calcium abnormalities in skeletal muscles and is associated with variants in *RYR1*, *CACNA1S*, and *STAC3* genes [2, 3]. MH diagnosis is conducted through genetic blood testing and/or in vitro contracture tests (IVCT) [1, 4]. Skeletal muscle fragments of MH-susceptible patients present with an abnormal contracture response when exposed to halothane/caffeine. However, there are differing sensitivities to the IVCT in muscle biopsies containing different *RYR1* variants, which could be related to the variable presentation of the MH crisis [5].

While the frequency of MH crisis ranges from 1 : 15,000 to 1 : 50,000, the estimated prevalence of MH pathogenic variants is 1 : 2,750 [3, 4]. This difference has been attributed to several facts: MH-susceptible subjects may not be exposed to anesthetic triggers or may have uneventful anesthetics before developing MH due to the reduced/incomplete penetrance of the MH trait (around 40%); paucisymptomatic crises may remain unnoticed due to the variable expressivity of MH; and MH reactions can be affected by the type/dose/duration of exposure of the volatile anesthetic [2]. Additionally, MH crises seem more frequent after strenuous exercise and pyrexia in the previous 72 hours [6].

Despite MH susceptibility being an autosomal dominant trait, there is a higher incidence of MH in younger males with a muscular body build [7]. Men have nearly 60% more total lean mass than women [8]. However, some individuals try to further improve their body image by using anabolic androgenic steroids (AAS), despite the risks of high levels of testosterone (greater metabolic rates/energy demands, immunity problems, hepatotoxicity, prostate cancer, and metabolic syndrome/cardiovascular diseases) [8, 9]. It is estimated that 6.4% of males use these steroids globally, with a predominance of recreational athletes [9]. Here we report two patients subjected to several surgical procedures who presented with an MH crisis after using AAS/illicit drugs, and discuss the potential predisposing action of these drugs.

The Ethical Committee of our institution approved this study (number 73681017.9.0000.5505; https://plataformabrasil.saude.gov.br/login.jsf). According to the Declaration of Helsinki, written informed consent to participate voluntarily in this study was obtained from all patients/relatives (the father of the first patient [deceased] and the second patient).

This study was based on a review of the records from our hotline center for MH between 2004 and 2024,

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as well as the medical records of patients evaluated for MH since 1997, in search of patients who presented with MH crises and AAS/illicit drugs use. We used the Clinical Grading Scale (CGS) to classify the MH crisis [10].

There were two male patients who spontaneously reported the use of AAS for esthetic reasons on a monthly basis before the MH crisis. Both patients had an active lifestyle, which included resistance exercises, and had undergone previous anesthesias without adverse events.

Patient 1: A 34-year-old male patient previously underwent four general anesthesias (GA) (3 septoplasties and 1 lumbar decompression for disc herniation) without complications. He started using testosterone (100 mg weekly) before his fifth GA for orthognathic surgery (osteotomy Le Fort I and osteoplasty for micrognathia). The fifth GA was induced with midazolam 2 mg, lidocaine 90 mg, propofol 200 mg, rocuronium 75 mg, and fentanyl 100 µg, followed by nasal intubation. GA was maintained with isoflurane, fentanyl 50 µg, and ketamine/dexmedetomidine via continuous infusion up to 3.5 mg/14 µg per hour. After 4.5 hours from the beginning of the anesthesia, he developed signs suggestive of an MH crisis: hypercapnia: 55 mmHg, hyperthermia: 41°C, hypotension: 70/30 mmHg, metabolic acidosis: pH: 7.17 and base excess: –14.7, hyperkalemia 5.9 mg $dL^{-1}$, and rhabdomyolysis (creatine kinase: 51.511 IU $L^{-1}$). Muscle stiffness was not reported. He received all the stock of dantrolene from the hospital (36 vials: 8.37 mg $kg^{-1}$ for a patient of 86 kg). Despite the management of the MH crisis according to the European Malignant Hyperthermia Group guidelines [11], he died 24 hours later with renal failure, disseminated intravascular coagulation, and refractory shock.

The CGS value of 65 points corresponded to an MH clinical probability of six out of six (almost certain). Next generation sequencing (NGS) of his blood sample showed a variant of unknown significance in the *RYR1* gene (p. Gly2733Cys; c.8197G>T). His asymptomatic father, also with a muscular body, had the same *RYR1* variant and a positive in vitro contracture test (IVCT, contractures of 2.32 and 1.68 g, respectively, after 2 mM caffeine and 2% halothane (threshold: 0.2 g)).

Patient 2: A 43-year-old male patient had previously undergone two general anesthesias without complications during the procedure (septoplasty and breast reduction, at the ages of 15 and 21 years). In the first anesthesia he received thionembutal, succinylcholine, pancuronium, and halothane. He complained about muscle pain in the thorax and back when he woke up. In the second anesthesia he received midazolam 7.5 mg per os as pre-anesthetic medication. GA was induced with dehydrobenzoperidol/fentanyl 1.25 mg/25 µg, alfentanil 200 µg, propofol 150 mg, and atracurium 40 mg. His trachea was intubated and GA was maintained with isoflurane, nitrous oxide, and alfentanil 1000 µg, without complications or postoperative complaints. He reported the use of the AAS nandrolone and stanozolol from 16 to 20 years of age, and irregular use of alcohol, cannabis, and cocaine since then. However, his family reported that he resumed the use of nandrolone before the third GA for a new septoplasty, at the age of 27 years. For this third anesthesia, GA was induced with midazolam 2 mg, fentanyl 200 µg, cisatracurium 7 mg, lidocaine 80 mg, and propofol 150 mg, followed by tracheal intubation. GA was maintained with isoflurane and nitrous oxide. After 10 minutes from the beginning of the anesthesia, he developed signs suggestive of an MH crisis (hyperthermia: 38.5°C, hypercarbia: 54 mmHg, sinus tachycardia: 172 bpm, and hyperkalemia: 4.6 mg $dL^{-1}$), additionally to hypertension (182/135 mmHg). Muscle stiffness was not reported. The surgery was interrupted; isoflurane was discontinued and switched to total intravenous anesthesia with 100% oxygen. No dantrolene was used, and he fully recovered. The CGS value of 33 points corresponded to an MH clinical probability of four out of six (somewhat greater than likely). His physical examination revealed scoliosis and a muscular body. His IVCT was positive (contractures of 0.32 g and 2.2 g, respectively, after 2 mM caffeine and 2% halothane). NGS molecular analysis did not identify any pathogenic or likely pathogenic variants in the *RYR1* gene.

We described two male patients with MH crisis concomitant to the use of AAS. As both patients had been previously anaesthetized without complications when not using AAS, we propose that the use of steroids could have increased their MH risk. Indeed, the exposure to higher levels of steroids could have increased both muscle mass and intracellular calcium.

Cong *et al*. [12] analyzed 12 studies indicating a greater incidence of MH crisis in males than females, while three studies found no differences. Mouse models confirm this male-dependent MH susceptibility [13]. The frequency of MH in males is more than double that in females [14], the penetrance of the MH trait is higher in males [2], the influence of the trigger agent succinylcholine is greater in males, and positive IVCT results have been correlated with male probands in many studies [15, 16]. However, the epigenetic silencing of the *RYR1* allele has been excluded as a cause of the lower frequencies observed in females [17]. These differences could result from the greater muscle development typically seen in males and linked to testosterone levels [8].

Testosterone and its by-products enhance muscle protein synthesis, promote muscle hypertrophy, activate satellite cells, and reduce catabolic processes/apoptosis through both genomic/non-genomic and anti-catabolic mechanisms [9]. The genomic effects are mediated by the transcripts of anabolic genes (*IGF*-1, *LPIN*, *GLUT3*, *GLUT4*, *CPT1*, *SAT2*, and *MYOG*), as well as the downregulation of genes linked to muscle atrophy (*IKKalpha*) [9, 18]. The non-genomic effects present rapid

onset (minutes) and are characterized by an increase in intracellular calcium levels and the subsequent downregulation of the myostatin pathway. Various second messenger signaling cascades are activated, including the calmodulin pathway, which is involved in the excitation-contraction coupling [9].

Despite the fact that AAS increase muscle cell size, they can be associated with acute negative muscular side effects, predisposing the individual to rhabdomyolysis [19–27]. Interestingly, the majority of the nine previous reports of rhabdomyolysis associated with AAS occurred in males engaged in physical activity such as bodybuilding [19–27]. Additionally, Capacchione *et al*., in 2009 [28], reported a patient presenting a questionable MH reaction possibly related to many concomitant factors, including not only illicit steroid use but also dietary supplements, systemic inflammatory response syndrome and trauma. Among the concomitant factors, cocaine/cannabis use was reported by the second patient from this report, and both substances have been previously associated with rhabdomyolysis [29, 30].

It is possible that the intracellular skeletal muscle milieu may have been modified, by the use of AAS and/or illegal substances, to increase the probability of an MH crisis in these two male MH-susceptible patients. It would be necessary to perform a systematic study about the possible association between MH crisis and previous use of AAS and illicit drugs.

Acquiring a history of other environmental factors that may modify calcium control may be decisive in identifying other triggers of the MH crisis that could increase the effect of the halogenated anesthetics and succinylcholine. Investigation of AAS and/or illicit drug use should be an essential element of the pre-anesthetic consultation.

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