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Postoperative Malignant Hyperthermia

An Analysis of Cases from the North American Malignant Hyperthermia Registry

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Background: **The initial presentation of malignant hyperthermia (MH) may begin in the postoperative period. However, the maximal latency period between the end of anesthesia care and the onset of postoperative MH is unknown. The authors hypothesized that this latency period is short and is not manifested by hyperthermia as the initial presenting sign. The authors sought to test this hypothesis and to describe the clinical characteristics of postoperative MH by analysis of suspected cases in the North American Malignant Hyperthermia Registry.**

Methods: **Of 528 possible or suspected cases of MH in the North American Malignant Hyperthermia Registry, the authors identified 64 possible reports of postoperative MH. The records were reviewed in detail by the authors, each of whom assigned a qualitative score of "likely," "not likely," "not enough information available," or "not applicable" (where MH was not the final definitive diagnosis). Postoperative MH was confirmed after a consensus meeting of the three senior authors who reviewed in detail all possible "likely" cases.**

Results: **The authors identified postoperative MH in 10 subjects. All received volatile agents and 5 also received succinylcholine. All demonstrated signs characteristic of acute MH, including generalized rigidity, hypercapnia and/or tachypnea, tachycardia, and hyperthermia. No subject demonstrated hyperthermia as the presenting sign. The latency period between the anesthesia finish time and the onset of a sign indicative of acute MH ranged from 0 to 40 min.**

Conclusions: **Postoperative MH is uncommon, occurring in 10 of 528 suspected MH cases (1.9%) reported to the North American Malignant Hyperthermia Registry. Postoperative MH began shortly after completion of the anesthetic care. Hyperthermia was not a presenting sign of MH.**

MALIGNANT hyperthermia (MH) may occur when a patient with an inherited MH-susceptible mutation is exposed to one or both types of anesthetic triggering agents (*i.e.*, volatile inhalational agents and succinylcholine). In most reported cases, signs and symptoms consistent with the hypermetabolic nature of MH have occurred during administration of the triggering agent. However, there are some reported cases in which the onset of MH began in the postoperative period. The definitive latency period between the discontinuation of an anesthetic triggering agent and the beginning of the manifestations of MH varies from case to case, but the maximal latency period is unknown. Therefore, the aim of this study was to define these latency periods and to describe the clinical characteristics of patients in whom signs and symptoms of acute MH began in the postoperative period, by using a database of suspected MH episodes in patients included in the North American Malignant Hyperthermia Registry (NAMHR). Furthermore, we examined the existing published cases of postoperative MH in an attempt to lend clarity to these cases using current knowledge regarding the clinical and pathophysiologic aspects of MH. Based on our review of the existing literature and our experience as MH hotline consultants, we hypothesized that postoperative MH represents a small overall fraction of existing MH cases and usually is identified in the early postoperative period.

Materials and Methods

After approval from the Institutional Review Board of the Stokes Research Institute of The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, we obtained de-identified data on the 528 possible or suspected cases of MH that were included in the NAMHR database as of January 1, 2005 (Microsoft Excel; Redmond, WA). The NAMHR, which was established in 1987, merged with the Malignant Hyperthermia Association of the United States in 1995 to provide ongoing support for collection of data. The Registry is currently directed by Barbara Brandom, M.D., at Children's Hospital in Pittsburgh, Pennsylvania.# The goal of the NAMHR is to acquire and disseminate case-specific clinical and laboratory information relevant to MH susceptibility to facilitate research. The goal of the NAMHR is also to facilitate clinical care of patients by releasing detailed patient-specific information to their anesthesiologists when the patient has given

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NAMHR Web site. Available at: http://www.anes.upmc.edu/research/res_NAMHR.htm. Accessed July 11, 2008.

their consent for such a release to the NAMHR. Registry functions are consistent with the Health Insurance Portability and Accountability Act of 1996, Office for Human Research Protections, and The University of Pittsburgh Institutional Review Board regulations.

The NAMHR is populated by submission of an Adverse Metabolic Reaction to Anesthesia (AMRA) report** by the medical practitioner who contacted the Malignant Hyperthermia Association of the United States hotline for advice or suspected a possible MH reaction in a patient. Hotline consultants who suspect a possible MH episode encourage and assist the caller with preparation and submission of the report to NAMHR. The submission of an AMRA is voluntary and underestimates the true number of calls or MH cases available. There is no definitive method with which to confirm the pathologic diagnosis of MH susceptibility in any given patient because the AMRA is usually submitted before diagnostic testing. Furthermore, to protect the confidentiality of the patient, the AMRA does not contain identifying information. Therefore, cross-referencing to additional databases, as would be available from contracture or genetic analysis testing sites, is not possible. When the NAMHR receives an AMRA with the contact information of the reporting anesthesiologist, that person is often contacted by NAMHR staff for additional information and details regarding the case (personal verbal communication, Barbara Brandom, M.D., Professor of Anesthesiology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, April 2008).

Subject reports were eligible for analysis if there was evidence from the AMRA that the initial signs of an MH reaction occurred after the completion of the anesthetic or surgical procedure. Although the AMRA contains detailed information about the anesthetic episode, it was not specifically designed to determine when, in the patient's clinical course, the MH symptoms first appeared. Therefore, we determined this information by the AMRA question that indicates the status of the patient at the time of onset of the adverse metabolic reaction: A patient identified for inclusion was noted to be in the recovery area or intensive care unit at time of onset of the signs or symptoms of the reaction. The "latency period" was defined as the time between the discontinuation of the volatile anesthetic and the time of the development of the first MH-related sign. If the discontinuation time was not listed, we used the anesthesia end time to calculate the latency period. In addition, the free-text narrative portions of all 528 cases were examined to determine whether the reaction may have begun in the operating room but after completion of the surgical procedure or discontinuation of the anesthetic agents. This initial screening yielded 215 potential cases for analysis. These cases were then subjected to a previously described MH clinical grading score to determine the likelihood of the patient having a true MH episode.[1] Based on clinical signs and laboratory data, a score less than 20 represents a MH likelihood of "almost never," "unlikely," or "somewhat less than likely," and therefore, these patients were excluded from further analysis, leaving a total of 64 patients with potential postoperative MH. The available AMRA records from these 64 patients were then reviewed in detail by four anesthesiologists, which included three senior-level attending physicians who are Malignant Hyperthermia Association of the United States hotline consultants (R.S.L., J.R.T., R.K.) and one senior (clinical anesthesia year 3) anesthesiology resident (C.D.F.). Each of the four independently reviewed the available information and made a determination of the likelihood of MH using the terms "likely," "not likely," "not enough information available," or "not applicable" (where MH was not the final definitive diagnosis). Subsequent to this initial analysis, the three senior authors met and reviewed each possible "likely" case in detail, and by consensus, arrived at a final number of cases to include for this report.

In an attempt to further clarify a patient's definitive diagnosis based on clinical or contracture testing of the 64 cases analyzed, one of the authors (R.S.L.) obtained a de-identified biopsy center database (from NAMHR), and a de-identified Malignant Hyperthermia Association of the United States hotline log database from similar years covered by the NAMHR database. An attempted cross-reference was made between all 64 eligible patients and these databases using approximate year of incident and other clinical factors in an attempt to gain more insight into the final diagnosis; however, it yielded no further diagnostic information.

Results

The initial screening of the 64 eligible patients resulted in a variety of opinions among the reviewers, ranging from 12 to 28 "likely" cases. The consensus meeting of the three senior authors resulted in a final determination of 10 postoperative MH cases (table 1). Their ages ranged from 6 to 75 yr (age was not specified in 2 subjects). The years of the suspicious reactions ranged from 1995 to 2003 (1 was not specified). All subjects received volatile agents and 6 also received succinylcholine. All subjects illustrated signs and symptoms consistent with those known to be characteristic of acute MH, including generalized rigidity, hypercapnia and/or tachypnea, tachycardia, and hyperthermia. All subjects exhibited a mixed respiratory and metabolic acidosis. Eight subjects exhibited generalized rigidity, and 1 exhibited abdominal

** AMRA report form. Available at: https://www.mhreg.org/forms/AMRA_9-1.pdf. Accessed July 11, 2008.

Table 1. Clinical Characteristics of Subjects with Suspected Postoperative Malignant Hyperthermia

Subject No.	Year of Reaction	Age, yr	Sex	Triggering Agent(s)	Additional Anesthetic Agents*	Surgical Procedure†	Duration of Anesthetic Care, min‡	Clinical Signs, in Order of Occurrence§	Estimated Time Interval Range between GA Finish and Beginning of MH, min
1	1995	19	M	Isoflurane	Propofol, N_2O, fentanyl, nalbuphine, rocuronium, neostigmine, glycopyrrolate	General surgery—unspecified	80	Hypercapnia, tachypnea, generalized rigidity, dark urine, rapid temperature increase to 39.1	15
2	1999	25	M	Isoflurane	Midazolam, famotidine, scopolamine, propofol, N_2O, fentanyl, morphine	Oral surgery	174	Tachycardia, tachypnea, hypercapnia, rapid temperature increase to 40.3, abdominal rigidity	16
3	1995	75	M	Isoflurane	Midazolam, propofol, N_2O, fentanyl	Kidney stone removal	140	Tachycardia, tachypnea, cyanosis, generalized rigidity, rapid temperature increase to 40.3, diffuse bleeding	10
4	Not specified	25	M	Isoflurane, succinylcholine	Ranitidine, midazolam, droperidol, thiopental, N_2O, fentanyl, morphine, vecuronium, neostigmine, glycopyrrolate	General surgery—unspecified	91	Tachycardia, rapid temperature increase to 41.8, hypercapnia	5
5	1998	36	F	Isoflurane, succinylcholine	Propofol, fentanyl	Obstetrics	35	Tachycardia, tachypnea, rapid temperature increase to 42.8, cyanosis, generalized rigidity	40
6	1999	26	M	Isoflurane, succinylcholine	Propofol, rocuronium	Kidney stone removal	58	Tachypnea, cyanosis, tachycardia, rapid temperature increase to 41.7, generalized rigidity, hypercapnia	7
7	1996	12	M	Isoflurane	Midazolam, propofol, N_2O, fentanyl	Plastic surgery—unspecified	230	Generalized rigidity, tachycardia, tachypnea, hypercapnia, rapid temperature increase to 39.7	10
8	1996	Adult	M	Isoflurane, succinylcholine	Midazolam, propofol, vecuronium	ENT, plastic surgery—unspecified	660	Tachycardia, generalized rigidity, tachypnea, hypertension, hypercapnia, rapid temperature increase to 40.0	15
9	2001	6	M	Halothane, succinylcholine	Propofol, N_2O, fentanyl, rocuronium, ondansetron	Plastic surgery, skin graft for burn	135	Tachycardia, generalized rigidity, tachypnea, hypercapnia	5
10	2003	44	M	Isoflurane, succinylcholine	Midazolam, sodium citrate, N_2O, fentanyl, morphine, cisatracurium, neostigmine, glycopyrrolate	Orthopedic—unspecified	440	Generalized rigidity, tachypnea, hypercapnia, cyanosis, tachycardia, rapid temperature increase to 40.0	0

* The Adverse Metabolic Reaction to Anesthesia report (AMRA) does not distinguish between premedications and anesthetic agents. † The AMRA lists surgical service, and not specific surgical procedure, although sometimes it is included in the narrative section. ‡ The AMRA lists anesthetic induction and end times but not surgical start and end times. § Some signs may have occurred concurrently.

ENT = ear, nose, and throat; GA = general anesthesia; MH = malignant hyperthermia; N_2O = nitrous oxide.

rigidity. No subject demonstrated hyperthermia as the initial presenting sign. All subjects were treated with dantrolene and survived the event.

Latency periods in all patients ranged between 0 and 40 min. In two patients (1 and 3 in table 1), the time of discontinuation of the volatile anesthetic was listed on the AMRA—these latency periods were 15 and 10 min, respectively. In patient 10, the AMRA was accompanied by a narrative statement: "Pt developed muscular rigidity, tachypnea, tachycardia, and hypertension just as he was extubated. Prior to that he was resting comfortably on his stretcher awaiting postop x-ray results." Although no time of anesthetic discontinuation was listed, we assigned a latency time of 0 min. In the remaining 7 patients, the latency periods were assigned based on the difference between the time of the first MH-related sign and the anesthesia finish time. These ranged from 5 to 40 min.

Discussion

As Malignant Hyperthermia Association of the United States hotline consultants, we (R.S.L., R.K., J.R.T.) have been impressed by the relatively large volume of calls from anesthesiologists seeking advice on the possibility of MH in patients with postoperative fever. Although numerous publications attest to the fact that postoperative fever is common[2–8] and not caused by MH,[9] we believe that many anesthesiologists are under the impression that the onset of MH may be delayed well into the postoperative period. Therefore, we undertook this analysis of the NAMHR to further understand the incidence of postoperative MH and its clinical characteristics. Our major findings are as follows: (1) Postoperative MH is uncommon—we believe it occurred in 10 of 528 suspected MH cases (1.9%) reported to the NAMHR; (2) when postoperative MH occurred, it usually began shortly after completion of the surgical procedure or in the initial stages of the postoperative period; and (3) hyperthermia was not the initial presenting sign in any of these cases.

Postoperative MH has been reported in the anesthetic literature. A careful evaluation of these published cases reveals that they seem to follow one of four clinical patterns: (1) classic acute MH occurring shortly after the completion of surgery and the general anesthetic (table 2)[10–13]; (2) atypical MH manifesting as delayed rhabdomyolysis in patients subsequently identified as MH susceptible by contracture testing[14–17]; (3) unsubstantiated reports made doubtful by the absence of positive contracture testing or unconvincing clinical characteristics[18,19]; and (4) cases in which the initial presenting signs of MH seemed to begin in the intraoperative period.[20,21]

Classic MH with an initial presentation in the postoperative period is rarely reported; in addition to the cases we found in the NAMHR, we could only identify three additional published reports.[10–12] The clinical characteristics of these patients resemble our cohort of cases with regard to presenting signs and the short latency time of onset after the completion of the general anesthetic. Of note, none of the published cases presented with hyperthermia without additional signs of acute MH.

Postoperative rhabdomyolysis in patients with proven MH susceptibility is more common. In all reported cases, the initial presentation was the onset of brownish discoloration of the urine, which then prompted further evaluation and discovery of rhabdomyolysis. Classic signs of MH such as generalized rigidity, tachypnea, tachycardia, and hyperthermia were absent. It is presently unclear whether patients who present with postoperative rhabdomyolysis and subsequently demonstrate an abnormal caffeine–halothane contracture test result have an MH-causing mutation or a subclinical muscle disease, which results in a false-positive contracture test result.

There are a number of limitations inherent in this methodology of examining an extant database that has been populated with cases of indeterminate cause. The NAMHR database relies on voluntary reporting of suspicious cases from anesthesiologists. These cases may or may not have been discussed with Malignant Hyperthermia Association of the United States hotline consultants, and in most cases, we suspect that the final diagnosis of MH was not confirmed by contracture testing. Although each record was closely examined for a final diagnosis, none made any mention of diagnostic testing for MH or alternative diagnoses. However, as recently pointed out by Burkman *et al.*[22] and Hopkins,[23] in the absence of contracture testing, the precise diagnosis of MH is difficult because there is no single pathognomonic feature and there are multiple differential diagnoses. Therefore, it is possible that we unknowingly included cases that were not true MH and, conversely, omitted cases of true MH. Furthermore, retrospectively reporting a cohort from an existing database is subject to limitations of incorrect data entry and, most importantly, absence of all possible cases of postoperative cases of MH that have

Table 2. Previous Reports of Classic Postoperative Malignant Hyperthermia

Study (Year of Publication)	Age, yr	Sex	Procedure	Time to Symptom Onset	Presenting Signs/Symptoms	Medical History	Diagnostic Modality
Beldavs *et al.*[10] (1971)	22	F	Ovarian cystectomy	<1 min	Generalized rigidity, cyanosis, hyperthermia to 105°F, hypotension	Spontaneous leg cramps, sister with high CK after GA	CHCT[13]
Newson[11] (1972)	10	M	Correction of velopharyngeal insufficiency	Not available (patient in recovery area)	Tachycardia, tachypnea, generalized rigidity, hyperthermia, cardiac arrest	Undescended testicles, lumbar vertebral anomalies, high-arched palate	Clinical only
Britt[12] (1988)	4	F	Cystoscopy	On arrival to PACU	Tachycardia, tachypnea, cyanosis	Unusually muscular, strong family history of MH	CHCT of family members

CHCT = caffeine–halothane contracture test; CK = creatine kinase; GA = general anesthesia; MH = malignant hyperthermia; PACU = postanesthesia care unit.

occurred. Nevertheless, one of the major aims of this investigation was to demonstrate that initial postoperative fever in the absence of signs of hypermetabolism is unlikely to be MH, and we believe that our examination of these cases as well as those known published cases substantiates this principle. If it exists, postoperative MH with signs and symptoms that begin more than 1 h after discontinuation of anesthesia seems to be such an infrequent presentation of this rare disease that it should warrant investigation of alternative diagnoses.

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