

## Prediction of Malignant Hyperthermia Susceptibility by Clinical Signs

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Malignant Hyperthermia (MH) is a potentially fatal disorder triggered by certain anesthetics which presents with multiple signs of variable intensity and time course. Most of the signs are not, in themselves, unique to MH, and each has an extensive differential diagnosis. Thus, the early diagnosis of MH during anesthesia is often difficult.

This study consists of two parts. First, we analyzed the initial anesthetic experience of a group of children who subsequently proved to be MH susceptible to determine which clinical signs might be predictive of MH susceptibility.

Second, we analyzed these patients' response to one specific general anesthetic technique often utilized for MH diagnostic muscle biopsy. Since dantrolene may affect interpretation of the halothane/caffeine contracture test used for the diagnosis of MH susceptibility, our patients did not receive dantrolene. Thus, we were able to evaluate the safety of presumed "non-triggering" anesthetic agents in the absence of the MH protective effect of dantrolene.

## METHODS

The hospital records of all children (n = 48, age 18 months to 13 yr) presenting for MH muscle biopsy from 1976-1984 were retrospectively reviewed, together with

questionnaires sent to the family and initial anesthetic records from the referring institution.

MH susceptibility was determined by the *in vitro* contracture response of muscle to halothane and caffeine. Patients were considered MH susceptible [MH(+)] if any of 4-8 muscle fascicle preparations developed >0.5 g contracture on exposure to ≤2% halothane, >0.7 g contracture to 3% halothane, or >0.3 g contracture upon exposure to 2 mM caffeine.<sup>1</sup> Susceptibility to MH was equivocal if muscle fascicle preparations developed 0.4-0.5 g contracture on exposure to <2% halothane, 0.6-0.7 g contracture to 3% halothane, or 0.3 g contracture upon exposure to 2 mM caffeine. All other muscle fascicle responses were considered negative; these patients were considered MH non-susceptible [MH(-)]. The reliability, accuracy, and limitations of the halothane/caffeine contracture test have been discussed elsewhere.<sup>1,2</sup> The biopsy was obtained from quadriceps (n = 45), gastrocnemius (n = 2), or rectus abdominus (n = 1) muscles.

Forty-two patients were biopsied because a previous adverse anesthetic reaction was clinically equivocal for MH. Patients with clear-cut MH, as evidenced by an otherwise unexplained fulminant hypermetabolic state, did not come to biopsy. Either initial anesthetic records (27/42) or letters summarizing operative events from referring anesthesiologists (15/42) were examined. Thirty-nine of 42 patients with prior adverse anesthetic reactions were referred by outside physicians.

Adverse anesthetic reactions were defined as otherwise unexplained: masseter or generalized muscle rigidity, acidosis (pH < 7.28 or base deficit > 6 mEq · l<sup>-1</sup>), hypercarbia (P<sub>CO<sub>2</sub></sub> > 46 mmHg), tachycardia (heart rate > 140 min<sup>-1</sup>), temperature elevation (temperature increase of >1.4 °C or temperature >38.8 °C), arrhythmia, myoglobinuria, and/or elevated creatine kinase (CK > 100 U/L). Arterial blood gases were measured in 8/17 MH(+) and 6/24 MH(-) patients. While all MH(+) patients had intraoperative or postoperative CK determinations, only 17/24 MH(-) and 1/2 MH equivocal patients had CK measurements. Because part of this retrospective study examined events occurring at several institutions, the quality and quantity of the data were variable. When no other source of information was available, qualitative clinical impressions made by the anesthetist at the time of the event were utilized.

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Received from the Department of Anesthesia, The Pennsylvania State University College of Medicine; the Department of Anesthesia and Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and The Department of Anesthesiology, Hahnemann University, Philadelphia, Pennsylvania. Accepted for publication October 15, 1986. Presented in part at the Annual Meeting of the American Academy of Pediatrics (Pediatric Anesthesia Section) Philadelphia, Pennsylvania, April, 1983, and at the Annual Meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October, 1983.

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Key words: Hyperthermia; Malignant.

TABLE 1. Indications for MH Muscle Biopsy and Biopsy Outcome

Biopsy Indication	Biopsy Result					Total No.
	MH(+)		MH(-)		Equivocal No.	
	No.	%	No.	%		
Adverse anesthetic reaction	17	100	24	83	1	42
Positive family history	0		3	10	1	4
Siblings with SIDS	0		1	3	0	1
High CK	0		1	3	0	1
Total patients studied	17	100	29	100	2	48

MH(+) = Malignant hyperthermia susceptible by halothane/cafeine contacture test (see text). MH(-) = Not malignant hyperthermia susceptible by halothane/cafeine contracture test. SIDS = Sudden Infant Death Syndrome. CK = Creatine kinase.

Six patients were biopsied for an indication other than previous adverse anesthetic reaction: four for positive family history of MH, one for CK > 10,000 with normal neurological and electromyographic exams, and one for sudden infant deaths of two siblings after viral illness (table 1).

Prior to muscle biopsy, a history and physical examination were performed on all patients. In many patients, a formal neurological exam (MH(+) 10/17 *vs.* MH(-) 19/24), CK determination (MH(+) 9/17 *vs.* MH(-) 17/24), and electromyography (MH(+) 12/17 *vs.* MH(-) 19/24) were obtained.

Muscle biopsy was performed under general anesthesia. The subgroup of 17 MH(+) patients was premedicated with pentobarbital (13/17), morphine (13/17), diazepam (1/17), atropine (6/17), and/or glycopyrrolate (3/17). Prophylactic dantrolene was not used. All patients were monitored with ECG, precordial stethoscope, and non-invasive arterial blood pressure monitor. Temperature was measured with rectal (15/17), or axillary (2/17) probes. End-tidal CO<sub>2</sub> and arterial blood gases (ABG) were measured in 13/17 and 3/17 cases, respectively. Current practice is to measure end-tidal CO<sub>2</sub> in all patients.

A general anesthetic, which included tracheal intubation in all but one case, was administered to all children *via* an anesthesia machine without vaporizers, which was flushed with air or oxygen at 6 l/min for 18 h. All tubing, connectors, and masks from the fresh gas outlet to the patient were new. Anesthetics used were: thiopental-N<sub>2</sub>O-O<sub>2</sub> (17/17), fentanyl (16/17), morphine (1/17), and pancuronium (16/17). Reversal agents were neostigmine and atropine (10/17), neostigmine and glycopyrrolate (5/17), and naloxone (2/17). All but two MH(+) patients received an anticholinergic and an anticholinesterase during the course of their anesthetic. A surgical procedure in addition to muscle biopsy was performed in 7/17 (41%)

of the children. The anesthetic, recovery room, and postoperative records for all muscle biopsy procedures were analyzed for complications.

Prognostic factors analyzed for their relationship to MH susceptibility included: indication for MH muscle biopsy; agents used during the initial adverse anesthetic; intraoperative and postoperative signs and abnormal laboratory findings in the initial adverse anesthetic reaction; and results of pre-biopsy history, physical (including formal neurological) exam, creatinine kinase (CK) determination, and electromyography. The relationship between masseter rigidity and MH susceptibility was reported previously in three of these patients.<sup>3</sup>

The relationship of single prognostic factors to MH susceptibility was evaluated using Fisher's exact probability test. For each adverse anesthetic reaction, the probability of a patient having a positive MH muscle biopsy divided by the probability of a negative biopsy (the odds ratio) was calculated. The joint significance of two or more prognostic factors was evaluated by the categorical data analysis method of Agresti.<sup>4</sup> The relationship between the number of adverse anesthetic reactions and MH susceptibility was evaluated by the  $\chi^2$  test.

## RESULTS

Seventeen of 48 children (35%) who underwent MH muscle biopsy were MH susceptible (MH(+)). Two biopsy results were equivocal. One occurred in a neurologically abnormal patient who experienced fever, prolonged emergence, and elevated CK during a previous anesthetic; the other occurred in a patient with a strong family history of MH. The remainder had normal halothane/cafeine tests (MH(-)).

Forty-two of the 48 children (88%) presented for biopsy because a previous adverse reaction to anesthesia was clinically equivocal for MH. All MH(+) children in this series derived from these 42 patients. Forty-one of the 42 (98%) initial anesthetics included halothane and/or succinylcholine (table 2). One MH(+) patient presented for biopsy because of masseter rigidity and bigeminy during his forty-fifth anesthetic with halothane and/or succinylcholine (Gibbons PA: Personal communication).

Generalized muscle rigidity was the only factor associated with MH susceptibility at the  $\alpha = 0.05$  level of significance (table 3). Thirteen of 17 children (76%) with a history of generalized muscle rigidity were MH(+), whereas only 3/24 MH(-) patients (12%) experienced muscle rigidity (odds ratio 18.4, 95% confidence interval 3.9-87.3,  $P < .0001$ ). In all patients, generalized muscle rigidity was associated with at least one other adverse reaction.

There was a significant association between the presence of two or more adverse reactions during any anesthetic, and MH susceptibility ( $\chi^2 = 4.097$ ,  $P < .05$ ). All MH susceptible patients experienced a combination of

two or more adverse anesthetic events. In seven MH(-) patients, masseter rigidity, acidosis, or temperature elevation were the sole adverse anesthetic events identified.

Twenty-one of 42 children (50%) with prior adverse anesthetic reactions had masseter rigidity reported. Of those patients with masseter rigidity, 10/21 (48%) were MH(+). However, masseter rigidity was not predictive of MH susceptibility at the  $\alpha = .05$  level of significance: 10/17 MH(+) patients (59%) versus 11/24 MH(-) patients (46%,  $P = .53$ ).

Six of 7 patients experiencing generalized muscle rigidity and/or masseter rigidity whose postoperative serum CK values exceeded 20,000 U/l were MH(+). Four of five masseter rigidity patients with recorded postoperative serum CK > 20,000 U/l were MH(+). The only MH(-) patient with masseter rigidity and a CK > 20,000 U/l was myopathic (Becker's dystrophy).

Halothane followed by succinylcholine triggered 13/16 episodes (81%) of generalized muscle rigidity. The three remaining episodes were triggered with halothane alone, succinylcholine given after thiopental, or succinylcholine and halothane given after thiopental. Halothane followed by succinylcholine triggered 19/21 episodes (90%) of masseter rigidity; the other two cases were triggered by succinylcholine given after thiopental.

Other prognostic factors, alone or in combination, did not add significantly to the probability of diagnosing MH susceptibility. These non-significant factors included hypercarbia, acidosis, arrhythmia, tachycardia, myoglobinuria, and fever.

Two of eight MH(+) patients had intraoperative ABGs without hypercarbia or acidosis; they received no dantrolene or bicarbonate.

If the initial anesthetic abnormal signs were excluded, the patient and family history were not predictive of biopsy

TABLE 2. Drugs Used during Initial Anesthetics and Relation to Biopsy Outcome

Anesthetic Drugs	Biopsy Result					Total No.
	MH(+)		MH(-)		Equivocal No.	
	No.	%	No.	%		
Halothane and succinylcholine	14	82	15	62	0	30
Halothane, no succinylcholine	2	12	6	25	0	7
Succinylcholine, no halothane	1	6	2	8	1	4
Unknown	0		1	4	0	1
Total patients with adverse anesthetic reaction	17	100	24	100	1	42

outcome. Abnormalities found on the prebiopsy physical exam were not predictive. When obtained, neither formal neurological examination, pre-biopsy CK, nor electromyography were predictive of biopsy outcome.

No MH(+) patient had significant MH related intraoperative or postoperative complications from the biopsy anesthetic. One patient had prolonged, but ultimately reversible, paralysis after repeated doses of pancuronium.

### DISCUSSION

In this series of patients, the only predictor of MH susceptibility was generalized muscle rigidity during the initial adverse anesthetic which included halothane and/or succinylcholine. In all MH(+) patients, generalized muscle rigidity was associated with other adverse reactions. No patient with a single isolated adverse anesthetic sign or abnormal laboratory finding was MH susceptible, as de-

TABLE 3. Clinical Data Recorded during Initial Anesthetic and Relation to Biopsy Outcome

Type of Adverse Reaction	Biopsy Result						Total	
	MH(+)		MH(-)		Equivocal No.			
	No.	%	No.	%		No.	%	
Generalized muscle rigidity*	13	76	3	12	0	16	38	
Masseter rigidity	10	59	11	46	0	21	50	
Myoglobinuria	7	41	6	25	0	13	31	
CK > 100 U/l	17	100	15	62	1	33	79	
CK 100 to 20,000	11	65	12	50	1	24	57	
CK > 20,000	6	35	2	8	0	8	19	
Acidosis	5	29	4	17	0	9	21	
Hypercarbia	4	24	0		0	4	10	
Hypoxemia	1	6	1	4	0	2	5	
Temperature elevation	4	24	9	38	1	14	33	
Tachycardia	5	29	8	33	0	13	31	
Arrhythmia	5	29	5	21	0	10	24	
Total patients with adverse anesthetic reactions	17	100	24	100	1	42	100	

\* MH(+) group vs. MH(-) group,  $P < 0.0001$ , see text.

terminated by muscle biopsy. While not a useful predictor of biopsy outcome, 48% of all patients with masseter rigidity were MH(+), which is in agreement with other reports.<sup>3,5</sup>

Even though generalized muscle rigidity is a recognized sign of MH, the value of rigidity as a prognostic factor for MH susceptibility during clinically equivocal MH has not been reported previously.<sup>6</sup>

No children were reported to have limb muscle rigidity in the Flewellen and Nelson study of masseter rigidity.<sup>5</sup> However, of the 11 children judged to be MH(+) by Flewellen, ten had a phenotype K response only (abnormal contracture to caffeine in the presence of halothane). These ten patients would not have been diagnosed MH(+) by our laboratory, so it is not surprising that they did not experience generalized muscle rigidity.

Ellis and Halsall reported succinylcholine-induced muscle rigidity in 43% MH(+) versus 28% MH(-) patients.<sup>7</sup> Our results may differ from the Ellis study because the Ellis study included both adults and children, did not differentiate generalized muscle rigidity from masseter rigidity, and did not report the frequency of muscle rigidity in non-succinylcholine anesthetics.

Schwartz *et al.* reported a 1% incidence of masseter rigidity in children who were induced with halothane and then given succinylcholine.<sup>8</sup> Ninety percent of our patients with masseter rigidity received both halothane and succinylcholine. Contrary to Schwartz's 100% MH susceptibility rate in masseter rigidity patients, we find a 48% susceptibility rate with others finding rates between 51% and 64%.<sup>3,5</sup> Schwartz's results may be related to the calcium uptake assay used to determine MH susceptibility, since this technique is incompletely verified and not correlated with the *in vitro* contracture response of muscle to halothane and caffeine.<sup>2</sup>

This report is in agreement with the results of Rosenberg and Fletcher, who found that a postoperative CK  $\geq 20,000$  after succinylcholine induced masseter rigidity is indicative of either MH susceptibility or an underlying myopathy.<sup>3</sup>

Our patients underwent several selection processes: referral was made to us, a biopsy was recommended, and then parents agreed to the biopsy. It is not known whether the predictors for MH susceptibility which we identified also apply to patients who did not undergo biopsy, or who were referred elsewhere. For these reasons, we cannot report incidence rates of MH.

Analysis of initial anesthetics was limited by variations in monitoring, treatment, and documentation. For example, infrequent arterial blood gas measurement obscured analysis of the potential predictive value of hypercarbia and acidosis. Analysis of the potential predictive value of formal neurological examination, pre-biopsy CK,

and electromyography was limited by the more extensive evaluation of the MH(-) patient.

A more accurate data base is needed to allow further study of these predictors. We propose establishing a central registry for all suspected MH reactions to facilitate a prospective study of the relationships between specific adverse anesthetic events and MH susceptibility. Potential benefits could include improved clinical diagnosis of MH, and reduced need for muscle biopsy.

Our study of 17 pediatric patients with documented MH susceptibility indicates that an appropriate general anesthetic for MH muscle biopsy may include thiopental, N<sub>2</sub>O-O<sub>2</sub>, pancuronium, and narcotic. Anticholinesterase and anticholinergic drugs caused no apparent adverse effects. This finding is in agreement with Ording and Nielsen's recent study of adult MH susceptible patients.<sup>9</sup>

In summary, generalized muscle rigidity during an anesthetic is a valuable, but not absolute, predictor of MH susceptibility; its presence was associated with a significant 18-fold increase in risk of being MH susceptible, as determined by subsequent muscle biopsy testing. Only patients with two or more adverse anesthetic signs or abnormal laboratory findings were MH susceptible. A central registry of suspected MH reactions is proposed, to permit prospective investigation of this important subject. Thiopental, N<sub>2</sub>O/O<sub>2</sub>, narcotic, pancuronium, neostigmine, atropine, and/or glycopyrrolate appears to be a safe anesthetic regimen for MH susceptible children.

The authors thank Julien F. Biebuyck, M.B., D.Phil., and John J. Downes, M.D., for their valuable suggestions and review of this manuscript, and we thank P. A. Gibbons, M.D., for informative discussions. We thank Ms. Vera Rogers for her assistance with medical records.

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