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Masseter Muscle Rigidity and Malignant Hyperthermia Susceptibility in Pediatric Patients

An Update on Management and Diagnosis

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Background: **Controversy exists regarding the definition of masseter muscle rigidity (MMR) and anesthetic management after MMR. This study reports current anesthetic management after MMR, estimates the incidence of clinical malignant hyperthermia (MH) in patients with MMR, and is the first to evaluate the coincidence of MMR with malignant hyperthermia susceptibility (MHS) according to the 1987 North American Malignant Hyperthermia Group protocol.**

Methods: **Practicing anesthesiologists referred pediatric patients for biopsy between 1986 and 1991 based on evidence of MMR after succinylcholine (1975–1991). The clinical scenario was described as MMR alone or MMR followed by signs of MH, including arterial CO_2 tension > 50 mmHg, arterial *p*H ≤ 7.25, and base deficit > 8. Patients had caffeine–halothane muscle contracture testing to determine MHS.**

Results: **Seventy patients (50 boys and 20 girls) were evaluated. Eighty-three percent (58 of 70) of anesthetics were halothane–succinylcholine. In 68% (48 of 70) of cases, the anesthetic was discontinued, whereas anesthesia was continued with nontriggering agents in 11% (8 of 70) and with triggering agents in 13% (9 of 70). Fifty-nine percent (41 of 70) of patients were diagnosed as MHS by muscle biopsy. In 7% (5 of 70) of patients, clinical MH developed within 10 min of MMR.**

Conclusions: **This study, by using the current North American Malignant Hyperthermia Group protocol, reaffirms the high incidence (59%, 41 of 70) of MHS associated with MMR as confirmed by muscle biopsy. Of the MHS patients, 5 developed signs of clinical MH. Most anesthesiologists in this study, when confronted with MMR, discontinued anesthesia. Because of the potential lethality of MH and the > 50% concordance between MMR and MHS, the most conservative course of action after MMR is to discontinue the anesthetic and observe the patient for clinical evidence of MH. An acceptable alternative, depending on the urgency of the surgery, would be to continue anesthesia with nontriggering agents for MH, with appropriate monitoring. (Key words: Anesthetics, volatile: halothane. Malignant hyperthermia: masseter muscle rigidity. Neuromuscular relaxant: succinylcholine.)**

MASSETER muscle rigidity (MMR) occurs with an incidence of 0.3–1% in pediatric patients after induction of anesthesia with halothane followed by intravenous succinylcholine for tracheal intubation.[1–3] Currently, controversy exists regarding the definition of MMR and the anesthetic management after MMR. Because of the strong association of MMR with malignant hyperthermia susceptibility (MHS) by the caffeine–halothane contracture test *in vitro*,[4–7] it has been recommended that after trismus, anesthesia be discontinued[4,8] or continued with a nontriggering agent.[9] The association of MMR as a harbinger for malignant hyperthermia (MH) has been questioned,[10] however, and one study has even recommended continuing anesthesia with triggering agents after MMR.[1] Because the MH syndrome does not always occur on exposure to triggering agents, many MHS patients have undergone previous uneventful anesthetics with a triggering agent.[11,12]

The purposes of this study are to report the current anesthetic management of MMR in a pediatric population referred to us for diagnostic evaluation; for the first time to evaluate the coincidence of MMR with MHS according to the 1987 North American Malignant Hyperthermia Group (NAMHG) standardization[13] of the caffeine–halothane muscle contracture test; to estimate the incidence of clinical MH in patients after MMR; and to extend the population of patients with serum creatine kinase (CK) > 20,000 IU/l after MMR to estimate the predictability of MHS by this indicator.

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Materials and Methods

Approval for these studies was obtained from the Hahnemann University Human Studies Committee. Seventy pediatric patients (ages 2–15 yr) in whom MMR had developed after succinylcholine (1975–1991) were evaluated for MHS between 1986 and 1991. The patients were referred to Hahnemann University by practicing anesthesiologists. Information concerning the anesthetic management, clinical course, and pertinent laboratory data of the patients was obtained from a retrospective chart review, patient examination, and referring physicians. The clinical scenario was described as MMR alone or MMR followed by signs of MH. Clinical MH was judged to be present when arterial CO_2 tension > 50 mmHg with adequate controlled ventilation, arterial $pH \leq 7.25$, and base deficit > 8 occurred during the anesthetic. If all of these signs were present, the patient was deemed as having clinical MH.

The procedure for the muscle biopsy has been described previously.[14] All muscle biopsies were performed with regional anesthesia, which included a femoral and lateral femoral cutaneous nerve block with 1.25% mepivacaine and intravenous sedation with midazolam or fentanyl or both.

In our previous investigation,[4] we used a method of diagnosis that differs from the 1987 NAMHG standardization[13] in several ways. First, the number of fiber bundles is fixed at six by the NAMHG protocol. Our previous approach had not fixed a number of fascicles, but usually we had used six to eight. Second, the NAMHG protocol requires that three strips be tested with halothane and three with caffeine. Previously, most of our fascicles were tested only with halothane. Third, by the NAMHG protocol, we now equilibrated the preparations for 30–60 min, whereas previously we had equilibrated only for a few minutes. Fourth, by the NAMHG protocol, we used halothane at a concentration of only 3%. Previously, we had tested the fascicles at 1, 2, or 3% halothane. Fifth, the time of caffeine exposure was fixed at 4 min by the NAMHG protocol, whereas previously the time of exposure had been 2 min. Sixth, the concentration range of caffeine by the NAMHG protocol (0.5–32 mM) differed from our previous range (0.125–16 mM).

MHS was determined by muscle biopsy according to the 1987 NAMHG standardization of the caffeine–halothane contracture test.[13,15,16] According to this protocol, the vastus muscle group is the preferred biopsy site and was the muscle used in all cases. A recovery period of at least 2 months passed between the MMR episode and the muscle biopsy procedure. Histologic examination of all muscle specimens was performed. The contracture testing was completed within 5 h after the muscle specimen had been obtained.

For the contracture test, strips of muscle weighing 50–150 mg were placed in a 37°C bath of modified Krebs solution bubbled with 95% O_2–5% CO_2.[17] Three muscle bundles were exposed to halothane for each patient. After 30–60 min of equilibration, 3% halothane was added to the gas stream and the contracture measured. In three additional fiber bundles, incremental doses of caffeine were added and the contracture measured. Patients were diagnosed as MHS if any one of three muscle fiber bundles tested exhibited a contracture of > 0.7 g when exposed to 3% halothane or if any one of three muscle fibers tested exhibited a contracture of > 0.3 g when exposed to 2 mM caffeine during a dose response. The NAMHG protocol specifies that a positive caffeine contracture is > 0.2 g with 2 mM caffeine.[13] However, because this cutoff point may cause a relatively high incidence of false positive results (15.2%),[18] we raised the threshold to > 0.3 g.

Data were analyzed by a two-tailed grouped *t* test or by a two-tailed test for significance of differences by two proportions, with $P \leq 0.05$ denoting significance.

Results

Seventy patients (50 boys and 20 girls) with MMR were evaluated for MHS by muscle biopsy. Anesthesia was induced in most cases (83%, 58 of 70) by inhalation of halothane and nitrous oxide followed by intravenous administration of succinylcholine (1.5–2.0 mg/kg). The most common surgical procedure (63%, 43 of 70) was an otorhinolaryngologic procedure, in most cases tonsillectomy and adenoidectomy. Analysis of demographic data confirmed intergroup comparability between MHS and MH-nonsusceptible (MHN) patients based on the results of muscle contracture testing. There were no differences between MHS and MHN patients when compared in terms of age (7.3 ± 2.7 and 6.5 ± 2.8 yr), sex (29:12 and 21:8 male:female), and type of surgery (otorhinolaryngologic 27 and 16, orthopedic 2 and 3, urologic 3 and 2, oral surgery 4 and 1, and other 5 and 7).

In 68% (48 of 70) of patients the anesthetic was discontinued (fig. 1). In cases in which the anesthetic was continued, a nontriggering agent was used in 40% (8

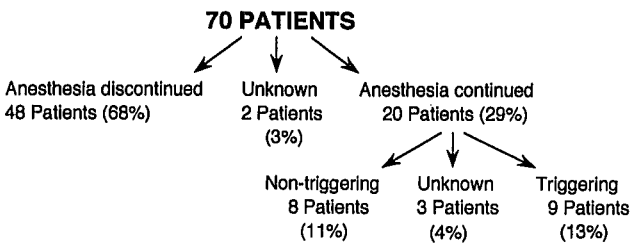

Fig. 1. Anesthetic management after masseter rigidity.

of 20) and a triggering agent in 45% (9 of 20). Anesthetic management was not recorded in the remaining 15%. Eleven percent of patients were treated with dantrolene.

Fifty-nine percent of the patients with MMR (41 of 70) were diagnosed as MHS by muscle biopsy (fig. 2). In all cases, results of histologic examination were unremarkable and showed no evidence of muscle destruction. In 12% (5 of 41) of those diagnosed as MHS, clinical MH developed as manifested by arterial CO_2 tension > 50 mmHg with adequate controlled ventilation, arterial $pH \leq 7.25$, and base deficit > 8 within 10 min of MMR, but there was neither mortality nor morbidity. In 4 of these 5, the anesthetic was discontinued, and in 1 it was continued with a nontriggering technique. Three of the 5 patients were treated with dantrolene. In none of the MHN patients did signs of clinical MH develop.

Of patients with serum CK > 15,000 IU/l (n = 13), 77% were MHS, and of those with serum CK > 20,000 IU/l (n = 5), 80% were MHS. Although the values we report for serum CK were the highest recorded, they are not necessarily peak values: because this study is retrospective, it is impossible to know when serum CK concentrations were highest. In patients for whom the records indicated that urine myoglobin was tested, it was more commonly found in MHS patients (9 of 15) than in MHN patients (1 of 7) ($P = 0.022$, two-tailed test for significance of differences between two proportions). In no patient did a hyperthermic response (temperature > 37°C) develop, either during the anesthetic or in the postanesthesia care unit.

Discussion

This study, using the 1987 NAMHG protocol,[13] reaffirms the high incidence (59%) of MHS by the *in vitro* contracture test associated with MMR in the pediatric population when halothane and succinylcholine are used together.[4-7] Although earlier work reported an association of myopathic conditions in some patients with MMR,[4] for no patient in the current study group was there a myopathic finding on histologic examination or clinical presentation.

The sensitivity of the caffeine–halothane contracture test was found to be 96% and the specificity 95% in swine genotyped for the MH defect[19] using the cutoff points in the current study. In previous studies, MHN patients received anesthesia with triggering agents, and in none did clinical MH develop.[20,21] Based on a study of a large number (109) of control subjects and 24 MHS subjects, the sensitivity and specificity of the 1987 NAMHG protocol with a cutoff point of ≥ 0.5 g for halothane and ≥ 0.3 g for caffeine were estimated to be 100 and 78%, respectively.[22] These cutoff points for halothane and caffeine are similar to those used in this study.

The quantitation of the clinical presentation of MMR is very subjective for the clinician. Kaplan[23,‖] has hypothesized that there are three populations of response of the masseter muscle to succinylcholine and that the population with actual MMR (termed "jaws of steel") is the least frequently observed and is most frequently associated with MHS. One definition of incomplete jaw relaxation after succinylcholine (termed "stiffness") is subclinical and can only be measured by a highly sensitive traction device.[10] This response is a variant of the normal population and does not seem to be related to MHS. A second definition of incomplete jaw relaxation after succinylcholine (termed "jaw tightness") is clinically detectable and interferes with intubation. The mouth can be opened partially, and intubation is possible but difficult. A small number of these patients may be MHS. A third definition of incomplete jaw relaxation after succinylcholine is that in which the mouth cannot be opened even with extreme

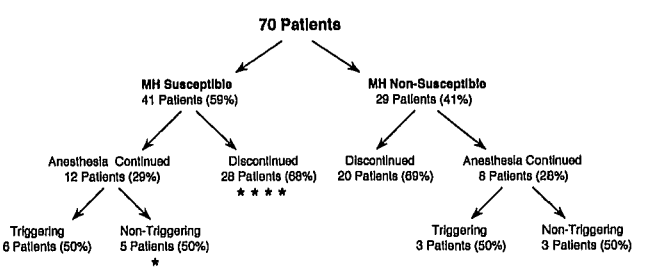

Fig. 2. Anesthetic management based on the results of the muscle contracture test. *Patient with clinical signs of malignant hyperthermia, manifested as arterial CO_2 tension > 50 mmHg, arterial $pH \leq 7.25$, and base deficit > 8.

force (termed "jaws of steel"). It is this group that has true MMR and is presumably most often associated with MHS (biopsy results positive).

Considering the differing presentations of jaw tightness and the various associated probabilities of MHS, Kaplan[23,‖] has recommended various approaches to management, depending on the degree of jaw relaxation after succinylcholine. Because there is minimal MHS associated with subclinical stiffness (detected only with a special traction device) and moderate jaw tightness (partial opening of jaw with interference of intubation), Kaplan recommends for these groups that the anesthetic be continued with nontriggering agents. Kaplan has hypothesized that the third group, in which severe tightness of the jaw prevents intubation (jaws of steel), is highly associated with MHS and therefore is at increased risk for MH. Certainly, if peripheral muscle rigidity also is present, then the likelihood of MHS is very high.[24] Management of this group would include discontinuation of anesthesia and observation of the patient for the development of additional clinical signs of MH.

Of the MHS patients in the current study (n = 41), 5 (12%) developed signs of clinical MH, defined as having all of the following: arterial CO_2 tension > 50 mmHg with adequate controlled ventilation, arterial $pH \leq 7.25$, and base deficit > 8. Of the total number of cases in which MMR developed (n = 70), clinical MH defined by those criteria represents at least 7%. Although all patients in this study who developed clinical signs of MH did so within 10 min, we strongly caution the clinician that 10 min may not be enough time for MH to develop in some patients. None of these patients experienced morbidity or mortality, probably because of the early discontinuation of the triggering agent. That hyperthermia was not observed in any patient reinforces that this sign can be a late phenomenon of MH. In none of the MHN patients did clinical signs of MH develop.

Data gathered from the Malignant Hyperthermia Association Hotline# as well as from the North American MH Registry may shed light on the apparent discrepancy between the low clinical incidence of MH after MMR and the observation that in 50% of patients experiencing MMR, results of muscle biopsy are MH-positive. As defined in this study, approximately 7% of all cases of MMR were associated with clinical signs of MH. Based on Hotline consultation reports# during 1990, 12 of 71 (17%) of MMR cases could be classified as having clinical signs of MH. The reason why, in 50% or more of patients experiencing MMR, results of muscle biopsy examination for MH with caffeine-halothane are positive, and yet the clinical incidence of MH is much less (7% in this report), most likely relates to several factors:

1. The false positive rate of the caffeine–halothane contracture (78% specificity)[18]
2. The finding that not all exposures to trigger agents result in MH,[11] even in susceptible patients
3. A high likelihood ($\approx$ 50%) of MHS occurs in a subpopulation of masseter response to succinylcholine (jaws of steel), despite the possibility that MMR may result from a normal response to succinylcholine in most cases[10]

Both jaw tightness and jaws of steel are termed succinylcholine-induced MMR. However, those responding so vigorously to succinylcholine that the trachea cannot be intubated are a small proportion of the entire group of MMR patients. Assuming that the clinician is more concerned by the jaws of steel response and is more likely to refer members of that group for muscle biopsy, then the incidence of a positive contracture test for MH will appear to be higher in the entire MMR group because of this selection process.

We again noted a wide range of serum CK values after MMR. This laboratory value is routinely increased after an episode of MMR. As for a positive predictive test of MHS, we again found that a serum CK value > 20,000 IU/l is strongly associated with MHS. We previously stated that a serum CK > 20,000 IU/l in the absence of myopathy was predictive of MHS. We now know of two patients (one in this study and one described by Kaplan and Rushing[25]) with serum CK > 20,000 IU/l who have tested MHN. Neither patient as yet has evidence of myopathy. Lower serum CK concentrations (< 20,000 IU/l) do not rule out MHS: in 24 patients with positive results on muscle biopsy testing, CK values were < 20,000 IU/l. Littleford *et al.*[1] reported peak serum CK values as high as 185,000 IU/l in apparently normal patients, but muscle biopsy results were not reported.

Why should patients who have had an episode of MMR undergo a muscle biopsy? First, a negative result rules

‖ Kaplan RF: Malignant hyperthermia, ASA Refresher Courses in Anesthesiology. Vol. 22. Edited by Barash PG. Philadelphia, JB Lippincott (in press).

Greenberg C, Rosenberg H: Presentations of MH in the community: The MH Hotline 1990 (abstract). ANESTHESIOLOGY 75:A869, 1991.

out MH for the patient and offspring. Second, at times a myopathic condition not related to MH may be found on the histologic examination of the tissue. This finding may influence subsequent clinical care of the patient. Third, many families will accept the risk of a false positive test to identify whether MH is present. Finally, data are necessary to create clinical profiles of those at risk and to provide further information regarding research into the genetics of MH.

A recent report[26] has suggested that even a negative contracture test does not always rule out MH. In a small number of reported cases, patients undergoing an MH episode have had a negative contracture test by the European MH Group protocol. Of additional concern are the observations that certain drugs administered *in vivo* may alter the outcome of the subsequent contracture test.[27,28]

The outcome of the NAMHG protocol with regard to the high percentage of patients with MMR subsequently diagnosed as MHS ($\approx$ 60%) is similar to that in our previous study with a different protocol. Approximately 7% of patients with MMR subsequently exhibited signs of MH. A CK $\geq$ 20,000 IU/l and MMR are reliable predictors of MHS ($\approx$ 80%) by contracture testing.

In this study, we found that most anesthesiologists, when confronted with MMR, discontinued anesthesia. Because of the potential lethality of MH and the concordance between MMR and MHS, we believe that the most conservative course of action after MMR is to discontinue the anesthetic, closely observe the patient for further clinical signs of MH, and determine MHS by muscle biopsy at a later date according to the 1987 NAMHG standardization of the caffeine–halothane contracture test[13] or the European MH Group protocol.[29,30] An acceptable alternative, depending on the urgency of surgery, is continuation of anesthesia with nontriggering agents for MH and observation of the electrocardiogram, the end-tidal CO_2 tension, and temperature with vigilant attention for additional clinical signs of MH.

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