Annual Anesthesiologists Meeting Highlights

Malignant Hyperthermia Issues

The American Society of Anesthesiologists (ASA) annual meeting in San Francisco last October was notable for MHAUS and those interested in malignant hyperthermia (MH), not only in showcasing what has been accomplished, but what still needs to be done.

“We need to work more intelligently through the ASA to ensure that MH is not written off as a problem solved,” said MHAUS President Dr. Henry Rosenberg.

“For example, there was no refresher course on MH this year. We need to educate the leadership as to how MH is important for the future of anesthesia research.

“The future of rational drug use will depend on pharmacogenetics practice guidelines to reduce risk. That’s what MHAUS is doing. In my view, the molecular genetics of MH has implications beyond the OR (operating room). This is yet another opportunity for anesthesiology to be a player in the world of medicine beyond the OR.”

In a separate example of how MHAUS needs to work through the ASA, Dr. Rosenberg commented on how routine temperature monitoring during anesthesia has long been one of MHAUS’ core recommendations. CMS and quality organizations are requiring post anesthesia and normothermia for colon and rectal surgery. MHAUS recommends it for all surgery.

“MHAUS and the MHAUS professionals believe that routine temperature monitoring during general anesthesia should be required and is considered a standard of care in the community,” said Dr. Rosenberg. “Unfortunately, several committees within the ASA have failed to agree on this recommendation.”

The ASA is also developing an endorsement process for simulation centers. “MHAUS needs to be part of this process,” said Dr. Rosenberg. “We can add many scenarios based on our Hotline cases. Those of you at institutions and simulation centers should be looking into this, and hopefully involved.”

There was a very well done computer-based anesthesia simulation program demonstrated at the ASA that could be of exceptional interest for an MH case. Created by Dr. Sem Lempotang and developed at the University of Gainesville, it consists of video with the ability to view the virtual OR and visualize what each person is doing. It was exhibited by one of the drug companies using it for educating people on use of neuromuscular agents.

The MHAUS Recognition Reception was very well attended during the ASA Annual Meeting in San Francisco last October, with about 70 people in attendance.
ABC’s Grey’s Anatomy Depiction of MH “Deceptive” and “Untrue”

If you watched the November 1, 2007, episode of ABC’s Grey’s Anatomy and was shocked and confused by the show’s depiction of a malignant hyperthermia (MH) episode, you weren’t alone. MHAUS received numerous calls from concerned individuals as a direct result of that program – one in particular who had a relative going in for heart surgery and was now concerned that the relative would be left to die!

MHAUS’ reaction to the program was swift and direct, first posting a clarification of the cause and treatment of MH on its website, and then submitting a letter to the show’s Co-Executive Producer and Director Peter Horton.

“The episode is unrealistic and deceptive in the extreme,” the letter read. “The depiction of an episode of MH is untrue.”

In the program, a fictionalized patient undergoes cardiac catheterization and then has open heart surgery, off pump, under awake epidural because of what is described as an “allergy” to anesthesia. Simply put, one does not make such a diagnosis without data, but more disturbing is the description of MH as an “allergy.” MH is an inherited disorder that leads to an increase in body metabolism on exposure to certain (but not all) anesthetics. The patient who is at risk to MH may undergo general anesthesia, but not with the gas anesthetics. There are many other alternatives.

MHAUS also pointed out in the letter the absence of involvement of any anesthesia professional in the care of the patient before, during or after the surgery. This “insults the over 60,000 anesthesia professionals who have dedicated their professional lives to the care of patients,” the letter read.

Further, MHAUS noted in the letter statements by the show’s network that medical professionals review the show for authenticity prior to airing. “If so,” the letter read, “someone was not doing his or her job.”

MHAUS has offered to help in the future through the review by any of its Professional Advisory Council (PAC) members – all MH experts. “The success of the Grey’s Anatomy program should convey the power and believability of your work to your audience,” the letter read. “While ABC’s writer’s license is understood, you must also take on the responsibility of researching what is presented to the public.”

MHAUS has spent 25 years educating the public and the medical profession on how to manage MH, emphasizing repeatedly that the MH-susceptible patient may have general or local anesthesia and necessary surgery should not be avoided just because of the susceptibility to MH.

As of yet, MHAUS has not received a response to its letter.

The Malignant Hyperthermia Association of the United States is a not-for-profit organization dedicated to reducing the morbidity and mortality of malignant hyperthermia and other heat-related disorders by:

- improving medical care related to MH; providing support information for patients; and improving the scientific understanding and research related to MH and other kinds of heat-related syndromes.

For more information or for materials on malignant hyperthermia or MHAUS’ programs, call 607-674-7901; write MHAUS, PO Box 1069, Sherburne, NY 13460; or visit us on the Internet at www.mhaus.org.
Dantrolene Muscle Weakness, Exercise-Induced Rhabdomyolysis, and CHCT Testing Updates Among Topics Discussed

The annual Hotline Consultant Breakfast Meeting was well attended during the American Society of Anesthesiologists (ASA) meeting in San Francisco last fall.

The issue of muscle weakness post dantrolene and the need to have a more rational dosing schedule was discussed. A statement is being distributed to Hotline Consultants for further comments. Dr. Barbara Brandom said Registry data show 20-25% of patients on dantrolene experience clinically significant muscle weakness. Dr. Jerome Parness commented on the pharmacokinetics of dantrolene with single dose studies, where a small amount of muscle weakness would be expected; if, however, a patient is put on continuous infusion of dantrolene in order to prevent recrudescence, there is concern of profound depression of skeletal muscle function, which should return to normal after cessation of the infusion.

On a separate topic, Dr. John Capacchione described his research regarding the possible link between exercise-induced rhabdomyolysis and MH-susceptibility. A number of patients with unexplained exercise-induced rhabdomyolysis also have RYR1 variants as well as positive muscle contracture tests. These patients may be susceptible to other triggers besides known anesthetic triggering agents. Furthermore, about 50% of patients studied with asymptomatic hyperCKemia had positive muscle contracture tests; an investigation of these patients for RYR1 variants is being pursued. Dr. Capacchione plans to discuss these issues further with geneticists and members of the American College of Sports Medicine.

Dr. Sheila Muldoon summarized the activity at the muscle biopsy centers, noting that the busiest center is Wake Forest. All the centers are in need of administrative help with respect to submitting biopsy reports to the Registry. She also emphasized the need to streamline genetic testing with smoother processes for obtaining Hotline case data and AMRA forms for submission to the Registry.

Dr. Muldoon provided an update on the Registry, noting there are 579 AMRAs in the Registry and 1,950 consent forms. She also said that there is a misconception that submission of an AMRA report or issuance of a medic alert bracelet automatically constitutes registration in the Registry. This is not true, as the patient must call the Registry and fill out a consent form. She also noted that the AMRA form needs to be revised; a suggestion was made to contact the PAC to see who should be on the committee.

In other topics, MHAUS Executive Director Dianne Daugherty circulated a first draft of the Consensus Roundtable summary report, “MH - A Clinical Practice Protocol,” and asked that the Hotline Consultants review the draft and provide input. Dr. Marilyn Larach also summarized the MH genetic testing meeting held at the Children’s Hospital of Philadelphia last September. (A full report of this meeting can be found on page 10 in this newsletter).

In other news from the meeting, MHAUS President Henry Rosenberg, MD, noted the hiring of three new employees: Doreen Bates, Cynthia Gardiner and Nicole Viera. He also introduced and explained the responsibilities of Dr. Sharon J. Hirshey Dirksen, PhD., MHAUS’ new scientific officer. (An introduction of Dr. Dirksen appeared in the last issue of The Communicator. Dr. Rosenberg also mentioned the new company that is manufacturing Dantrolene, U.S. WorldMeds, LLC, and announced the postponement of the MH genetics meeting supported by the NIH Office of Rare Diseases.

MHAUS Holds Annual Hotline Consultant Breakfast Meeting in San Francisco
Seven Outstanding Contributors Honored at Recognition Reception

MHAUS held its annual Recognition Reception at the American Society of Anesthesiologists (ASA) meeting in San Francisco last fall, where seven individuals were honored for outstanding contributions.

MH Hotline Partnership Awards
James Chapin, MD of University of Nebraska Medical Center in Omaha, Nebraska and Dorming Wong, MD of California Anesthesia Associates Medical Group in Newport Beach, California, were the recipients of the 2007 MH Hotline Partnership Awards. This award recognizes special cases in which the 24/7 MH Hotline was used to solve MH cases in real time via telephone or Internet. Dr. Wong called the hotline because he was dealing with signs of MH during a surgical procedure in a 72-year-old woman undergoing off pump cardiac surgery. After much discussion they eventually concluded that the case was probably MH and was recommended for a muscle biopsy at UCLA. Dr. Chapin has volunteered his time as a Hotline Consultant for over 20 years. (Note: Dr. Wong was unable to attend the reception).

Outstanding Dedication to MH Award
Harvey K. Rosenbaum, MD, Clinical Professor of Anesthesiology at David Geffen School of Medicine at UCLA received a special recognition, the Outstanding Dedication to MH Award, for his leadership and vision in the promotion and development of the “MH Case of the Month” on the MHAUS website.

Special Recognition Awards
Co-recipients Paul Allen, MD, PhD of Brigham and Women’s Hospital in Boston, Massachusetts, and Susan Hamilton, PhD of Baylor College of Medicine in Houston, Texas, received Special Recognition Awards. Dr. Allen was recognized for his outstanding work in understanding the pathophysiology of MH and the development of a new animal model for MH. Dr. Hamilton was recognized for her outstanding work in understanding the structure and function of the ryanodine receptors and the development of a new animal model for MH. Dr. Rosenberg said that Drs. Hamilton and Allen have been investigating the special characteristics of cellular structure and function in MH susceptibles. They worked through the details of developing an animal blocking agents.

There were many notable exhibits at the ASA. “I was impressed with several exhibits demonstrating the feasibility of downloading printed information as well as images to PDAs and iPods,” said Dr. Rosenberg. “We intend to explore adding the capability to download our material in this fashion. Our podcasts are very successful, with a large number of hits and growing rapidly.”

The MHAUS exhibit also received heavy traffic, with many compliments to the Hotline Consultants and the organization for their help and support. Interestingly, an anesthesiologist from the Philippines stopped to get more information and indicated an MH organization in his country was discussing the creation of a testing center.

Indeed, MHAUS is proud of the many accomplishments in helping to identify and treat MH over the last 26 years. But there is still much more to do. MH is not a problem solved. The North American Malignant Hyperthermia Registry (NAMHR) needs to be included along with other registries at the ASA. And MHAUS needs to alert those speaking and writing on pharmacogenetics at the ASA and other forums related to anesthesia to include MH in their discussions, not just the molecular genetics of metabolizing enzymes.

Said Dr. Rosenberg, “I would welcome your input, your suggestions, and comments to ensure that we can continue the educational research risk management and patient care services of MHAUS and the NAMHR.”

continued on page 5
Continued from page 4

model that expresses the mutations that are responsible for rendering an animal MH-susceptible. The animal model has already suggested that environmental temperature can modulate the development of an MH episode. The animal model will provide greater information concerning the relation of DNA changes to the expression of MH.

**Special Mention Manuscript Award**
Laura Schleelein, MD of Children’s Hospital of Philadelphia received the Special Mention Manuscript Award for “Hyperthermia in the Pediatric Intensive Care Unit – Is it Malignant Hyperthermia?” Dr. Schleelein and coworkers used MH Hotline data to explore how often MH is expressed in the Pediatric Intensive care unit.

**Media Award**
MHAUS Media Award recognized Robert Morell, MD Editor and Chief of Anesthesia Patient Safety Foundation in Niceville, Florida, for his support of the educational mission of MHAUS by encouraging the publication of information that relates to the clinical findings of MH. (Note: Mr. Morell was unable to attend the reception).

**Daniel Massik - MHAUS Anesthesiology Resident Award**
The Daniel Massik- MHAUS Anesthesiology Resident Award was established through the generosity of an MHAUS founder, George Massik, in memory of his son, Daniel. First place went to Frank Schuster, MD of the University of Wurzburg, Department of Anesthesiology in Wurzburg, Germany for his manuscript entitled “A Minimally-Invasive Metabolic Test Detects Probands at Risk for Malignant Hyperthermia.” Dr. Rosenberg said the work of Dr. Schuster and his colleagues have creatively applied physiologic information about MH to developing a minimally invasive diagnostic test for MH that might reduce the use of the standard open muscle biopsy.

(Above) Laura Schleelein, MD, of Children’s Hospital of Philadelphia received the Special Mention Manuscript for her manuscript “Hyperthermia in the Pediatric Intensive Care Unit – Is it Malignant Hyperthermia?”

(Above) Frank Schuster, MD, of the University of Wurzburg, Department of Anesthesiology in Wurzburg, Germany received the Daniel Massik - MHAUS Anesthesiology Resident Award for his manuscript entitled “A Minimally-Invasive Metabolic Test Detects Probands at Risk for Malignant Hyperthermia.”

(Above) James Chapin, MD, of University of Nebraska Medical Center in Omaha, Nebraska and Dr. Dorming Wong (unable to attend), of California Anesthesia Associates Medical Group in Newport Beach, California, were the recipients of the 2007 MH Hotline Partnership Awards.

Paul Allen, MD, PhD of Brigham and Women’s Hospital in Boston, Massachusetts received the Special Recognition Award in recognition of his outstanding work in understanding the pathophysiology of MH and the development of a new animal model for MH. Susan Hamilton, PhD of Baylor College of Medicine in Houston, Texas received the Special Recognition Award for her outstanding work in understanding the structure and function of the ryanodine receptors and the development of a new animal model for MH.
MH Research Well Represented at 2007 ASA Meeting

by Dr. Sharon Hirshey Dirksen, MHAUS Scientific Officer

As is the case with many inherited disorders, a significant amount of research is currently in progress in the area of molecular genetics, in an attempt to identify the genetic defect(s) associated with the development and presentation of MH. It is well known that various mutations in the gene encoding the ryanodine receptor in skeletal muscle (RYR1) have been implicated in the pathogenesis of MH. Over the years, researchers have focused on specific areas of this gene, believing them to be hot spots for mutations and thus genesis of this disorder. This knowledge, along with the sheer size of the gene (and protein encoded) led researchers to target their efforts and resources available on sequencing these hot spot regions of the RYR1 gene in MHS (Malignant Hyperthermia-susceptible) individuals. Unfortunately, this strategy results in a low sensitivity of this particular genetic test for MHS individuals.

More recent research in multiple laboratories within and outside the U.S. indicates that this strategy is changing. Researchers are now in general agreement that screening should not be limited to RYR1 hot spot regions but should cover the complete RYR1 coding sequence.

One example of this change in strategy is illustrated by the work being performed by Dr. Sambuughin at the Uniformed Health Services University, Bethesda, MD. Dr. Sambuughin and her team utilized tissue from MHS individuals who tested positive for MH via muscle contracture testing and analyzed the entire RYR1 gene in order to increase the sensitivity of this particular genetic test for MHS individuals.

Additional novel RYR1 mutations outside the hot spot regions were reported by Dr. Kravea (University of Toronto) and by Dr. Weigl (Medical University of Vienna). Through analysis of the entire RYR1 gene sequence, Dr. Kravea identified novel mutations in Canadian subjects with both MH and Central Core Disease (CCD), while Dr. Weigl identified a novel mutation in Austrian families diagnosed as MHS by positive muscle contracture test findings. These novel mutations have not yet been proven to be causative for MH.

Interestingly, in both Dr. Girard's and Dr. Kravea's research laboratories, a significant percentage of compound heterozygotes were identified; that is, some MH patients were found to harbor more than one RYR1 mutation in their genes. Characterization of the mutations in these compound heterozygotes is ongoing in order to determine the functional significance of these mutations. The implications of these findings with regard to the clinical presentation of MH are unclear, as are many other observations in this field of research. Further progress in this area is needed before we will be able to predict with absolute certainty how an individual's genotypic makeup will affect his/her phenotype with regard to the risk for an MH event.

Understanding the Presentation of MH in the Clinic

While basic researchers continue to progress in their efforts to understand the molecular mechanisms which trigger MH, clinical researchers are also making strides in their understanding of the clinical presentation of this syndrome, as well as its differential diagnosis. A key avenue leading to improvement in knowledge regarding MH diagnosis, presentation, and treatment is the careful review and analysis of information contained in two databases: the MH Hotline database and the North American MH Registry (NAMHR), both resources developed by MHAUS. Two poster presentations, the result of data mining efforts from each of these key resources, were shared with ASA meeting attendees.

Utilizing MH hotline data, Dr. Laura Schleelein (Children’s Hospital of Philadelphia) examined the etiologies of various pediatric hyperthermia cases where symptoms started in the ICU. Eight of sixty-three cases which met these eligibility criteria were ultimately diagnosed, in the hotline consultant’s opinion, as definite or probable MH. Remaining diagnoses included hyperthermia with infections, CNS, or undetermined origin. In addition, the use and apparent benefit of dantrolene in the treatment of hyperthermia, regardless of its etiology was noted. As an aside, Dr. Schleelein’s research was limited by the data she had at hand; in many instances, demographic or outcome information was omitted. We at MHAUS hope to improve the data collection and reporting process with regard to the hotline system, so that the MH hotline resource continues to be a valuable and inviting one for the research community.

The analysis of data contained in the NAMHR formed the basis of the second poster presentation utilizing a key MHAUS asset. Dr. Marilyn Larach (Penn State College of Medicine)

continued on page 7
Continued from page 6

reviewed 19 years worth of Registry data to identify factors associated with fatal outcomes in MH cases. Significant differences between the fatal (n=4) and non-fatal (n=299) groups were found with respect to many clinical characteristics, with the most significant differences being the increased likelihood of the occurrence of DIC (disseminated intravascular coagulation) or the need for CPR (cardiopulmonary resuscitation) for those with fatal outcomes, and the life-threatening events are devastating to family members and to health care providers as well.

Dr. Rosero’s team reports a nationwide MH case number as high as 556 in 2004; he also notes a mortality rate as high as 23.9% in 2001. During the question and answer session following his presentation, Dr. Rosero agreed that the database utilized has certain limitations and although MH was indeed diagnosed, the deaths which occurred may not have been due specifically to the MH event. Nevertheless, even after excluding all equivocal diagnoses, Dr. Rosero’s team calculates a mortality rate of approximately 10%, still higher than expected. Dr. Rosero and Larach’s presentations indicate that, although there have been advances in early diagnosis and treatment of MH, still, we cannot let our guard down. Deaths due to MH may occur, and when they do, these events are devastating to family members and to health care providers as well.

What’s on the Horizon

**New formulation of dantrolene IV**

A major issue in the treatment of patients with MH is the currently marketed form, is a challenge to solubilize. Current recommendations include dissolving the dantrolene powder in pre-warmed sterile water so as to speed its solubilization. A formulation of dantrolene which is easier to dissolve would be a welcome addition to the current pharmaceutical armamentarium. Research presented by Drs. Jan Schotte and Mark Gerbershagen (University of Witten-Herdecke, Cologne, Germany) indicate that Ryanodex, a novel dantrolene formulation, may fit this requirement.

Drs. Schotte and Gerbershagen presented the results of their studies of Ryanodex, a novel formulation of dantrolene which is 150 times more water soluble than the currently available formulation. Results of safety and efficacy studies carried out in MHS swine indicate that ryanodex is comparable to dantrolene, and has a much shorter preparation and administration time.

Thus, it appears that Ryanodex may well be a promising agent for the treatment of MH in clinical practice.

**Minimally-invasive muscle contracture test?**

As noted earlier in this article, steady progress is being made toward the identification of mutations in the RYR1 gene which are causative for MH events in susceptible individuals. However, the in vitro muscle contracture test is still the only means to detect MH-susceptibility in individuals in whom an MH-causative mutation is not found. This muscle contracture test, although recognized as the “gold standard,” is an invasive test, requiring a muscle biopsy from the patient. Research presented by Dr. Schuster (University of Wurzburg, Germany) indicates that a less-invasive diagnostic test is in the works. This test involves injecting certain triggering agents (caffeine and halothane) into a patient’s muscle through tiny cannulae, and measuring the metabolic response by means of lactate levels. Early indications point to the usefulness of this test in distinguishing individuals who are susceptible to MH versus those who are not. A larger trial is in the planning stages which will allow for a more detailed analysis of the sensitivity and specificity of this test.
MH Hotline Activity – Sept. through Dec. 2006

by Margaret Weglinski, MD

During the months of September through December 2006, 16 volunteer physicians answered 122 calls to the MH Hotline. Eighty-three calls involved patients who were experiencing at least one symptom suggestive of MH and the caller was asking for assistance in determining whether or not the patient actually had MH (case consultations). Thirty-nine calls involved only questions about MH. Consultants working on the Hotline included Drs. Adragna, Chapin, Gronert, Litman, Melton, Miller, Millman, Parness, Rosenberg, Skoog, Theroux, Tobin, Watson, Wedel, Wong, and Weglinski. Three of the case consultations were deemed definitely MH and 14 of them were deemed probably MH by a Hotline Consultant. There were two deaths and six of the cases occurred in a non-hospital setting. Twenty-six of the 83 case consultations (31%) involved children less than 18 years of age. Seven of the 26 children were less than one year old.

The majority of callers were anesthesiologists from the United States (representing 32 states). Calls were also received from Canada, Puerto Rico, and Peru. In addition to anesthesiologists, the Hotline was contacted by nurse anesthetists, anesthesia residents, adult and pediatric intensivists, a surgical resident, cardiothoracic surgeon, plastic surgeon, ENT surgeon, emergency medicine physician, pulmonologist, internal medicine resident, internal medicine physician, pharmacist, intensive care unit RN, recovery room RN, materials manager of an ambulatory surgery center, and administrator of an association of ambulatory surgery centers.

Upon review of the 83 case consultations, one trend that emerged was the number of calls (five) involving patients undergoing laparoscopic surgery who developed impressively elevated end-tidal carbon dioxide levels shortly after insufflation of carbon dioxide into the abdomen. This continues a trend noted in both the Spring 2007 and Summer 2007 editions of The Communicator. All of them involved isolated increases in end-tidal carbon dioxide with a corresponding respiratory acidosis on arterial blood gas measurement. In several cases, subcutaneous emphysema was noted. The respiratory acidosis resolved in all cases after the abdomen was deflated. None of the patients were suspected to have MH.

Of the three case consultations that were deemed to be definitely MH, the most dramatic involved a 23-year-old male construction worker who nearly severed his thumb. Three weeks prior to his MH episode, he had undergone a general anesthetic to complete the amputation of his thumb. The anesthetic was unremarkable. He then presented for a toe-to-thumb transfer under general anesthesia. About 7 hours into the case, the nurse anesthetist switched the volatile agent to desflurane and 45 minutes later the patient's end-tidal carbon dioxide was noted to be “off the scale.” The patient was treated with dantrolene, cooling, and switching to a non-triggering anesthetic. Cooling was successful, but his anesthesia team was unable to control his hypercarbia (elevated blood levels of carbon dioxide) and hyperkalemia (elevated blood levels of potassium). An attempt was made to place the patient on cardiac bypass, but the surgeons were unable to cannulate his vessels and he died. The caller wanted to know if the patient might have an MH episode or an adverse reaction to succinylcholine. The Hotline Consultant didn't think this was an episode of MH. They thought it might be related to the succinylcholine if the patient had a myopathy and developed hyperkalemia after receiving succinylcholine. The consultant felt there was too little information to make an accurate diagnosis.

It's interesting to note a case report of two children with FSS who developed masseter muscle rigidity after inhalation induction with halothane (one also received succinylcholine). One of the children also developed generalized muscle rigidity that was unresponsive to...
Meet This Issue’s Hotline Consultant

Dr. Margaret Weglinski, Assistant Professor of Anesthesiology at the Mayo Clinic in Rochester, Minnesota, has been a Hotline Consultant since 1997.

“What I like best about my work with the Hotline is the chance to speak with health care providers from around the country,” she says. “Whether it’s answering a straightforward question about MH or trying to determine whether or not a patient is experiencing an MH episode, I find it rewarding to (hopefully) be of assistance.

In her spare time, Dr. Weglinski likes to travel, bike and hike, and says she tries to combine the three as often as possible.

In the U.S. and Canada, the MH Hotline is 1-800-MH-HYPER (1-800-644-9737)
Outside the U.S., call 1-315-464-7079

Continued from page 8

pancuronium (a muscle relaxant drug) and required a dose of dantrolene (Jones R, Dolcourt JL. Anesthesiology 1992; 77:599-600). Both children showed a significant increase in their serum creatine kinase levels postoperatively. While it’s been suggested that children with FSS have an underlying myopathy that predisposes them to MH, there are several case reports of children with FSS who were anesthetized with halothane and succinylcholine without complication.

September through December 2006 proved to be a busy period for the MH Hotline with consultants fielding 122 calls from a wide variety of health care workers located throughout the United States (and a few outside the U.S.). This speaks to the need for real-time information about MH and the increasing awareness of the MH Hotline amongst medical personnel.

Note: You can view a glossary of MH-related terms on the MHAUS website at www.mhaus.org.
MH Molecular Genetic Testing Workshop Summary

by Marilyn Green Larach, MD

The third Malignant Hyperthermia Molecular Genetic/Diagnostic Testing Workshop, sponsored by the Malignant Hyperthermia Association of the United States (MHAUS), was held on September 7-8, 2007 at The Children’s Hospital of Philadelphia, PA. The organizing committee for this workshop consisted of Drs. Barbara Brandom, Robert Dirksen, Ronald Litman, Sheila Muldoon, and Henry Rosenberg. Dr. Litman hosted this meeting.

Objectives of the conference were to:

1.) Review and update activities related to the caffeine halothane contracture test (CHCT) and alternative tests.
2.) Review and discuss findings related to molecular genetic testing for malignant hyperthermia (MH).
3.) Discuss perioperative and exertional rhabdomyolysis and its potential links to MH.
4.) Develop strategies for increased enrollment of patients in CHCT and genetic studies.

Dr. Muldoon presented data obtained from a survey of 6/7 North American MH diagnostic centers performing the CHCT. During the past three years, 134 CHCTs have been performed with 73 individuals having a positive outcome. The total number of index (where the patient being biopsied was the individual who experienced a possible MH event) cases biopsied was approximately 25. Uniformed Services University of the Health Sciences is the only center performing biopsies on individuals who have experienced exertional rhabdomyolysis. Currently, only 3/7 biopsy centers consistently report results of the MH Biopsy to the MH Registry. Many biopsy centers have waiting lists. Difficulty in obtaining insurance coverage frequently interferes with patients undergoing CHCT.

To date, there are 5 MH loci that have been identified with two of these loci (chromosome 19q13.1 encoding the RYR1 gene and chromosome 1q32 encoding the CACNA1S gene) having proven causative mutations. The genetic testing error rate is 1-3% with an overall 40% detection rate in Europe. Estimates for North America are unavailable. The type of genetic variant identified in MH-susceptible patients varies by country in Europe. We have not analyzed sufficient numbers of patients in North America to know if the same holds true for regions within the U.S. and Canada.

So far, 29 genetic mutations have been found to be causative for malignant hyperthermia. The European MH Group requires four criteria to be met in order to declare an identified variant an MH causative mutation. They are: full description of the genetic mutation both at the DNA as well as the protein level; co-segregation of the mutation with the disease in at least two pedigrees (families); absence of the identified sequence change from 100 controls (individuals without MH-susceptibility) to rule out polymorphisms (non-significant gene variation); and functional characterization of the mutation in either myotubes, microsomal sarcoplasmic reticulum, lymphoblasts, or MH knock-in animals.

There are currently 174 genetic variants described in the European and North American MH-susceptible populations. The variants found in the North American population have been frequently novel (not identified in European populations). The significance of these genetic variants awaits further study. A significant challenge for North American genetic researchers is that gene variants or polymorphisms vary according to racial groups. Thus, what may be a significant variant that is likely to be disease causing for a Caucasian individual may be a normal, not significant, variation for an African-American individual.

Multiple speakers repeatedly emphasized the importance of having a well developed phenotype established for an individual and his/her family prior to attempting to genotype that family. Phenotyping can only be done through obtaining a careful anesthetic and medical history of a full-blown MH event or with the MH muscle biopsy (CHCT or IVCT). All North American MH researchers have found a low yield in genetic variant identification when there is a weak phenotype (such as a non-specific anesthetic difficulty in a family member).

In North America, there are two CLIA genetics laboratories testing for MH-susceptibility. The University of Pittsburgh laboratory (Dr. Kant) has a genetics counselor for individuals being tested and the data collected from individuals as well as the genetic results of analysis are shared with the NAMH Registry of MHAUS when appropriate consent has been obtained. It has a 12% yield doing a 12 exon analysis. A non-targeted analysis costs approximately $700 – 900. A targeted analysis (when a family mutation has already been identified) runs around $300.

PreventionGenetics (Dr. Weber) is the second laboratory. There is no genetic counseling available for the individual being tested, there is no significant acquisition of clinical history; no linkage to the Registry, and feedback is given only to the referring physician who is frequently the patient’s primary care doctor. PreventionGenetics has a 24% yield and does a three tier screening which is sequentially done to analyze up to 38 exons. If all three tiers are done, then the cost is $1690.

continued on page 11
A first tier analysis only is approximately $800. Single exon tests are done at a cost of approximately $300.

Uniformed Services University of the Health Sciences (USUHS, Drs. Muldoon and Sambuughin) has an MH molecular genetics research laboratory. It is linked to the University of Pittsburgh genetics counselor (Ms. Steele) and to the NAMH Registry (Drs. Muldoon and Brandom). It has a 48% yield from analyzing 30 exons. Thus far it has identified 45 different genetic variants in MH-susceptible individuals.

MHAUS is supporting the screening of 100 patients who have been well phenotyped prior to the screening. In order to be eligible for genetic screening by USUHS, the patient must either have: a strongly positive CHCT, a personal experience of a “very likely” or “almost certain” MH event, or be a family member of an individual with a known ryanodine receptor variant. Separately, USUHS will also screen all survivors of an MH associated cardiac arrest and all individuals who had a positive CHCT but a negative genetic screening by the CLIA laboratories.

The following issues were discussed at the meeting by the participants.
1.) Reporting of MH events and a patient’s family history must be improved by linking the Registry AMRA Report with the MH Hotline Report, preferably with direct computer entry.
2.) Patients need improved access to MH diagnostic testing for both the CHCT as well as genetic testing. Without CHCT results, development of a less invasive genetic or alternative test cannot occur.
North American MH Biopsy Centers need to be better financially supported.
3.) There is a disconnect between the patient’s family physician and the biopsy center as regards referral and follow up on MH molecular genetic screening.
4.) There is no consensus on how to anesthetically manage a family member who is negative for an identified familial genetic variant but who has not undergone CHCT. Should this individual be treated as MH susceptible (as in Europe) or non-susceptible?
5.) Dr. Brandom will coordinate access of patients to the USUHS molecular genetic study.
6.) MHAUS will help pay the costs of molecular genetic screening at a CLIA laboratory for patients who have had a positive CHCT.

Have you visited us lately? Log on to www.mhaus.org to get the latest information on MH, order materials, post a message to the bulletin board or challenge yourself with the “Hotline Case of the Month.”
MHAUS Happenings, Events and Notices

❑ THANKS! MHAUS is grateful for the financial support of the following State Societies of Anesthesiology: California, Connecticut, Florida, Illinois, Maine, Maryland, Michigan, Nevada, Ohio and Pennsylvania. Our appreciation also goes to the following state components of the American Society of PeriAnesthesia Nurses: Arkansas, Colorado, Delaware, DC, Illinois, Kansas, Maryland, Missouri, Nebraska, New Hampshire, New Mexico, North Carolina, Pennsylvania, Texas, Vermont and Wyoming. Call the MHAUS office to ask how your group can join their ranks!

❑ MH-Associated Diseases Symposium
Dr. Ron Litman, The Children’s Hospital of Philadelphia, is holding a one day symposium at the Society for Pediatric Anesthesiology (SPA) meeting in April 2008 in San Diego, California. The symposium, sponsored by MHAUS, will focus on MH-associated diseases, as well as the difficult questions regarding which patients require a non-triggering agent. You can find further details about the SPA meeting and Dr. Litman’s symposium at www.pedsanesthesia.org.

❑ Upcoming MHAUS Meeting Dates and Locations
AORN, Anaheim, CA, March 30 - April 3; APA, Washington, DC, May 3-8; AACN-NTI, Chicago, IL, May 5-8; ASPAN, Grapevine, TX, May 5-7; FASA, San Antonio, TX, May 14-17; AANA, Minneapolis, MN, August 9-13; MH Mini-Conference, Phoenix, AZ, September 27-28; ASHRM, Boston, MA, October 2-5; APNA, Minneapolis, MN, October 15-18; ASA, Orlando, FL, October 18-22.

❑ Neuroleptic Malignant Syndrome Information Service presents the 4th Annual NMSIS Promising New Investigators Travel Scholarship Program
Residents, fellows and students are invited to submit a manuscript on psychotropic drug safety and side effects by February 4, 2008. Scholarships of $2500 and $1500 will be awarded at the American Psychiatric Association Meeting in Washington, DC, May 2008. Papers may be submitted to info@nmsis.org or faxed at (607) 674-7910. For more information, visit www.nmsis.org. This program is supported by an educational grant from Janssen, L.P., administered by Ortho-McNeil Janssen Scientific Affairs, LLC.