



Malignant Hyperthermia Association of the United States
and the North American Malignant Hyperthermia Registry

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The

Communicator

*Hotline Partnership Awards
New Prospects for the Millennium
Helping the Registry Work
plus, Hotline Activity*

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Malignant Hyperthermia (MH) is an inherited muscle disorder which, when triggered by potent inhalation anesthetics and some other drugs, may cause a life-threatening crisis. The incidence of MH is low, but, if untreated, the mortality rate is high. Since the advent of the antidote drug, dantrolene sodium, and with greater awareness of the syndrome, the mortality rate has decreased.

Great advances in our understanding of MH have been made since it was first recognized in the early 1960s, but the nature of the fundamental defect(s) is still unknown.

MHAUS advocates that all surgical patients undergoing general anesthesia should receive continuous temperature monitoring, that adequate supplies of dantrolene be stocked near the OR and that thorough family histories be obtained.

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New Prospects for the Millennium... the Ninth International Workshop

by Henry Rosenberg, MD

The 9th International Workshop on Malignant Hyperthermia took place in Copenhagen Denmark on August 25-28, 1999. The program was hosted by Drs. Helle Ording and Diana Bendixin, founding members of the European MH group. Participants came from many European countries, the United States, and from as far away as Japan, New Zealand and Australia.

Presentations covered the gamut from the epidemiology of MH to clinical presentations of the syndrome; relation of MH to other myopathies; potentially new diagnostic tests for MH that are less invasive than the current contracture test utilizing biopsied muscle (IVCT); studies of the molecular genetics of MH as well as the biochemistry and pathophysiology of the disorder. In contrast to previous meetings there was less emphasis on "improving" the IVCT muscle test and a greater emphasis on identification of MH based on DNA analyses.

Perhaps that is because those who are performing muscle biopsies and who have been sharing data for many years have realized that the test is just about as accurate as it can get given the heterogeneity of MH. It is also clear that the false negative rate is close to zero even though there are false positives.

The new millennium will bring a new era of medical practice for all of medicine. The basis of disease diagnosis will soon rest on analyses of the DNA that make up our genes. Knowledge of the molecular genetics of invading organisms will enable scientists to formulate more effective drugs and determine whether the body is infected by a foreign organism. The diagnosis of MH will be made more accurate and easier by these techniques.

It has already been determined that genetic abnormalities (mutations) exist in several genes in patients and swine susceptible to MH.

These genes code for the structure of proteins that are essential to muscle function. If the gene produces an abnormal protein (because of a mutation) the muscle cell may not function normally. In the case of MH this means an abnormal release of intracellular calcium may occur when the patient is exposed to anesthetic agents.

There are now about 30 genetic mutations that are felt to be causal for MH. (In pig breeds one or two mutations are causal.) Evidence was presented at the meeting that specific mutations are associated with MH susceptibility (as defined by IVCT) in specific families around the world.

Unfortunately, in most cases each family harbors a mutation specific to its members. For example, a large Maori family (indigenous to New Zealand) was found to have a specific mutation of the calcium release protein channel (RYR-1) that correlated in almost all family members with MH susceptibility.

Families in Australia, Germany, Ireland and other countries were also demonstrated to have specific mutations that correlated with MH status. In those families, if the mutation is present MH susceptibility may be presumed. However, no one is yet ready to state that if the mutation is absent then the patient is not MH susceptible. That level of confidence will require more years of research.

In addition, only about 50% of families seem to harbor a mutation of the RYR-1 protein. That is because other genetic abnormalities may also cause MH. For example the gene for the dihydropyridine receptor protein (also linked to calcium release) has been found to be mutated in some families.

Even if 30, 40, 50 or more causal mutations are found, it will be possible in the future to determine if the DNA from a patient suspected to be MHS harbors one or more

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.

mutations by using relatively straightforward analytic techniques. Since DNA may be extracted from white blood cells, the testing can be based on a blood sample.

This dream of a simple accurate blood test appears to be arising through the mists of the future. MHAUS has recently started a fund - The Kristin Duell Fund - to support and hasten the arrival of that day. In addition, we plan to provide a grant each year to aid in the development of a molecular genetic test. The first grant of \$25,000 will soon be awarded. However, that sum is barely adequate to support a simple straight forward project.

There are fewer than 6 centers worldwide working on the project of unraveling the genetics of MH as their main goal, none in the US. I feel that this situation should be remedied as soon as possible, since the molecular genetic makeup of MHS patients in the US may be very different from those in other parts of the world. Other approaches to MH diagnosis were also presented.

One approach being developed by Dr. Yoshi Sei in Dr. Sheila Muldoon's laboratory (Bethesda, MD) depends on the extraction of certain forms of white blood cells (lymphocytes). These lymphocytes express the RYR-1 protein - the same that is found in muscle. When the lymphocytes from MH patients are exposed to caffeine they release a larger quantity of calcium than lymphocytes from MH negative patients.

Another test was explained by Dr. Werner Klingler of Dr. Frank Lehmann-Horn's laboratory in Ulm, Germany. Muscle cells cultured and grown from MH patients release larger amounts of hydrogen ions upon exposure to agents that cause muscle contractures than cells from MH negative patients. Also using cultured muscle cells, Kathryn Censeir and Dr. Albert Urwyler of Basel Switzerland have shown that cells from MH patients release larger amounts of calcium on exposure to MH trigger agents than non MH patients.

All of these tests are promising, but preliminary. They also require expensive, sophisticated equipment. Fortunately, muscle cells for culture growth may be obtained by needle biopsy using small amounts of tissue.

Other presentations showed that succinylcholine induced masseter (jaw) muscle rigidity is often associated with clinical MH (New Zealand), that MH or MH like events leading to cardiac arrest often occurs late in an anesthetic or

even in the recovery room (USA) - 9 such events were collected by the MHAUS hotline over the past 5 years. Unexplained elevation of CK is often associated with MH susceptibility (Germany) and that mitochondrial myopathies are not associated with MH (Germany).

From the point of view of the relation of MH to other disorders, Dr. Brandt from Germany demonstrated that mutations on the RYR-1 gene responsible for other uncommon muscle disorders - (central core disease, and hypokalemic periodic paralysis) occur very close to those mutations responsible for some cases of MH.

This area of the RYR-1 protein seems to be responsible for calcium fluxes that mediates muscle contraction. The information from molecular genetic studies will enable us to understand the underlying defects in MH and how MH is related to other muscle disorders. The abstracts of this meeting may be found on the web at: www.iwmh.dk for the next several weeks. We hope to have them archived on the MHAUS web site (www.mhaus.org.)

As we enter the new millennium we are likely to see many improvements in medical diagnosis and treatment.

However, because MH is one of many orphan disorders the funding necessary to make rapid progress and take advantage of new insights and developments is difficult to secure. Large foundations and government agencies are focused on disorders such as AIDS, cancer and heart disease; diseases that affect large segments of the population.

Your contribution to MHAUS is therefore essential in order to ensure that accurate, minimally invasive diagnostic testing - the first step in prevention - will be available and affordable - maybe even by the time of the next International Workshop in 2002 in Washington DC!

Having Trouble Deciding What To Get That Special Someone This Year?

We have the perfect holiday solution. Give a donation to MHAUS in the name or memory of a loved one. It's a one-size fits all gift that will continue to give joy all year, not just sit in a drawer. And the full tax-deduction will come in handy this time of year, as well. Call 1-800-98-MHAUS today for details. We'll even giftwrap.

For more information or for materials on malignant hyperthermia or MHAUS' programs, call 1-800-98-MHAUS; write MHAUS, 39 East State Street, Box 1069, Sherburne, NY 13460; or visit us on the internet at www.mhaus.org.

Anesthesiologist Barbara Brandom and Pediatric Resident Delwyn McComber Awarded Hotline Partnership Honors

MHAUS presented the Seventh Annual MH Hotline Partnership Award to anesthesiologist and MH Hotline Consultant

Barbara Brandom, MD, Children's Hospital of Pittsburgh, Pennsylvania and Delwyn McComber, MD, pediatric resident, Kosair Children's Hospital, Louisville, Kentucky at the

MHAUS Hotline Breakfast held during the American Society of Anesthesiologists meeting this past October in Dallas.

"Dr. Brandom and Dr. McComber demonstrated great teamwork during the post-op care of a three-month old boy who triggered an MH episode in the OR," explained Dr. Henry Rosenberg, President of MHAUS.

The Malignant Hyperthermia (MH) protocol was followed in the OR and the baby was transferred to intensive care under the charge of Dr.

McComber. Dr. McComber immediately called the MHAUS Hotline.

Over a four-day period, Dr. McComber had multiple discussions with Dr. Brandom to get expert guidance in managing the events including muscle stiffness, decreased kidney function, elevated potassium levels and hyperthermia.

"I am very glad that I called the MH Hotline," Dr. McComber says. "Dr. Brandom gave me invaluable, timely advice on how to effectively manage the clinical course of MH. She was available whenever I needed her and her guidelines helped me stabilize the patient in the ICU."

Dr. Brandom recalls, "The doctors in the OR did a very good job of quickly identifying MH and following the MH treatment protocol including the administration of dantrolene. Dr. Raju, the anesthesiologist, called the attending ICU pediatrician into the OR and gave him a clear understanding of the patient's status and evolution of the problems. It is important for medical personnel in the OR, ICU, recovery room and emergency room to be aware of critical resources that are available to them including the MH Hotline."

Dr. Rosenberg concludes, "The effective management of this case clearly illustrates the depth of Dr. Brandom's commitment and dedication to MHAUS to help reduce MH morbidity and mortality. In addition to her volunteer work on the MHAUS Hotline and Quality Assurance Committee, she is highly respected for her work in the pediatric anesthesia community."

Some Recent MH Abstracts:

- Dantrolene and Recovery from Heat Stroke, Moran D et al
Aviation Space and Environmental Medicine 70: 987-,1999
(dantrolene attenuates heat production in rats under heat stress)
- Case of the Month: Feb 1999 - 54-Year-Old Man with Severe Muscle Weakness - MD Hill & JM Bilbeo; Brain Pathology 9:607-608 (1999)
- Differential Effects of Sevoflurane, Isoflurane, and Halothane on CA2+ Release from the Sarcoplasmic Reticulum of Skeletal Muscle - G Kunst, B Graf, R Schreiner, E Martin, RHA Fink; Anesth (Jul 1999) 91,1:179-186
- Lower Limb Compartment Syndrome Resulting from MH - IAT Johnson, JC Andrzejowski, SA Currie; Anaesthesia and Intensive Care (June 1999) 27: 292-294
- Rhabdomyolysis in association with Duchenne's muscular dystrophy - R Obata et al; Can J Anesth (1999) 46,6:564-566
- Segregation of malignant hyperthermia, central core disease and chromosome 19 markers - JL Curran, et al; British Journal of Anaesthesia (1999) 83,2:217-22
- Suspected recurrence of MH after postextubation shivering in the intensive care unit, 18 h after tonsillectomy - JA Short, CMS Cooper; British J of Anaesth (1999) 82,6:945-7

For more abstracts relating to MH, visit our website at www.mhaus.org

Completing AMRA Forms After MH Events Helps the Registry To Work Better

The North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States (MHAUS) gathers, analyzes and disseminates patient-specific clinical and laboratory information on malignant hyperthermia (MH) to anesthesiologists and other health professionals caring for MHS patients and to scientific investigators.

Data are submitted to the Registry on standardized Adverse Metabolic Reaction to Anesthesia (AMRA) forms from health care providers managing a patient at the time of an adverse anesthetic event and MH biopsy center directors at the time a patient undergoes a biopsy. These report forms are entered into the Registry's computerized database which now contains the world's largest collection and laboratory data on MHS individuals.

This database permits the Registry to pursue its research mission to: 1) standardize the clinical and laboratory diagnosis of MH; 2) identify the genetic defects causing MH susceptibility in patients who have been clinically diagnosed as MHS; 3) investigate the epidemiology of MH and other adverse musculoskeletal anesthetic reactions; and 4) improve treatment of MH crises.

Individual MH Hotline Reports

Prior to anesthetizing an MHS individual, the anesthesiologist may contact the Registry to obtain a

one-page MH Hotline Report, which summarizes the patient's database entry including: adverse anesthetic event, MH family history, muscle biopsy result and subsequent anesthetic course. The Registry has prepared more than 1,334 MH Hotline Reports; these may be accessed by calling the Registry database manager at (717) 531-6936. Prior to calling, the anesthesiologist should have at hand the patient's full name, birth date and the patient's mother's maiden name.

Current Goals of the Registry

This past year, the Registry began a study to determine whether the previously identified mutations linked to MH-susceptibility are present in the clinically well base. We hope that the Registry database will soon contain linked clinical, laboratory (including MH muscle biopsy) and molecular genetic data on many MH-susceptible individuals in North America. The Registry also uses its database in order to study the epidemiology of MH in order to aid in the proficient treatment of the disorder.

The Registry encourages anesthesiologists to continue to report adverse perianesthetic metabolic and/or musculoskeletal events so that expanded studies of MH treatment and epidemiology may be conducted. Registry report forms may be obtained from MHAUS (607) 674-7901 or the Registry Database Manager at (717) 531-6936. ■

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Hotline Activity for April-June 1999



During the months of April, May and June, 1999, thirteen Hotline consultants responded to 80

Hotline calls from 32 States, as well as from Canada and Germany. Fifty-nine of these calls were placed by anesthesiologists, 6 by nurse anesthetists, 4 by registered nurses, and 11 by a variety of others including surgeons, laboratory staff members, medical residents, and office personnel.

Twenty-nine of these calls involved specific questions about patient management, such as one from a laboratory supervisor who asked how frequently laboratory tests had to be done for a malignant hyperthermia susceptible (MHS) patient about to undergo surgery (same as anyone else).

Several questions were asked concerning the safe use of local anesthetics (they're as safe in MH patients as in anyone else), the use of specific medications in MHS patients, preparation of anesthesia equipment, and availability of testing for susceptibility to MH.

Fifty-one calls involved consultations for patient management.

Of these, several involved patients who were in the midst of an MH reaction. As in the past, most of the acute cases of MH occurred in patients under the age of 15 years.

One particularly difficult case was that of a 4-month-old boy who developed signs of MH, and then developed severe bronchospasm (much like an asthmatic attack) while the anesthesiologist was treating him for MH.

Rapid and almost simultaneous institution of proper therapy for both life-threatening complications prevented permanent injury to the patient and he made a complete recovery.

Another case involved a 2 year old boy who was given sevoflurane (a commonly used anesthetic gas which can trigger MH) but was not given muscle relaxants, since they were not needed for this surgery. He immediately developed several of the early signs of MH, including a very high pulse rate, a very high respiratory rate, and he began exhaling carbon dioxide at almost twice the normal concentration.

The sevoflurane was stopped, he was treated with dantrolene, and he recovered quickly.

The youngest patient helped during this three-month period

was a 3-month-old who was born 9 weeks prematurely and needed surgery for correction of a birth defect. He was given sevoflurane by mask to induce unconsciousness, and all proceeded normally for about twenty minutes.

Suddenly the carbon dioxide concentration the baby was exhaling rapidly increased to more than twice normal, the pulse rate rose abnormally high, and blood tests showed a great deal of acid in his blood. Many abnormalities can cause an acid buildup in the blood, but one of these things is MH, and when combined with the other symptoms in this patient, the anesthesiologist correctly diagnosed an MH reaction and treated the patient successfully. While he is far too small for a biopsy, this patient's family was referred to a biopsy center for evaluation to determine who else in his family may be susceptible to MH.

An interesting episode

A very muscular 33 y/o male was being given an appropriate anesthetic for a relatively straightforward surgery when he suddenly increased the concentration of carbon dioxide he was exhaling, his pulse rate and temperature rose dramatically, and he began to accumulate acid in his blood. He was given dantrolene, but with little effect. While the caller was in the operating room on the phone with the Hotline consultant, the patient's heart suddenly developed ventricular tachycardia (a bad heart rhythm) and then the patient had a cardiac arrest.

Everyone concentrated their efforts on resuscitating

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

(reviving) this patient, and after a while his heart returned to a fast but otherwise normal rhythm. Dantrolene was given, along with other drugs, the patient gradually recovered, and he is now undergoing physical therapy. Since MH is a muscular disorder, a reaction can cause functional injuries to the muscles.

Additionally, having a large muscle mass can and often does make the symptoms of such a reaction worse for other parts of the body, such as the heart and kidneys. One reason for this is that the muscles store large amounts of myoglobin (a muscular protein) and potassium (an electrolyte) which during an MH reaction can come out into the blood. If this happens, the myoglobin can cause the kidneys to fail, and the potassium can stop the heart.

A 14-year-old rollerblader was hit by a car and was given an anesthetic to repair a broken bone. Four hours into surgery, the carbon dioxide concentration rose in his breath and his temperature began to rise. The anesthetic was changed to a non-triggering type (using drugs that will not trigger an MH reaction) and he was given dantrolene, but with little effect. More dantrolene was given, and finally, after several doses, the reaction gradually subsided.

Many other calls involved patients who exhibited some of the signs of MH...

Many other calls involved patients who exhibited some of the signs of MH, but who had other reasons for having such signs, and the Hotline consultant would point these out to the caller and help them come to a correct diagnosis.

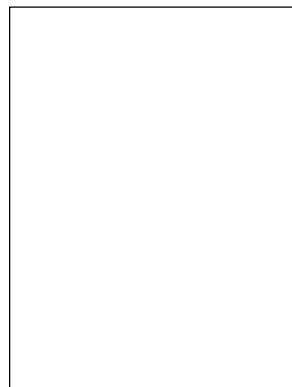
Very common among such calls are cases of fever in a patient who has had surgery for treatment of a source of infection, such as infected tonsils or a ruptured appendix.

While these patients can and do develop MH, careful

distinctions must be made between MH and syndromes that look like MH but are in fact something else. These are often very difficult decisions, for much depends upon the accuracy of the diagnosis.

The physicians who gave their time assisting the callers during this three month period were Drs. Wedel, Landers, Melton, Greenberg, Weglinski, Antognini, Millman, Rosenberg, Miller, Rosenbaum, Watson, Wong and Adragna.

Meet This Issue's Consultant



Hotline Activity was summarized for this period by Michael G. Adragna of SUNY Buffalo and Erie County Medical Center, where he is an Attending Anesthesiologist. Dr. Adragna was the Hotline Partnership Award winner in 1998 for his tireless dedication to fighting MH. He is one of the Hotline's original consultants.

Dr. Adragna lives in New York with his wife of 28 years and their son and daughter.

Because of the rarity of MH, Dr. Adragna feels the Hotline is invaluable to those who suddenly find they need information.

"Those of us who are called upon frequently to assist in the management of an MHS patient remain current with the practices in management and care of MH episodes and can concentrate on delivering the state of the art care."

MHAUS was still in its formative stages when Dr. Adragna, then a consulting director of the anesthesia department at a small rural hospital came up against five MH cases within a year and a half.

"I knew *that* many cases was unusual, so I took it upon myself to educate myself on every aspect of MH," he recalls. "Dr. John Ryan of Harvard, who had written some of the earliest articles on MH spent a lot of time on the phone helping me learn, as did Dr. Henry Rosenberg."

"If there's one word to describe our consultants, it's enthusiastic. We're always looking for ways to deal with MH better. And if you look back ten years, it's clear we are doing things better."

MHAUS Happenings, Events, and Notices

❑ **Article on Chromosome 19 published in recent National Geographic:** MH was briefly mentioned in a recent issue of National Geographic magazine (October 1999) in a genetics article. For more current MH abstracts, please visit the “Latest News” section of our website at www.mhaus.org, or see the partial list on page 4.

❑ **Congratulations to Hotline Consultant Dan Sessler, MD:** One of our hotline consultants, Dan Sessler, and his colleagues have done a study showing that oxygen reduces nausea and vomiting. The article was picked up by AOL medical news and doctors guide.

❑ **MHAUS Medical Identification Tags Available:** Do you want the peace of mind that the MH Hotline will be called FIRST if you or your MH-susceptible loved ones are in an emergency? The tags are imprinted with the MH Hotline number which allows your physician to access your complete medical conditions and be connected with an MH expert within minutes. Call 1-800-98-MHAUS for more information about the MH ID program.

❑ **We extend our condolences to the family of MH researcher Dr. Hugo Reyford:** Dr. Reyford, age 44 was killed by a train outside Istanbul recently while attending the ESRA meeting there. He had just been awarded his PhD for the body of his work and was just published in Anesthesiology. Our hearts go out to his family and colleagues.

❑ **Will Your Employer Match Your Gift to MHAUS?** Many businesses and corporations have “matching contributions” programs. These programs are set up as a means for an organization to support its employees by supporting the employees’ personal charitable interests.

Some matching programs are 100% matching. This means the employer will “match” each dollar the employee donates. If the employee contributes \$50 to MHAUS, for example, the employer will also contribute \$50 to MHAUS.

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