In his Keynote lecture, Dr. Nelson, a pioneer of MH research, spoke about the evolution of the MH concept, how the exciting first discoveries in skeletal muscle calcium regulation have led to the understanding of MH etiology, and how subsequent research have laid the foundation for current advances in basic science and clinical management of MH.

Among the main topics at the Conference were recent advances in MH genetics and the need to develop a non-invasive and sensitive genetic testing for MH. Dr. Gonsalves (National Institute of Health, USA) discussed their approach to apply the revised ACMG/AMP guidelines for assessment of RYR1 variants’ pathogenicity. The availability of an expanded list of the validated RYR1 variants, labeled as pathogenic or likely pathogenic, would make possible genomic screening for MHS in a wider population and could ultimately lead to a dramatic reduction in mortality and morbidity from MH.

Dr. Weber (PreventionGenetics Laboratory, USA) summarized their data on screening the complete RYR1 gene in patients with either personal or family history of MH. Among those patients, 21% carried a pathogenic RYR1 variant, 17% carried a variant of unknown significance and about 4% of the patients carried more than one RYR1 variant.

Dr. Kushnir and his group (Columbia University Medical Center, USA) aim to develop...
Malignant Hyperthermia (MH) is an inherited muscle disorder which, when triggered by potent inhalation anesthetics and succinylcholine, 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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We make a LIVING by what we get, but we make a LIFE BY WHAT WE GIVE
– Winston Churchill

MHAUS Executive Director

This particular issue of The Communicator will be arriving early in the New Year – at a time which most of us have already made major year-end donations to causes we can “get behind” because the organization makes a difference in the world and is in line with our goals. Please know that if you haven’t already given, it’s not too late to consider MHAUS as an organization that deserves your support.

Our mission is to assure appropriate MH education is available for healthcare providers and patients alike. This action, with other changes and discoveries over more than 35 years, has reduced mortality from malignant hyperthermia from 70 - 80% to about 5%. Your monetary support throughout the year will provide a solid base to continue this positive work. This was evidenced by an anesthesiologist who took time at the American Society of Anesthesiologists (ASA) Annual Meeting to record her personal testimonial, wherein she encouraged others to donate to MHAUS as an extremely worthwhile organization that provided an MH expert to consult and lend a hand to her and her patient in their time of need. You can give back to others at any time and help us to save lives from MH by making a tax-deductible donation to MHAUS.

Ongoing MH research has discovered that the number of genetic mutations found to be causative for MH has increased to 44. More genetic locations in the body are being studied and, hopefully, in the years to come scientists will find them all. With this knowledge, perhaps a genetic test could be done prior to any surgical procedure to either rule in or rule out MH as a contributing factor.

During our exhibit hours at the ASA meeting in Boston, we not only shared MH educational materials with the attendees, but also provided access to some of our MH expert hotline consultants at the booth; they shared their expertise with visitors who had specific questions about their personal patients who experienced MH events. The MH experts who support our organization are examples of Winston Churchill’s statement as they “make a life by what they give” to others. They are available to assist their peers 24/7/365 and regularly donate their time to the MH Hotline, freely provided to you by MHAUS. Those of you who are members of the ASA may have visited our booth with questions and received help. We also are very thankful for those who often come to the booth to thank us for what we do; it makes our day! Your ongoing support helps us maintain the MH Hotline as a ready lifeline for all.

MHAUS continues to work with the ASA on projects of common interest and shares feedback and assistance whenever we can. As worldwide recognized MH experts, the members of our MHAUS Board of Directors, Professional Advisory Council and MH Hotline Consultants share perspectives, when requested. For instance, feedback is being made available to the Anesthesia SimSTAT program with regard to the portion of their training dealing with MH. The combined intellectual property available within MHAUS is one of the strongest components of our organization and priceless in value! Customers who reach out to MHAUS via telephone, email or through the online contact forms on the MHAUS website are allowed to reach some brilliant minds who genuinely care about the advice they give.

MHAUS’ products and programs are designed to share important MH education easily and efficiently so the end user can quickly put them into place and improve the quality of care at their facility. The website provides answers to questions, regular updates with regard to MH education, and all types of products to address an unexpected MH event.
a reliable predictive method for assessment of functional and clinical effects of RYR1 variants by using high resolution, cryo-electron microscopy structures of RyR1 and analyzing the spatial localization of a variant relative to functionally characterized RYR1 mutations and known RyR1 functional domains. Ultimately, these structure-function predictions, validated by functional in vitro and ex vivo studies, will help guide the clinical management of patients and the development of novel therapies for RYR1 myopathies.

Dr. Dirksen and his Lab (University of Rochester, USA) studied a role of a novel MH gene, STAC3, in muscle excitation-contraction (EC) coupling. Using electron microscopy, electrophysiology, and dynamic imaging of muscle fibers in a zebrafish model, they showed that STAC3 controls EC-coupling by regulating Ca2+ channel activity and by promoting DHPR stability. Their study also showed that STAC3 mutation in Native American myopathy caused an increased caffeine-induced Ca2+ release, possibly due to higher sarcoplasmic reticulum Ca2+ levels in mutant fibers, supporting an involvement of this gene in MH susceptibility.

Development of non-invasive and sensitive methods for MH diagnostics that could replace the invasive CHCT was another focus of the conference. Dr. Riazi (MHIU, University of Toronto, Canada) presented the results of skeletal muscle metabolomic profiling in patients with MH. Their study identified key metabolites and metabolic pathways that allowed diagnostic differentiation between MHS and MHN individuals. Currently, the MHIU Lab in Toronto explores the feasibility of MH metabolomic profiling using blood samples.

Dr. Klingler (Ulm University, Germany) presented the results of evaluation of metabolic activity in native B-lymphocytes by acidification (proton release) rate measurements. Their study showed that, similar to cultivated myotubes and immortalized lymphoblastoid cell lines, native B-cells from MHS patients displayed significantly higher acidification rate compared with MHN patients when stimulated with a potent RyR1 agonist 4-chloro-m-cresol. These results indicate the possibility of using metabolic assays in peripheral blood B-lymphocytes for prescreening for MHS.

Several presentations were focused on the links between MH and other neuromuscular disorders. Dr. Butala (Allegheny Health Network, USA) talked about the long term sequelae of MH episodes, such as muscle pain, cramps and fatigue, which are indicative of skeletal muscle metabolic dysfunction in patients with MH susceptibility.

Dr. Silvestri (University of Buffalo, Jacobs School of Medicine, USA) discussed data on the potentially increased risk of MH in patients with a wide range of neuromuscular disorders. The data showed a strong link between MH and RYR1-related congenital myopathies. However, currently there is no clear evidence of increased risk of MH in patients with muscular dystrophies, metabolic myopathies, Brody disease, and idiopathic hyperCKemia.

The study presented by Dr. Vladutiu (Children’s Hospital of Buffalo) indicated that pathogenic variants continued on page 5
Available from Par Sterile Products, LLC

For more information on Dantrium® IV and for Full Prescribing Information please visit parsterileproducts.com
in RYR1 and CACNA1S likely contribute to the risk of metabolic crises triggered by certain drugs, such as statins, in a subset of patients. However, the question of whether patients with a demonstrated statin myopathy are at a higher risk for MH remains open.

One of the main points of discussion at the conference was the emerging evidence of association between MH, exercise rhabdomyolysis (ER) and exertional heat illness (EHI). Dr. Hosokawa (University of Connecticut & Korey Stringer Institute, USA) spoke about EHI, pathophysiology of exertional heat stroke (EHS), early signs and diagnostic criteria of EHS. Her presentation highlighted common features of EHS, MH and ER, such as hypermetabolism, hyperthermia, muscle damage, genetic disposition, suggestive of association between those conditions.

Dr. Roberts (University of Minnesota, USA) spoke about the recognition and field treatment of the EHS in athletes. He reviewed EHS pathophysiology, discussed EHS clinical presentation, diagnostic criteria and complications.

Dr. Capacchione (University of Minnesota, USA) described a diagnostic algorithm for patients with recurrent unexplained EHI/ER that includes neuromuscular exam, exercise-intolerance gene panel, myoglobinuria panel, histology, CHCT, and genetic screening. Dr. Capacchione pointed out that despite a possible overlap in etiology of these conditions and MH, no definite conclusions regarding the risk of MH in patients with EHI/ER could yet be made.

Dr. Sambuughin (Uniformed Services University of the Health Sciences) presented the results of the exome sequencing of MHS patients with EHI or ER that revealed variants in genes responsible for skeletal muscle structure and function, muscle metabolism, and genes associated with hyperCKemia. These results underscore heterogeneous etiology and a complex genetic nature of EHI or ER.

Dr. Marcantonio, ARMGO Pharma, Inc., presented a new group of drugs, Rycals, as a potential treatment of RYR1- and RYR2-related disorders caused by leaky RyR1 and RyR2 channels. The ex-vivo studies on muscle samples from patients with RYR1 myopathies showed that Rycals stabilize the closed state of the RyR1 channel and inhibit Ca2+ leak, thus reducing cytoplasmic calcium levels. Dr. Hepner from Eagle Pharmaceuticals described clinical application of Ryanodex dantrolene sodium nanosuspension, DSN, in the treatment of MH and for the prevention of MH in patients at high risk. Nonclinical and clinical data show that DSN is also beneficial for treatment of EHS and for treatment of psychostimulant drug-induced toxicity (PDIT). Ryanodex is a preparation that has an advantage of rapid dantrolene reconstruction and fast administration, which are critical when treating acute life-threatening conditions.

The Conference ended with a round table discussion of the role of registries and databases. Drs. Larach and Rosenberg discussed the role of North American MH Registry and how it has evolved over the years, and they also acknowledged the continued support provided by the MH Hotline Consultants to all practicing anesthesiologists and nurse anesthetists in North America. Dr. Goldberg, president of RYR1 Foundation, discussed the role of the organization in helping to fund the RYR1-related research and providing constant support for patients and families of the patients who carry RYR1 variants/mutations. Jennifer Geurts, MS, CGC, discussed the role of genetic counselor and the importance of the multidisciplinary approach in planning patient care.

Despite advances in the clinical and basic science of MH, the disorder remains an issue of concern for anesthesiologists. The wide-range and in-depth discussions of the latest findings in the field of MH and MH-like disorders provided a strong motivation for clinicians and scientists to continue their research aimed at improvement of MH diagnostics and MH patient management.

**Faces of MH**

*These MH stories illustrate the power of knowledge. Visit the MHAUS website for more Faces of MH.*

**Ruth Ann’s Story**

Twenty-eight years ago in June, my 7-year-old son went in to have surgery for his tonsils; it was routine surgery that his sister had a few months before. Our small town hospital was going through bankruptcy but the anesthesiologist refused to do the surgery without dantrolene... even though, at the time, we had no knowledge of MH running in our family. Praise the Lord! Our son was life-flighted out due to an MH crisis during the surgery. After the MH episode, it was suggested that my family be tested for MH. My son’s father also has MH. My son and his family now wear medic alert bracelets. If that anesthesiologist hadn’t made sure he was prepared, who knows what would have happened. Knowledge is power.

**Richard’s Story**

I had severe varicose veins with phlebitis. Rockford Memorial was suggested for the vein operation. When we set up the appointment, it was mentioned that MH ran in our family. My sister died in 1947 from complications associated with an appendix operation and my brother died in 1948 from complications associated with a car accident. Both deaths were thought to be MH related. With that information, Rockford Memorial gave the okay for the vein operation. However, the doctor and the anesthesiologist suggested that I get tested for MH prior to surgery. So, an appointment was made at the Mayo Clinic for the test. My son came along with me and tested negative while I tested positive. We then went ahead with the vein operation with no issues because the doctors and anesthesiologist were able to take the proper precautions after receiving definitive knowledge of my MH.
Choose **RYANODEX**: formulated for rapid reconstitution and administration with fewer vials and less fluid volume.¹

**RYANODEX® is formulated for speed and efficiency during the critical challenges presented by malignant hyperthermia (MH)²⁴**

- Simple and rapid reconstitution within 10 seconds²
- One-minute administration of a loading dose by 1 provider¹²
- Significantly fewer vials and less IV fluid volume required²⁵⁶
  - One vial of RYANODEX® provides the same amount of dantrolene sodium as 12.5 vials (13 vials reconstituted) of other formulations

**RYANODEX®: Because every minute counts³⁴**

Learn more at Ryanodex.com or call 855.318.2170

**Indications**

RYANODEX® (dantrolene sodium) for injectable suspension is indicated for the treatment of malignant hyperthermia in conjunction with appropriate supportive measures, and for the prevention of malignant hyperthermia in patients at high risk.

**Important Safety Information**

RYANODEX® is not a substitute for appropriate supportive measures in the treatment of malignant hyperthermia (MH), including:

- Discontinuing triggering anesthetic agents
- Increasing oxygen
- Managing the metabolic acidosis
- Instituting cooling when necessary
- Administering diuretics to prevent late kidney injury due to myoglobinuria (the amount of mannitol in RYANODEX® is insufficient to maintain diuresis)

² Data on file. Eagle Pharmaceuticals, Inc.

Please see Brief Summary of full Prescribing Information on the adjacent page.

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Woodcliff Lake, NJ
RYA-MH-2016-043 7/2016
RYANODEX® (dantrolene sodium) for injectable suspension, for intravenous use.

Brief Summary of Prescribing Information. See Package Insert For Full Prescribing Information

INDICATIONS AND USAGE
RYANODEX® is indicated for:

- Treatment of malignant hyperthermia in conjunction with appropriate supportive measures (see Dosage and Administration) and
- Prevention of malignant hyperthermia in patients at high risk.

DOSAGE AND ADMINISTRATION (Selected Information)

In addition to RYANODEX treatment, institute the following supportive measures:

- Discontinue use of malignant hyperthermia (MH)-triggering anesthetic agents (i.e., volatile anesthetic gases and succinylcholine).
- Manage the metabolic acidosis.
- Institute cooling when necessary.
- Administer diuretics to prevent late kidney injury due to myoglobinuria (the amount of myoglobin in RYANODEX is insufficient to maintain diuresis).
- Administer RYANODEX by intravenous push at a maximum dose of 1 mg/kg. If the physiologic and metabolic abnormalities of MH continue, administer additional boluses up to the maximum cumulative dosage of 10 mg/kg. If the physiologic and metabolic abnormalities appear to resolve, repeat RYANODEX dosing by intravenous push starting with 1 mg/kg.

Dose for Prevention of Malignant Hyperthermia

The recommended prophylactic dose of RYANODEX is 2.5 mg/kg administered intravenously as a period of at least 1 minute, starting approximately 75 minutes prior to surgery. Avoid agents that trigger MH. If surgery is prolonged, administer additional individualized bolus doses of dantrolene sodium during anesthesia and surgery.

Dose for Pediatric Patients

The recommended weight-based dose of RYANODEX for pediatric patients in the treatment and prevention of MH is the same as for adults for these indications (see Dose and Administration).

Reconstitution and Administration Instructions

The suspension of RYANODEX must be reconstituted prior to administration. Reconstitute each vial of RYANODEX lyophilized powder by adding 5 mL of sterile water for injection (0.9% sodium chloride injection). Shake the vial to ensure an orange-colored uniform suspension. Visually inspect the vial for particulate matter and discoloration prior to administration.

Must use the contents of the vial within 6 hours after reconstitution. Store reconstituted suspensions at controlled room temperature (15°C to 30°C). (See Dose and Administration Section, see Full Prescribing Information)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Muscle Weakness

RYANODEX is associated with skeletal muscle weakness. The administration of RYANODEX to human volunteers has been associated with loss of grip strength and weakness in the legs. Patients should not be permitted to ambulate without assistance until they have normal strength and balance.

RYANODEX has been associated with dyspnea, respiratory muscle weakness, and decreased respiratory capacity. Monitor patients for the adequacy of ventilation.

SIDE EFFECTS

Adverse reactions observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a study designed to evaluate the safety and tolerability of RYANODEX, healthy volunteers were randomly assigned to receive treatment with RYANODEX or an active comparator at doses ranging from 1 mg/kg to 2.5 mg/kg.

- The RYANODEX dose was infused over the course of 1 minute for each of the doses evaluated.
- The active comparator was an inept placebo formulation of dantrolene sodium that differed from RYANODEX in that it contained dantrolene sodium and mannitol at concentrations of 0.33 mg/ml and 50 mg/ml, respectively, whereas RYANODEX contained the preservative sodium nitrite.

The active comparator was infused at a rate that administered 20 mg of dantrolene sodium per minute for each of the doses evaluated.

Table 1 displays the most common adverse events in this study. These data are not an adequate basis for comparison of the frequencies of adverse events between RYANODEX and the dantrolene sodium comparator.

Adverse events increased in frequency with increasing doses in the trial, but did not differ in frequency between the two treatment groups. RYANODEX-treated subjects were more likely to report adverse immediate adverse events of flushing, dysphoria, and dizziness than those receiving the active comparator.

In all dose groups, hand grip strength declined after dosing. In general, the decline in hand grip strength was more pronounced and occurred more rapidly in the RYANODEX-treated subjects in the 1.0, 1.75, 2.0 and 2.25 mg/kg treatment groups. In the 2.5 mg/kg treatment group, the decline in hand grip strength both in amount and duration was similar to the two treatment groups.

Table 1: Adverse Events in Healthy Volunteers

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Percentage of subjects</th>
<th>Dantrolene Sodium Comparator (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryangex (n=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Severe myalgia</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion site pain</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of another formulation of dantrolene sodium for injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Events

There have been reports of pulmonary edema development following the use of dantrolene. Symptoms of pulmonary edema have been reported in patients receiving dantrolene in combination with calcium channel blockers. Particularly in the treatment of malignant hyperthermia.

Detection of malignant hyperthermia in patients with a history of cardiac disease is recommended.

Muscle Weakness

The concomitant administration of RYANODEX with calcium channel blockers may potentiate the effects on the central nervous system (see Warnings and Precautions).

Intravenous Use

RYANODEX has been associated with dizziness and somnolence. See Warnings and Precautions.

Dizziness and Somnolence

The use of RYANODEX has been associated with dizziness and somnolence. See Warnings and Precautions.

Driving or Operating Machinery

Sedation and impaired judgment may occur. Some of these effects may persist for up to 40 hours. Patients must not operate an automobile or engage in other hazardous activities during this time (see Warnings and Precautions).

References

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Exertional Heat Illness: An Overview

Although data demonstrating associations among MHS, EHS, and ER are of interest and a possible connection cannot be ruled out, future research will be required to elucidate the extent of overlap between EHI/ER and MH and their genetic and pathophysiological links.

Patricia Deuster, PhD, MPH, FACSM, CNS, is a Professor in the Department of Military and Emergency Medicine and Director for the Consortium for Health and Military Performance (CHAMP) at the Uniformed Services University of the Health Sciences, Bethesda, MD.

Francis G. O’Connor, MD, MPH, FACSM is a Professor and Chair in the Department of Military and Emergency Medicine and Medical Director for the Consortium for Health and Military Performance (CHAMP) at the Uniformed Services University of the Health Sciences, Bethesda, MD.

Exertional heat illness (EHI) can occur during physical exertion among young athletes or warfighters when the external heat from the environment and internal metabolic work exceeds the individual’s ability to effectively dissipate the heat through conduction, convection, radiation and/or evaporation. During exercise body temperature increases due to the enhanced metabolic heat production, and a modest rise in temperature is thought to represent a favorable adjustment that optimizes physiologic functions and facilitates heat loss mechanisms as previously described. With compensated heat stress (CHS), the body achieves a new steady-state core temperature, which is proportional to the increased metabolic rate and available means for dissipating heat. Uncompensated heat stress (UCHS) occurs when the body’s cooling capacity is exceeded and the warfighter or athlete can no longer maintain a steady temperature. Continued exertion in the setting of UCHS results in a progressive rise in core body temperature and increases the risk for severe EHI.

EHI comprises a complex of conditions ranging from relatively mild conditions (heat cramps, syncope) to more extreme conditions, e.g., exertional heat stroke (EHS). The prevalence of EHI and EHS among the civilian sector is relatively uncertain because no central surveillance system for reporting exists. However, the highest rates are among football players (1). Yeargin et al. (2) noted that EHI rates for youth, HS, and college football were between 5.7 and 18.2 per 1,000 athlete exposures, defined as one athlete participating in one game/practice. Among runners at the well-known Falmouth road race, the rate of EHS over a period of 18 years was approximately 2.1 ± 1.62 cases per 1,000 runners. In 2016 in the military, where surveillance is excellent, there were 1.96 cases and 0.31 cases per 1,000 person-years for EHI and EHS, respectively, or 2,536 warfighters with some form of EHI, with 401 cases being EHS (3). Since EHS can be life-threatening, sometimes co-occurring with exertional rhabdomyolysis (ER) (4), taking preventive measures is key.

Importantly, some warfighters and athletes are at greater risk than others and a variety of factors can modify risk. Factors that contribute to a higher likelihood of developing EHI include how fit you are, whether you have suffered from a previous heat illness or have a concurrent illness, are taking selected medications or nutraceuticals, and have a genetic predisposition. Other risk factors that should be considered are temperature and humidity, type/intensity of exercise, clothing worn, protective equipment and other gear, and state of acclimatization. Interestingly, sometimes the most motivated and physically fit person – the one who gives it their all – experiences EHS because they are pushing themselves beyond their physical limits. Ultimately, being in tune with and aware of your level of exertion, discomfort, physical sensations and physical limits will be part of the prevention strategy.

Under certain circumstances, those who experience EHS may need to undergo additional testing and evaluations, depending on the associated conditions and underlying risk factors, to facilitate a prudent return to play or duty decision. Two such additional considerations are heat tolerance testing (HTT) and the possibility of Malignant Hyperthermia Susceptibility (MHS). Heat tolerance testing (HTT) is increasingly used by civilian and military providers to help make these challenging decisions. A physician following a patient recovering from EHS must – at some point – make a clinical determination regarding when and if the patient may return to normal activities and resume physical exercise, because no gold standard tests are “approved” to help inform the decision and the decision may be a high-stakes one because an individual’s “career” is on the line. In the military, the decision can have even greater impact as the failure of an individual can affect both the team and the mission. Although physicians must rely on their best clinical judgment, HTTs are being performed each year to help make that decision of
NMSIS Founded By MHAUS 20 Years Ago
Its Important Work Continues on NMS and Other Heat-Related Disorders

Visit the MHAUS website and you’ll find a link in both the medical professional and patients sections for the NMS Information Service. Those unfamiliar with NMS might overlook the links. So what is NMS? And why is it associated with MHAUS?

The Neuroleptic Malignant Syndrome Information Service (NMSIS) serves as an international resource center for knowledge on neuroleptic malignant syndrome in addition to other heat-related disorders and drug side effects. In short, NMSIS serves its purpose by:

- Developing educational support programs
- Supporting clinical and new product research and development
- Implementing updated web-based and published materials
- Providing evidence-based informational and consultative services

NMSIS is entirely supported by contributed funds from members and their families, medical professionals and corporations.

The recognition, diagnosis and treatment of NMS and related hyperthermic disorders is critical in avoiding morbidity and mortality. However, there is often a lack of sufficient data or consensus on the management of NMS, and practitioners are often confused by the baffling differential diagnosis of uncommon but serious NMS-like disorders.

To assist clinicians and advance consensus and understanding of NMS, the Neuroleptic Malignant Syndrome Information Service (NMSIS) was founded in 1997 by the Malignant Hyperthermia Association of the United States (MHAUS) along with a group of prominent psychiatrists with extensive experience in researching and treating NMS.

NMSIS is endorsed by the American Psychiatric Association (APA) and the American Psychiatric Nurse Association (APNA), the Canadian Psychiatric Association and serves patients, families and medical professionals. MHAUS expanded into this area in keeping with its mission to research ways to educate patients and clinicians on NMS and related drug-induced disorders.

Mission
The mission of NMSIS is to serve as an international resource center for educational and research initiatives to promote awareness, improve patient safety, and reduce morbidity and mortality in relation to heat-related disorders. These conditions are uncommon and may be unfamiliar to most practitioners, but can be encountered during the course of routine clinical practice in psychiatry and medicine.

Purpose
NMSIS is dedicated to reducing morbidity and mortality of NMS by improving medical and psychiatric care of patients with heat-related disorders; providing support information for medical professionals, patients and families, and improving scientific understanding of these conditions through research.

Goals
NMSIS has four primary goals:

- Encourage and support research to determine the cause of NMS;
- Advise and prepare all medical and psychiatric facilities for prompt diagnosis and immediate treatment of NMS;
- Develop a standard NMS diagnosis and treatment protocol;
- Promote awareness of NMS to help NMS patients and their families.

For more information, call (607) 674-7920 or email info@nmsis.org.

History of NMSIS
On Nov. 21, 1996, a meeting was held at the Philadelphia County Medical Society to discuss the development of an association to foster the study and recognition of neuroleptic malignant syndrome or NMS. NMS was first identified in the 1960s as a dangerous side effect of certain medications used mostly to treat patients suffering from psychosis. However, this side effect was not well known and was often missed by practicing clinicians.

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NMSIS has served as a unique, world-wide resource for information on NMS and related disorders. NMSIS has published numerous educational pamphlets and articles for patients and professionals. NMSIS has also sponsored several regional and national scientific symposia to increase knowledge of NMS and promote patient safety.

The Shah Educational Awareness Fund was established in 2000 thanks to the generous support of the Shah family to help support educational outreach and further the mission of NMSIS to prevent morbidity and mortality from NMS. A popular family-oriented pamphlet was supported through a generous gift from the Speakman family.

Two decades since its inception, NMSIS continues its successful mission to research ways to educate patients and clinicians on NMS and related drug-induced disorders.

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NMSIS has four primary goals:

- Encourage and support research to determine the cause of NMS;
- Advise and prepare all medical and psychiatric facilities for prompt diagnosis and immediate treatment of NMS;
- Develop a standard NMS diagnosis and treatment protocol;
- Promote awareness of NMS to help NMS patients and their families.

For more information, call (607) 674-7920 or email info@nmsis.org.
when to return athletes and warfighters back to play/duty.

The standard HTT protocol used by the Consortium for Health and Military Performance (CHAMP) at the Uniformed Services University of the Health Sciences was developed by our Israeli colleagues and partners (S-8). It consists of walking for two hours on a treadmill at 3.1 miles per hour and at 2% incline, which is less than 5 metabolic equivalents. The test is conducted in an environmental chamber with the temperature set 40°C and 40% relative humidity when the person is both well-rested and hydrated. During the HTT, heart rate, core temperature, skin temperature at five locations (chest, shoulder, thigh, calf and triceps), sweat rate, fluid intake, and other variables are monitored while the individual performs steady state exercise. The individual’s results are then used to determine whether he/she is able to physiologically adapt to exercise in the heat. As initially discussed, the test attempts to demonstrate that the individual can successfully “compensate” (CHS) to a moderate heat load with a relatively low aerobic demand.

A MH-like syndrome should also be considered by clinicians when a diagnosis of EHS or ER cannot be fully explained by the clinical signs and symptoms presented, when recurrent episodes of EHS or ER (or both) are unexplained, or there is a personal or family history of malignant hyperthermia (9). The association between EHI was first picked up when EHI/ER cases underwent caffeine-halothane contracture testing – and a large proportion were found to be positive (Riazi, 2017 #10). Since then, genetic links among the entities have also been proposed, but the data are not compelling. The ryanodine-receptor one (RyR1) gene is the gene most studied in association with MHS, although at least two other genes – the Calcium Voltage-Gated Channel Subunit Alpha1 S (CACNA1S) and the SH3 and cysteine-rich domain-containing protein 3 (STAC3) genes – have also been associated with MHS (10). Research has shown that a substantial number of patients with EHS/ER also have mutations in the RyR1 gene as well (10), but many others do not (12). Moreover, it appears that some of RyR1 variants identified in EHI/ER patients are rare with unknown functional significance (11) and not those associated with MHS. Thus, although data demonstrating associations among MHS, EHS, and ER are of interest and a possible connection cannot be ruled out, future research will be required to elucidate the extent of overlap between EHI/ER and MH and their genetic and pathophysiologic links. What is clear is that EHI/ER and MH are all complicated and for the most complex cases of EHI and ER, interactions among genetic, lifestyle, medical history, and environmental factors must all be considered.

References

The U.S. and Canada MH Hotline is 1-800-MH-HYPER (1-800-644-9737) Outside the U.S., call 1-209-417-3722
We have blogs, Facebook, Twitter, FAQs, and webinars will be increasing in numbers in the coming months. We welcome suggestions for webinar topics you feel would be helpful. As reference, we have held one specifically for regulatory surveyors and one for patients to date. Recently, we took registrations for another that dealt with issues ambulatory surgery centers and office-based surgicenters face. This was held December 14th at 2:30 pm (ET). The webinars are recorded and are available on the MHAUS website free to members, or at a small fee for non-members, following the actual presentation.

Additionally, we attempt to review and update our products every 2-3 years. A new method of delivery is being developed for the MH In-service to allow those of you who prefer using this MH training on your facility’s intranet. In the next few months, tune into our website for notification of the revised In-service – focused precisely on a clear description of malignant hyperthermia, its presentation, treatment in the acute and post-acute phase, specific details on what happens to the muscle during MH, how to communicate effectively within the team and shares answers with regard to testing options. The product will be available as an online “2 year subscription” and, should you need it, for a small additional charge a hard copy of the printed materials and DVD will also be available for purchase. The MH Mock Drill Training Kit will also be going through an update to present a few different scenarios that will include an event in a hospital AND in an ambulatory surgical setting. Look for it in the spring!

We all at MHAUS appreciate your membership support and want to wish you a wonderful and fulfilling New Year in 2018! Bless you!

Dianne Daugherty
MHAUS Executive Director

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Did you know?

MHAUS offers a lifesaving Hotline, free-of-charge, for any healthcare professional who unexpectedly comes face-to-face with a malignant hyperthermia emergency and quickly needs help. The cost per call to MHAUS is $100.00, and includes the contracted service to transfer your call to a consultant, the costs associated with the MH Hotline Coordinator, who assures there are consultants ready every day on a 24-hour basis for you. Dedicated MH Hotline Consultants, all well-known MH Experts, freely volunteer their time to help their fellow healthcare professionals through an intense situation.

Consider making at least a $100.00 donation (to cover a single call) specifically to help us maintain this lifesaving tool provided by MHAUS to all healthcare professionals.

Enclosed is my tax-deductible contribution of $__________________ in support of the lifesaving MH Hotline.

Please make checks payable to: MHAUS and send to PO Box 1069, Sherburne, NY 13460.

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THANKS! MHAUS thanks the American Association of Nurse Anesthetists and the following State Society of Anesthesiology – New Jersey, Ohio, and Wisconsin – for their financial support. Call the MHAUS office to ask Gloria how your group can join their ranks.

EMHG Group Meeting, May 17-18
The European Malignant Hyperthermia Group (EMHG) meeting is scheduled for May 17-18, 2018, in Ferrara, Italy. As of press, the EMHG has not released details of the meeting, but you can stay up to date on the upcoming meeting by visiting the EMHG website at www.emhg.org.

Join us at the AORN Global Surgical Conference & Expo, March 24-28
MHAUS will exhibit at the AORN Global Surgical Conference & Expo in New Orleans, March 24-28. (The exhibit opens March 25). MHAUS will have the opportunity to connect and network with more than 5,800 prospective customers and affiliate companies at the most highly anticipated event for the perioperative suite. The conference and expo provides 70 live educational sessions designed to generate ideas and provoke new thinking, introduce the latest technology and trends, and provide fabulous events and networking opportunities with more than 5,800 colleagues from around the world. To learn more, visit www.aorn.org.

MHAUS Blog Seeks Contributors
MHAUS monthly blog is open to Board members, the Professional Advisory Council, staff, Hotline Consultants, and MHAUS members-at-large. The only conditions are that the topic relate to MH or MH-like disorders, not exceed 2,000 words, and be appropriate and respectful of all viewpoints. MHAUS invites those interested to comment on MH-related subjects or how MH has affected them and their family. If you have questions or want more information, please email info@mhaus.org.

Did You Miss the Latest MH Patient Webinar?
If you missed any of the MH patient webinars, you can still watch them along with over two dozen other videos posted on the MHAUS website. Just visit the home page and click on “videos” in the navigation bar. You’ll find a host of videos related to education, MHAUS and MH history, MHS patient information, MHAUS programs, MH testing centers, and more.

MHAUS Posts Powerpoints to Enhance Your Professional Development
Visit the MHAUS website for PowerPoint presentations on the “MH Syndrome” and “Rhabdomyolysis in the Perioperative Period.” A third PowerPoint comes from a past presentation at the ASA. You can also test yourself with quizzes.

MHAUS
P.O. Box 1069
Sherburne, NY 13460-1069
www.mhaus.org