REPORT OF A SCIENTIFIC MEETING

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The 3rd International Symposium on malignant hyperthermia (MH) and the 7th International Workshop on MH were held in Hiroshima, Japan, from July 16 to 19, 1994. The meeting organizers were Michio Morio, Hirokazu Kikuchi, and Osafumi Yuge. Participating in the workshop and symposium were 222 investigators from 21 countries. After a brief review of the history of MH by Dr. Beverly Britz, the meeting covered the range of clinical presentations, diagnostic tests, molecular genetics, and biochemistry.

Clinical Presentation

The clinical presentations of MH were reviewed by representatives from Denmark, Austria, Italy, Japan, North America, Australia, South Korea, Kuwait, and China. Although the number of anesthesiologists administered in most countries is difficult to estimate, those countries having access to such information were consistent in estimating that the anesthetics administered in a single year are about 8–10% of the population size. This is especially useful information for estimating the morbidity and mortality of MH. The overall incidence of MH-like reactions, as judged by clinical presentations, is still estimated at about 1:50,000. This is probably an underestimate of the prevalence of the gene, because an episode of MH is not always triggered on exposure to anesthetics. For example, in Austria, up to three uneventful episodes were reported in about 30% of the patients with an MH episode. The morbidity and mortality have been decreasing in most countries with a heightened awareness of MH and the availability of dantrolene. Additionally, Dr. H. Ørding proposed that a decreased use of succinylcholine and the potent volatile anesthetics and an increase in regional anesthesia were major factors for this trend in Denmark. Current estimates of mortality ranged from about 4% (Austria) to 15% (Japan). The somewhat higher mortality rate in Japan may be due to the number of anesthetics conducted by surgeons, who may be less familiar with MH and using only fulminant cases in the estimate.

Virtually all countries report a significantly high percentage of young (<15 yr) males (about 3:1 over females) with clinical presentations, despite the relative infrequency of surgery in this age group (about 5% of the North American surgeries). With regard to gender, Dr. H. Ørding reported that the type of anesthetic differs greatly between males and females, with the former receiving anesthetics more likely to trigger MH. However, other investigators believed that, although this may play some role, factors more specific to gender seemed to contribute toward the predominance of the morbidity in the male population. The gender difference also was supported by studies reported in swine, which additionally addressed strain-related differences in expression of the MH mutation (Dr. P. J. O'Brien). The combination of a halogenated volatile anesthetic and succinylcholine is consistently the most frequently associated trigger of MH.

In most countries, the greatest percentage of MH cases was associated with otolaryngologic surgeries, and a study of the North American Registry presented by Dr. M. G. Larach cited orthopedic surgeries as a second major population of concern. Significant regional differences in morbidity were noted within Austria (Dr. W. Mauritz; up to 1 incident per 2,600 procedures) and Italy (Dr. V. Tegazzini), and these were attributed to the high prevalence of the MH gene pools within certain areas of the country.

An analysis of the German MH hotline (Dr. U. Schulte-Sasse) suggested that, if anesthesiologists were not consistent on observing increased temperature as an indicator for MH, the sensitivity of detection of episodes in the early stages might be improved. Also, administration of insufficient amounts of dantrolene, failure to increase minute ventilation, and preoccupation with nonspecific facets of therapy distracted from adequate reversal of an episode. MH-like signs during surgery could result in a false conclusion that a subject had an episode of MH. Establishing which patients have had a clear MH episode is essential to determining the sensitivity of the diagnostic test and in advancing the genetic studies. Three clinical grading scales designed to evaluate the probability that clinical signs were the result of an MH episode were discussed. The first, presented by Dr. M. G. Larach, was the outcome of the North American MH Group and North American Registry in collaboration with members of the European MH Group and has been termed the International Clinical Grading System (Anesthesiology 80:771–779, 1994). Although this scale would underestimate the likelihood of MH in those cases in which insufficient data have been gathered, it is a powerful tool for identifying patients with the most convincing MH episodes. The second scale was the Japanese Conventional Criteria originally proposed by Dr. M. Morio. This latter scale judges a clinical episode as MH by a maximum body temperature >40°C or a rate of temperature increase of 0.5°C/15 min with a maximum >38°C and significant clinical findings such as muscle rigidity or serious acidosis. The fulminant cases, as judged by the Japanese Conventional Criteria, were mostly MH ranks 4–6 by the International Clinical Grading System. A third scale, presented by Dr. R. Krivosic-Horber, has some similarities to the International Clinical Grading System but has a provision to account for clinical signs that were not recorded. Although the International Grading System might lack sensitivity at the cost of specificity, it would seem that this third scale would sacrifice some specificity for a higher sensitivity.

Relationship to Other Disorders

Among the disorders addressed were the neuroleptic malignant syndrome (NMS), central core disease (CCD), sudden infant death syndrome (SIDS), and exertional heat stroke. The general consensus is that NMS is a centrally mediated disorder, as reviewed by Dr. S. Yamawaki. Dr. P. Adnet presented in vitro contracture test data demonstrating that the responses in 3 of 33 subjects with NMS were equivocal and none MH-susceptible by the European MH Group Protocol. A relationship between SIDS and MH has been more difficult to establish. However, there are interesting arguments for and against an association with subpopulations of MH-susceptible subjects for NMS and SIDS. Dr. F. Lehmann-Horn reviewed neuromuscular disorders and presented a classification scheme for various associations of these with MH. As addressed under the genetic studies, there is a
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strong but not completely clear association between CCD and MH. Although some members of families with CCD appear also to have MH susceptibility, some of these families do not test positive for MH. While at one time considered unlikely by many in the field, the case for a relationship between exertional heat stroke (reviewed by Dr. K. Shingu) and associated mitochondrial myopathies and a small subpopulation of MH subjects has become much stronger with data presented by Dr. G. Kozak Ribbens.

Another emerging area of interest is succinylcholine-induced muscle breakdown and skeletal muscle disorders such as muscular dystrophy. In a subpopulation of these subjects, a number of deaths have been associated with hyperkalemia and cardiac arrest. Although these events are rare (about six documented per year in North America), the mortality is high, and they suggest that treatment of hyperkalemia after unexpected cardiac arrest should be included in the resuscitation guidelines in the operating room.

Genetics

The only thing that is clear about the genetics of MH is that they are quite confusing. Dr. D. H. MacLennan reviewed the evolution of the genetic studies on the ryanodine receptor and the identification of linkage and specific mutations in porcine and human MH and CCD. The pioneering studies of Dr. MacLennan and Dr. T. V. McCarthy in human and porcine MH seem to have identified a locus on the human genome (chromosome 19q13.1) that is important in causing about 25–50% of human MH. Although a specific defect in the ryanodine receptor (encoded at 19q13.1 on the human genome) plays an important role in porcine MH, the role of specific mutations in the ryanodine receptor causing human MH is less clear. Proteins other than the ryanodine receptor are encoded within 19q13.1 and, considering the potentially complex pathogenesis of MH, these should not be ruled out. Perhaps the most indisputable finding is that a defect in any of at least two (and likely more) genes can cause MH. These findings have been reported by Dr. R. C. Levitt, Dr. D. E. Illes, Dr. F. Lehmann-Horn, Dr. T. Deufel, and Dr. A. Oakey. Drs. I. Hughes presented studies in a very large population of swine that suggested the existence of a genetic component of the halothane reaction independent of the reported ryanodine receptor mutation.

Among the gene candidates are the ryanodine receptor (RyR1) and the α-subunit of the adult skeletal muscle sodium channel (SKM1). Another gene candidate was suggested at the meeting and has now appeared in print (ε2/3/β-subunit of the dihydropyridine receptor). As regards the sodium channel α-subunit, considerable controversy surrounded the involvement of mutations in this gene and "true" MH. For years, the paramyotonia congenita and other demonstrated defects of this protein have been associated with abnormal responses to succinylcholine, including muscle rigidity. Dr. R. C. Levitt addressed the need to determine whether defects in the sodium channel α-subunit are the manifestations of myotonia or whether these mutations may lead to life-threatening MH under certain circumstances.

There seems to be a close association between MH and CCD, both possibly being caused by defects in the ryanodine receptor in some cases. An interesting poster by the Leed's group (Dr. Halsall and Dr. Ellis) strongly suggests that this association is not absolute and can be a far looser association in some families than in others.

Dr. A. D. Roses (Duke University Medical Center), an invited guest speaker, drew some interesting parallels between research in MH and that in other areas, such as the myotonia and Alzheimer's disease. His emphasis was on treating the multiple manifestations of the syndrome as the "malignant hyperthermias" and looking for mechanisms that would explain heterogeneity.

Currently, there is little optimism for a genetic test for MH in the near future. On a more optimistic conclusion, we are learning much about MH by synthesizing the results of the genetic and biochemical studies. Things just are not as clear as originally proposed. Improving the reliability of the diagnostic test to the present state and the development of clinical grading scales may be important steps in assisting the progress of genetic studies.

Diagnosis

In contrast to the more experimental nature of MH diagnosis several years ago, the current trend in Europe and North America is toward standardization and refinement of the halothane and caffeine in vitro contracture tests of biopsied skeletal muscle. The Europeans were the first to adopt a standardized protocol. The North American MH Group has conducted extensive statistical analysis of data pooled from several centers to arrive at standard cutoffs with acceptable sensitivity (about 95%) and specificity (about 80%). In Australia, some laboratories are following the European and others the North American MH Group protocol. The Australians, primarily Dr. M. Denborough, were pioneers in the protocol adopted by the North Americans. Other centers using these protocols are located in South Africa, New Zealand, and Brazil. The outcome of the halothane contracture test was found to be easily reproducible in nine separate biopsies from the same animal, and Dr. G. Kozak Ribbens reported that the biopses was an acceptable biopsy site for diagnostic testing.

Diagnostic testing in Japan has focused on comparing Ca2+-induced Ca2+ release and caffeine-induced Ca2+ release from skinned skeletal muscle fiber preparations. Using the Japanese Conventional Criteria, Dr. A. Takagi reported that the more specific determination appeared to be Ca2+-induced Ca2+ release, with caffeine-induced Ca2+ release somewhat less specific. Dr. M. Endo elaborated on the Ca2+-induced Ca2+ release methodology, and he and Dr. Y. Kawan and Dr. M. Mukaida discussed the successful outcome of the method when applied using the Japanese criteria. Because 22% of the subjects with fulminant MH by the Japanese criteria did not have an accelerated Ca2+-induced Ca2+ release, this was interpreted by Dr. Y. Machara as suggesting that mechanisms other than Ca2+ release should be considered as causative of MH.

Overall, studies comparing the outcome of the three major diagnostic testing protocols (North American, European, and Japanese) would seem to be desirable, as would adding tests bridging these approaches, such as ryanodine testing. Such studies will greatly aid the genetic studies, as proper phenotyping is essential for genotyping. The outcomes of the North American MH Group protocol were compared to the outcomes of the European MH Group protocol in the same subjects. Although there were some differences, they were essentially the same by either approach. The trend toward routine inclusion of histologic evaluation to rule out other muscle disorders has been highly useful in some cases.

Biochemistry

Dr. M. Endo reviewed excitation-contraction coupling and the potential role of the ryanodine receptor in MH. Dr. T. E. Nelson presented the first data highly suggestive that dantrolene acts either di-
directly on the ryanodine receptor or on a system acting on the ryanodine receptor. Dr. Nelson’s data also raised the possibility that low doses of dantrolene may exacerbate the MH episode. Dr. T. Hayashi found that dantrolene stabilizes the plasma membrane in neuroblastoma cells. Dr. J. R. Mickelson identified the presence of the altered ryanodine receptor in the brains of susceptible swine, suggesting central involvement in MH, and also found that the ryanodine receptor mutation does not appear to be directly responsible for the hypersensitivity of contractures to caffeine. Dr. H. Reiford reported on a hypersensitivity of skinned fibers from the masseter muscle to caffeine, possibly explaining the exaggerated response of normal subjects to succinylcholine.

The evidence is building for the existence of a modulator of the MH syndrome that is required for expression of the MH genetic mutation. Among the potential modulating systems are fatty acids, IP$_3$ (or phospholipase C), and a defective antioxidant abnormality. The marked enhancement of halothane-induced Ca$^{2+}$ release in the presence of fatty acids also was reviewed. The complex interplay among these processes and the difficulties in establishing clear cause-effect relationships were reviewed. The metabolism of IP$_3$ and its excess production in MH was reviewed by Dr. P. S. Foster. Under the conditions examined, there were no consistent changes during an MH episode that could be attributed to exacerbating the crisis. Perhaps the production of IP$_3$ by phospholipase C could be one of many events setting the stage for a reaction.

Two groups focussed on the antioxidant abnormality originally addressed by Dr. G. Duthie. Dr. K. S. Cheah, who also reported a method of diagnosis of porcine MH based on deteriorating Ca$^{2+}$ accumulation, found that vitamin E, a free radical scavenger, if given prophylactically, reduces the abnormalities in membrane function, elevated fatty acid production, and the poor meat quality in MH swine. Dr. J. Peacock demonstrated that n-acetylcysteine, a sulfhydryl agent effective in disorders of antioxidant defense, reversed the MH syndrome in the six of ten swine with MH. Additionally, Dr. G. E. Deboer found abnormal free radical scavenging enzyme activities in erythrocytes of MH humans.

Animal Models

Dr. G. A. Gronert reviewed the impact that the porcine model of MH has had on the field. Although the porcine mutation described may not be relevant to most human MH, the pig may continue to play a useful role in understanding a subpopulation of human MH. The primary alternative animal model, the dog, was elucidated by Dr. T. E. Nelson. Some aspects of the canine MH episode differ from porcine MH, such as the lack of muscle rigidity or lactic acidosis in the former. Unlike the porcine model, which is autosomal recessive (although still debated), canine MH is autosomal dominant, making this an especially interesting model.

A rat model of MH using dinitrophenol to uncouple mitochondria before halothane, resulted in fever, rigidity, and acidosis. Dr. S. Cezarolino reported that these signs could be reversed by a membrane-permeable derivative of heat shock protein.

An additional rat model using hyperthermia, succinylcholine, and halothane (or isoflurane) found that low-dose vecuronium and dantrolene could antagonize the contractures induced in vivo under these conditions.

Our understanding of MH, both from clinical and research perspectives, is greatly increasing. This extremely well organized series of meetings truly summarized the most recent findings in the field.

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