MALIGNANT HYPERThERMIA: RELATIONSHIP TO OTHER DISEASES

A. K. W. BROWNELL

The vast majority of patients identified as carrying the MH gene, do not appear to have any other associated disease. There is, however, a small and apparently increasing number of patients in whom the MH trait is reported to be associated with a second disease within the same individual. When these associations are reported the assumption is made, rightly or wrongly, that having one of these diseases predisposes that individual to MH if exposed to the appropriate triggers.

In this paper I explore the relationship between MH and these other diseases and attempt to identify those disease associations which may be significant. For each association I discuss, I shall assign it to one of two categories: what I believe to be significant associations, and associations that seem only to be chance occurrences. It is not my aim to review and enumerate the entire literature relating to this topic.

Problems associated with the task

When one begins a task such as this, several problems immediately become apparent. First, a decision has to be made on criteria that must exist before one will accept that MH has in fact occurred. Second, if there has not been a clinical MH reaction, what evidence is there that the MH gene exists in a particular individual? Third, the diagnostic criteria for the proposed associated disease must be defined.

What, then, are the diagnostic criteria for one to accept the diagnosis of clinical MH? Will there need to be evidence that the patient had classical, full blown, clinical MH, supported by all the appropriately documented laboratory test abnormalities that are known to occur in such cases? If these are the criteria that must exist before one would be willing to accept the diagnosis of MH in case reports, and by implication that the MH gene exists in that individual, then almost all of the case reports that purport to document disease associations with MH would have to be ignored. In the older literature, where full blown clinical descriptions were more likely to be reported, rarely were the supportive diagnostic laboratory tests carried out, since MH was often a retrospective diagnosis. In the more recent case reports the full blown clinical picture is almost never reported, because of the much greater index of clinical suspicion for MH amongst anaesthetists; also, definitive therapy would normally be instituted as soon as there is any clinical suspicion of the disease.

Fortunately there is a way out of the dilemma of trying to determine if MH has occurred, through the use of diagnostic tests for MH. If diagnostic tests for MH are undertaken in a person who had a clinical reaction suggestive of MH, and if they are abnormal, then one is on firm grounds in concluding that (1) the gene for MH exists within that particular individual and (2) the clinical episode was MH (even though the clinical features might have been very incomplete and the appropriate diagnostic laboratory studies missing).

If the presence of a specific test result is to be accepted as proof that the MH gene exists within an individual, one is obliged to evaluate the testing that has been proposed to be able to identify MH susceptibility, and in particular to consider its sensitivity and specificity. While there is general agreement that in vitro contracture tests carried out on biopsied skeletal muscle are reliable for identifying the MH trait, there still remains considerable variability in the interpretation of the results—that is what test response can actually be considered an abnormal response. Although these issues are far from being completely settled yet, considerable progress has been made in this area since the introduction of the first
contracture test in 1970 by Kalow and colleagues [17]. To date the European MH Group has made the greatest strides in developing standardization of test procedures and interpretation of test responses [10].

Tests other than in vitro contracture tests are also reported, by certain laboratories, to be able to distinguish MH-susceptible from normal individuals. Contracture tests carried out on skinned single fibres [39], sarcoplasmic reticulum calcium uptake [25] and platelet nucleotide assay [38] are examples of such tests. Attempts by other laboratories to validate the reliability of these tests either have not been reported or have been unsuccessful [27, 33]. Therefore, until there is more universal agreement on the validity of these tests, other than in vitro contracture tests, to “prove” the presence of the MH gene, when any of these tests are the only ones that have been used to identify or confirm MH susceptibility, there may be hesitation in accepting the conclusion that these individuals actually are at risk for MH.

Is the association significant?

In attempting to assess whether or not a reported co-occurrence of two different diseases is significant, there are several items that have to be considered. First, if one has reliable data describing the prevalence of the diseases in question and if both are rare diseases, intuitively, one thinks that the association may be significant. On the other hand, if one of the diseases has a relatively high prevalence within the population, then observations on much larger numbers of persons would be necessary before one would readily accept the association as anything more than chance. Unfortunately, there are no good data describing the MH gene frequency within the general population. What we do have are data on the frequency with which clinical MH episodes occur during general anaesthesia within various population groups [31]. Unfortunately this type of information is not nearly as useful as knowing what the actual gene frequency is when trying to assess the significance of postulated disease associations.

A second approach to assessing the significance of a reported disease association is to begin by reviewing the disordered mechanism in the one disease and then looking at the other disease to determine if there is any likelihood of a similarly disturbed mechanism in it. If a similarity in disturbed mechanism appears to exist, one will be more apt to conclude that the disease associations have significance. If there does not seem to be any similarity in their disordered mechanism (either known or proposed), then there will be the tendency to regard these reports as nothing more than chance associations or at least unproven beyond reasonable doubt. Unfortunately, this approach is quite limited because the disordered mechanism(s) is/are not fully worked out in MH and certainly not in most of the diseases for which an association has been proposed.

The third approach is one that analyses the disease associations in terms of the end-organ that is known to be primarily affected. In the case of MH the end organ is skeletal muscle.

The associations

All of the diseases that I categorize as appearing to be related (groups (1) and (2) in table I) fall into the broad general classification of myopathies. Since they all share, along with MH, the common property of having skeletal muscle as the defective end-organ, it is intellectually satisfying to speculate that they may indeed share some common disordered mechanism(s) which could allow them to have a significant inter-relationship. There is no such homogeneity within the other group of diseases and, as a result, it is difficult to hypothesize how they might share a common disordered mechanism of disease with MH and, therefore, how they might relate to each other in a significant way. Consequently I have decided to characterize diseases assigned to this group as nothing more than chance occurrences.

Diseases which appear almost certainly to be related

Central Core Disease (CCD). CCD is a morphologically distinct myopathy with quite variable clinical features. Thus patients may range from being asymptomatic to severely disabled as a result of muscle weakness. Diagnosis depends upon the demonstration of “cores” in a significant number of muscle fibres, using oxidative enzyme histochemistry applied to fresh frozen sections of biopsied skeletal muscle. Autosomal dominant inheritance is observed in most subjects [37].

The association of this, apparently rare, myopathy with MH was first reported by Denborough, Dennett and Anderson in 1973 [5]. Subsequently, others have also noted the association. In all
MH: RELATIONSHIP TO OTHER DISEASES

Table I. Diseases which have been reported to be associated with MH

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<thead>
<tr>
<th>Category</th>
<th>Diseases</th>
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<tbody>
<tr>
<td>(1)</td>
<td>Diseases which appear almost certainly to be related</td>
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<tr>
<td></td>
<td>Central core disease</td>
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<td>(2)</td>
<td>Diseases which appear possibly to be related</td>
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<td></td>
<td>Duchenne muscular dystrophy</td>
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<td></td>
<td>King-Denborough syndrome</td>
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<td></td>
<td>Myoadenylate deaminase deficiency</td>
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<td></td>
<td>Other myopathies, for example the Schwartz-Jampel syndrome, the Fukuyama type of congenital muscular dystrophy, Becker muscular dystrophy, periodic paralysis, myotonia congenita, the sarcoplasmic reticulum adenosine triphosphatase deficiency syndrome and mitochondrial myopathy.</td>
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<tr>
<td>(3)</td>
<td>Diseases in which the association appears coincidental</td>
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<td></td>
<td>Sudden infant death syndrome</td>
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<td></td>
<td>Neuroleptic malignant syndrome</td>
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<tr>
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<td>Other diseases, for example lymphomas, osteogenesis imperfecta and glycogen storage disease.</td>
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In patients with CCD in whom in vitro contracture tests have been carried out, with one exception (commented on by Harriman [15]), the results have been abnormal, indicating that the two conditions co-exist. To date, we have found the co-existence of MH and CCD in 11 patients [37]. In this group of patients there is very good correlation between the results of in vitro contracture tests and the clinical occurrence of MH, thus indicating that the abnormal test response is specific for MH. For example, in the 11 patients we have personally observed who have abnormal contracture responses, two of them have had MH reactions during general anaesthesia and a third developed masseter rigidity following the injection of suxamethonium.

Thus on the basis of the presently available evidence, all patients with CCD must be considered at risk from MH unless in vitro contracture tests indicate otherwise. This is the only disease association where there is such a tight correlation with MH.

Duchenne Muscular Dystrophy (DMD). DMD, an X-linked muscular dystrophy, is the commonest myopathy affecting children, even though it only affects males. Although there were suggestions that MH occurred in patients with DMD [23, 35], the first reports of abnormal in vitro contracture responses being used to reinforce a suspected clinical diagnosis of MH were published in 1982 [30] and 1983 [2]. The risk for MH in patients with DMD is unknown and the relationship is not similar to that described for CCD. In the family of the male child reported by Brownell, Fowlow and Pasuwe [1], investigation of other family members proved that the traits for DMD and MH were independent. Although there are now several cases of DMD and MH reported in the same patients, the results of family investigations are inadequate to determine whether the traits are occurring independently, as was the case in our family, or whether there may be a closer relationship in some pedigrees. Until such information is available, I recommend that the two traits be considered independent and thus family members who are free of the DMD trait cannot be advised that they are free of the MH gene unless definitive in vitro contracture testing has been carried out.

King–Denborough Syndrome. This syndrome was first reported after a review of cases of MH in Australia and New Zealand by King and Denborough in 1973 [20]. Subsequently it was labelled the King–Denborough syndrome by McPherson and Taylor [26] when they reported a further case and reviewed the literature. The syndrome as originally described was characterized by short stature, slowly progressive myopathy, thoracic kyphosis, lumbar lordosis, undescended testes, pectus carinatum, and an unusual facial appearance characterized by a small chin, low set ears and antimongoloid obliquity of the palpebral fissures. Unfortunately there were no laboratory features that distinguished the children with certainty. This appears also to have been so with the other reported cases, thus making it difficult to identify these patients with any degree of certainty. The muscle pathology is only briefly referred to in the reports and it is not clear if special studies such as enzyme histochemistry and electronmicroscopy were carried out to rule out a morphologically distinct myopathy such as CCD.
Certainly, the phenotype as described for the King–Denborough syndrome could be seen in patients with CCD.

**Myoadenylate Deaminase Deficiency (MDD)**

Absence of myoadenylate deaminase activity was first described in five of 250 human muscle biopsies by Fishbein, Armbrustmacher and Griffin [11]. Four of the patients with absent enzyme activity reported a degree of exercise intolerance manifested as muscle cramps, stiffness or soreness. Subsequently Kelemen and others [19] reported that MDD appeared to relate to a clinical syndrome of exertional myalgia, and in one family there was a suggestion of autosomal dominant inheritance.

Fishbein and colleagues [12] reported the results of a study that evaluated the hypothesis that there was an association between MH and MDD. Within their total group of patients was one family in which five members were studied. In this family the gene for MH appeared to be inherited from the paternal side, while the gene for MDD appeared to be inherited through the maternal side. This finding suggests that the association of the two diseases is nothing more than coincidental and similar to what was found in the pedigree where DMD and MH co-existed [2]. Although the exact frequency of the MDD gene in the population is unknown it appears to be quite common [11, 19]; thus it should not be surprising that the two diseases would occur together.

**Other myopathies.** There are several case reports in the literature where the conclusion has been reached that MH is associated with some other well defined myopathies. In some instances the association has been reported on the basis of clinical findings alone and in other instances on the basis of the outcomes of in vitro contracture tests. In none of them are there reports of both types of information, as has been the case with CCD and DMD.

The diseases listed here include the Schwartz–Jampel syndrome [36], the Fukuyama type of congenital muscular dystrophy [28], Becker muscular dystrophy [16], periodic paralysis (Brownell, unpublished observations), myotonia congenita [13], the sarcoplasmic reticulum adenosine triphosphatase deficiency syndrome [18] and a mitochondrial myopathy [29]. Much more extensive documentation of the anaesthetic experiences of this group of patients will have to become available before we will be able to state, with certainty, whether MH has in fact occurred in some of the patients and what proportion of patients are actually affected, and, through the study of pedigrees, to determine whether or not the diseases just co-exist.

**Diseases in which the association appears coincidental**

**Sudden Infant Death Syndrome (SIDS).** SIDS is the most common diagnosis in infants who die at 1 month to 1 year of age [40]. Attention was first drawn to its association with MH by Denborough [3], in the father of a child who had died of SIDS. Subsequently Denborough, Galloway and Hopkinson [6] reported that contracture responses were diagnostic for MH in five of 15 parents tested who had children die from SIDS. The documentation of abnormal anaesthetic events in this group of patients has been fragmentary. Ellis and Heffron [9] were not able to confirm the high frequency of the association that had been reported by Denborough, Galloway and Hopkinson [6]. Ellis and Heffron [9] concluded that their data, demonstrating six separate episodes of SIDS in 147 known MH susceptible families, was not significantly different from the reported incidence of two to eight episodes occurring per 1000 live births. Although we have not investigated nearly as many pedigrees in our unit in Calgary as either Denborough or Ellis, our experience would agree with Ellis' conclusion, since we have only recorded one instance of SIDS in our MH patient population.

**Neuroleptic Malignant Syndrome (NMS).** NMS is characterized by hyperthermia, hypertonicity of skeletal muscles and fluctuating consciousness, along with instability of the autonomic nervous system in a patient taking antipsychotic agents such as phenothiazines, butyrophenones and thioxanthines. The creatine kinase concentration is often markedly increased [14]. Because of the similarity of some of the clinical features of NMS and MH, it is not surprising that there should have been speculation that the NMS might somehow be related to MH. A very limited number of studies have been made in patients to try and answer the question as to whether or not there is an association. The case report of Lotstra, Linkowski and Mendlewicz [24] indicated that general anaesthesia consisting of thiopentone and suxamethonium, for electroshock treatment, was
given safely on numerous occasions to a patient who had previously had the syndrome. The patients reported by Denborough, Collins and Hopkinson [4] and Downey and colleagues [7] had abnormal \textit{in vitro} contracture responses that are typical for individuals with the gene for MH. On the other hand, not all patients with NMS show abnormalities when they are evaluated with contracture tests, as is shown by the reports of Scarlett, Zimmerman and Berkovic [34], Toltefson [41] and Krivosic-Horber and colleagues [21] who, in total, reported eight negative \textit{in vitro} contracture studies in patients who had previously been diagnosed as having had NMS.

The postulated disturbed mechanisms in NMS are felt to be in the CNS and the muscular activity is assumed to be secondary to the CNS abnormality. Thus it is difficult to envisage how these two diseases, with entirely different disordered mechanisms, could be closely related.

Other diseases. This list is quite brief and, as outlined in table I, includes Burkett's lymphoma [22, 42], osteogenesis imperfecta [32] and a biochemically uncharacterized glycogen storage disease [8]. In each instance it is possible to conclude that something other than MH might have happened which would equally well explain the clinical problem. In addition, for none of these patients was there confirmation, through the use of diagnostic tests, that the MH trait was in fact present.

IMPORTANT FUTURE ISSUES

Until the frequency of the MH gene within the population is known, interpreting the significance of proposed disease associations will continue to be problematic. Except for CCD, where the evidence suggesting a significant relationship with MH seems indisputable, I believe that it might be possible to account for every other disease association reported to date by chance. For such a conclusion to be valid, one would have to assume a fairly frequent occurrence of the MH gene within the population at large. The apparently higher incidence of MH within the total group of patients with myopathies could be explained if the MH gene was to be located in close proximity to the genes for the various myopathies. Of course, proof for such an hypothesis awaits identification of the various loci for the diseases under consideration.

Today, the presence of the MH gene within an individual can only be determined if a clinical MH reaction has occurred or if some other type of diagnostic testing has been carried out. Since neither of these identification techniques would ever be useful for determining the MH gene frequency within the population, it seems certain that it will be sometime in the future before definitive information will become available to resolve many of these problems. The development of a probe for the MH gene or a simpler diagnostic test for MH that would be suitable for mass screening of the population would provide the means whereby this information could be obtained. In the meantime, it is necessary to stress the importance of carrying out detailed family studies, using a combination of clinical, morphological (including histochemistry and electron-microscopy) and contracture studies, in all pedigrees where associations between MH and other diseases occur. Using these techniques, even though they are somewhat cumbersome, it is possible to decide just how much significance to attach to the various disease associations with MH that have been reported, provided that a sufficient number of patients and their families are studied in appropriate detail. There is no doubt the number of reports of new associations will continue to increase in the future, so we must be prepared to work diligently toward trying to resolve their significance, even though the tools for doing this are less than optimal.

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