HEREDITARY ASPECTS OF MALIGNANT HYPERTHERMIA

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A number of recent reports[1-27] have described the occurrence during general anaesthesia of a fulminant hyperthermia, often associated with rigidity. To date we are aware of over 115 such patients. A crude estimate of the incidence, using figures obtained from the Hospital for Sick Children in Toronto, is 1:10,000, with a range of 1:5,000 to 1:70,000, although it must be remembered that the incidence observed in a children's hospital is not necessarily representative of the population as a whole.[28]

The purpose of this paper is to demonstrate that this syndrome is in at least some instances hereditary in nature and to discuss the pattern of inheritance present in affected families.

The typical patient with the hereditary form of malignant hyperthermia is a child, adolescent, or young adult in whom the administration of succinylcholine is followed, not by the usual muscle fasciculation–paralysis sequence but rather by a sudden and prolonged rigidity.[28] The rigidity may be of modest degree or it may be so severe as to dominate the clinical picture. Intubation is often difficult because the jaws are clamped so tightly shut, although the cords are relaxed. Once intubation has been achieved, there does not appear to be any significant airway obstruction, although compliance is markedly reduced because of rigidity of the chest wall muscles.

The inhalational agent employed is frequently halothane but most other potent inhalational agents have also been used. When anaesthesia is maintained with an inhalational agent alone without the prior administration of a muscle relaxant to facilitate intubation, the onset of rigidity tends to be delayed and is more gradual in its development.[28]

During the early part of the anaesthetic the temperature may be normal or only slightly elevated, but after a variable period the temperature rather suddenly rises to an amazingly high level – in several instances up to 112° F. Severe metabolic and respiratory acidoses develop. The respiratory acidosis has been known to occur even when artificial ventilation has maintained a minute volume two or three times that recommended by the Radford nomogram. The final events in an alarming proportion of patients are cardiac arrest and death.

There has been no evidence of thyroid abnormality, pheochromocytoma, damage to the temperature controlling centre, infection, pyrogen contamination, or any other fever-producing condition. Faulty anaesthetic technique which could account for the hyperthermia has not been observed. Heat-losing mechanisms – sweating, and vasodilatation of skin vessels – also appear to remain competent in most patients. Moreover, since the temperature rise is accompanied by rigidity,

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and since the rigidity cannot be relieved by d-tubocurarine chloride, the principal defect must be peripheral to the neuromuscular endplate, namely in the skeletal muscle itself.

Description of familial occurrences

Patients considered to be affected with malignant hyperthermia are those in whom there has been:

1. no pre-existing fever;
2. no fault in anaesthetic technique likely to elevate temperature;
3. no untoward surgical event which might raise temperature;
4. fever during or immediately following anaesthesia;
5. muscular rigidity when this has been searched for and commented upon in the anaesthetic records by the anaesthetist. One exception is a patient who received special treatment. This case will be published at a later date by the physician concerned. In a number of other patients the presence or absence of rigidity was not remarked upon in the anaesthetic records.

Patients considered to be unaffected with malignant hyperthermia are those who have had neither fever nor rigidity during an anaesthetic in which a muscle relaxant and/or a potent inhalational agent have been employed.

Multiple cases have been described in at least eight human families.[2,8,9,14,17,22,26] While three Negroes[19,25] have been known to suffer from malignant hyperthermia, all the familial cases thus far recorded have been Caucasian. The number of known cases per kindred varies from 2 to 19. In all, of the more than 115 known cases, there are 43 known to be familial, to whom 48 hyperthermia-producing general anaesthetics have been administered. Several patients had received previous general anaesthetics without apparent ill effect, although in all the procedure was of relatively brief duration. The type of operation was quite variable (Table I). There does not appear to be any significant sex difference, there being 21 females and 22 males. The ages ranged from 3 to 47 years. Cardiac arrest and death occurred in 23 patients.

TABLE I

TYPE OF OPERATION

Orthopaedic	5
Otolaryngological	5
Ophthalmological	3
Genitourinary	2
Gynaecological and obstetrical	3
General	15
Unknown	15
Total	48

According to an abstract by Carpenter,[8] two siblings developed fever and rigidity during anaesthesia with subsequent muscle soreness, myoglobinuria, and mitochondrial degeneration demonstrated by electron microscopy.

The brother of a child reported from the Hospital for Sick Children in Toronto, who had been affected during two consecutive anaesthetics,[9] was recently anaesthetized in another city with fatal results.

In the September 1966 issue of the *Canadian Anaesthetists' Society Journal,* Davies reported a fatal case involving a 24-year-old female.[14] This year her older brother was anaesthetized and he too suffered a rapidly fatal reaction.

Purkis has described an aunt and a niece who both died during hyperthermic reactions within four months of each other in Halifax.[17]

We have recently investigated an uncle and a niece from Ontario who suffered non-fatal hyperthermic reactions during succinylcholine-halothane anaesthetics.

Dr. J. C. Kruse of Jacksonville, Florida recently anaesthetized a 24-year-old female patient who developed a high fever during the anaesthetic. She had also had an elevated temperature during two previous anaesthetics. Her younger brother has also been hyperthermic during anaesthesia.[26]

A large family was reported some years ago from Australia by Denborough.[2] In this family eleven people were affected, including the proband, out of the 38 known to be at risk, and all of these except the propositus expired during or immediately following general anaesthesia. While the anaesthetic records were inadequate or unobtainable in a number of these patients, the temperature was known to be significantly elevated in at least three of them and the skin of several of the remainder felt excessively hot.

The pedigree of an even larger family has recently been worked out by the authors (Fig. 1). This family is of central European origin and is centred on the
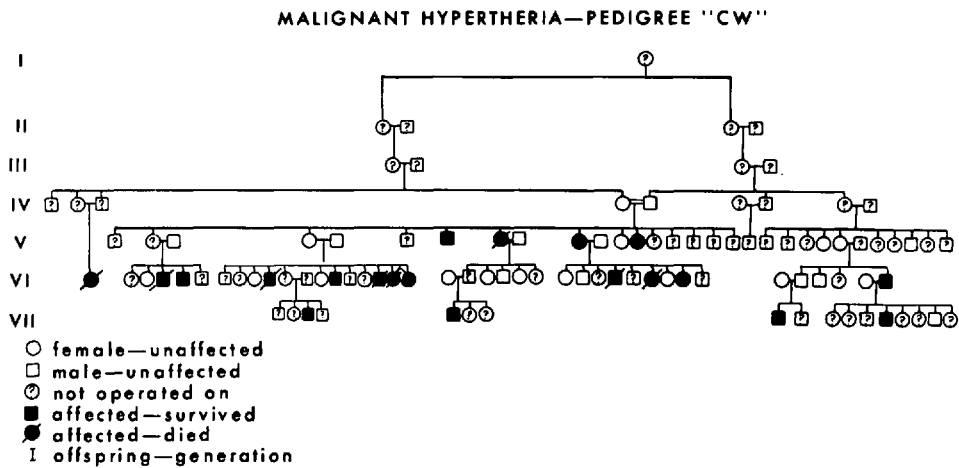
MALIGNANT HYPERTHERIA—PEDIGREE "CW"

FIGURE 1

small farming community of Wausau, Wisconsin. Here it has remained relatively isolated in the sparsely settled, rural environment of northern Wisconsin, with very little social or economic contact with the outside world, and so it has been subjected to relatively uniform environmental influences. It consists of about 450 individuals extending over eight generations who have extensively married into a second very large kindred of about one thousand members. Many sibships belonging to the later generations, which contained no known affected individuals, have not been included for lack of space. The earliest known ancestor

was born about the beginning of the nineteenth century. The presence or absence of the trait in at least the first three generations could not be ascertained because these individuals all lived at a time when the chance of their receiving a general anaesthetic was not great, especially in a rural community, and among the few who did, anaesthetic records were scanty or lacking completely. However, it is interesting to note that family tradition does ascribe several deaths among the more remote ancestors to anaesthesia.

Of 116 members of this Wisconsin family known to have been at risk, 20 previously healthy members have been affected during 21 anaesthetics, of which eight were fatal. The ages ranged from 4 to 37. The first case was detected in 1922 and the last in October of 1968.

Associated musculo-skeletal disorders

Because of the presence of pre-existing musculo-skeletal disease such as kyphoscioliosis, spontaneous herniated nucleus pulposus, congenital inguinal hernia, strabismus, and ptosis in about one quarter of the previously reported patients,[9,11,16,18,19] the Wisconsin family was specifically investigated for the presence of such abnormalities. As a control it was found possible to use distantly related unaffected branches of the family into whom the affected family had married. This control group was considered to be characteristic of the general population of northern Wisconsin.

The results of this study showed no correlation in this family between the occurrence of malignant hyperpyrexia and the above-named disorders ($\chi^2 = .0023$) (Table II). As can be seen from this table it would appear that a history of musculo-skeletal disease can be expected in a little more than a fifth of the general population.

TABLE II

MUSCLE DISEASE

	Present			Absent			Unknown		
	females	males	total	females	males	total	females	males	total
Affected individuals	0	3	3	7	8	15	1	1	2
Controls	6	15	21	45	37	82	1	0	1

In addition we examined more than 200 family members for myotonia by testing for rate of relaxation after hand shaking and for percussion myotonia of the tongue and upper arm muscles. Evidence of myotonia was not discovered in a single subject.

Muscle disease is known to be present in at least one of the seven other families in which multiple cases have occurred.[9] In this family the two affected male siblings were both operated upon for strabismus. Several other male members of the family also suffered from strabismus and ptosis. However, two of these have undergone general anaesthesia without record of apparent ill effect.

Pattern of inheritance

In attempting to work out the pattern of inheritance[29-31] we encountered difficulty from several sources. First, not all of the affected patients have necessarily been detected, since some have never been anaesthetized, or else have only been anaesthetized for a short duration or at the extremes of age. Secondly, because of the high mortality associated with this condition,[32] and because most affected individuals were unmarried at the time of detection, those affected often do not survive long enough to produce progeny. This markedly reduces the number of sibships within a given kindred available for genetic analysis. Thirdly, it is probably unwise to take for granted that the cause is the same in all kindreds. There may actually be several different primary defects.

Evidence for dominant inheritance

1. Presence in successive generations

The trait has appeared in three successive generations of the Wisconsin family (generations V, VI, and VII). The trait has not yet been detected in generation VIII because these individuals, being all very young, have had little opportunity to be anaesthetized and because their parents, being now aware of the problem, have on several occasions refused permission for their children to be anaesthetized.

2. One-to-one ratio present in offspring

A one-to-one ratio of affected to unaffected individuals appears to be present in the offspring of the Wisconsin family, as determined by both biased and unbiased estimates (Table III).

TABLE III

EVIDENCE FOR DOMINANT INHERITANCE
(1:1 RATIO IN OFFSPRING)

A. *Biased estimate* (offspring of families containing one affected parent and/or one or more affected offspring)

Affected			Unaffected		
females	males	total	females	males	total
8	12	20	10	10	20

B. *Unbiased estimate* (offspring of one affected parent)

Affected			Unaffected		
females	males	total	females	males	total
2	2	4	5	6	11

a. Biased estimate. By using a biased estimate we obtained values which were very close to a one-to-one ratio. By this method we counted all those offspring who had been exposed to general anaesthesia and who belonged to sibships with either one parent affected or one or more offspring affected. We found that 20

offspring were affected and 20 were unaffected. This estimate is suggestive evidence of dominant inheritance, but not conclusive as it excludes sibships which by chance have happened to contain no affected individuals.

b. Unbiased estimate. In estimating the ratio of affected to unaffected individuals, in order to eliminate the bias present in the above method, we counted only those offspring who had one affected parent. We also, of course, omitted those individuals who had never been exposed to a general anaesthetic. With these criteria we found that there were four affected and eleven unaffected offspring. These values are not significantly different from a 1:1 ratio ($\chi^2 = 2.40$).

Evidence against recessive inheritance

In generation IV of the Wisconsin family there is a consanguinous marriage of second cousins and this might predispose one to think of recessive inheritance. However, according to the Hardy-Weinburg Law, the frequency p of a gene in the general population equals the square root of the frequency of the trait, in this case, the square root of 1:10,000; i.e. $p = 0.01$. Then the frequency of heterozygotes in the general population would be $2pq$, that is $2 \times 0.01 \times 0.99 =$ approximately 0.02, or about 2 per cent of the general population. In this family there are at least ten persons who have married unrelated individuals and who have transmitted the trait to their descendants. If the inheritance was recessive these ten individuals would have had to have married a heterozygote in every case. The chance of this combination of events is $2/100^{10}$, which is such a rare probability that we can reasonably exclude its occurrence.

Evidence against X-linkage

1. Males and females are about equally affected.
2. The severity of affliction is not different in the two sexes.
3. There is direct transmission from an affected male father to an affected male son.

Evidence regarding reduced penetrance and variable expressivity

1. Reduced penetrance

There are at least four instances in the Wisconsin family and one in the Australian family[2,3] of generation "skipping"; that is, a parent not visibly affected has transmitted the trait to his or her offspring. Such a deviation from dominant inheritance is often referred to as "reduced penetrance." It may be due to the presence of a modifying factor in the form of another gene.

2. Variable expressivity

Perhaps variable expressivity occurs among different kindreds. This is suggested because the families reported by Carpenter[8] and more recently detected by ourselves in Ontario are less severely affected than the members of some of the other kindreds. In the former, survival was 100 per cent, although treatment in at least three of the four cases was not vigorously pursued. Moreover, the maximum temperature attained did not exceed 106° F in any of them. This could indicate either

that modifying genes are playing a role, or that the primary defects are not identical, or that environmental factors are contributing in an unknown manner.

Evidence against polygenic inheritance

The anaesthetic records show that offspring are about as severely affected as the affected parent; that is, the offspring do not represent a mean of the affected versus the unaffected parent.

Secondly, if polygenic inheritance was present the risk in affected sibship should be much less than one-half.[33] Since the risk appears to be one-half, polygenic inheritance is probably not a feature of this condition.

Sporadic cases

More than 50 sporadic cases (about half the total number of known cases) have been described with no known affected relatives. The primary defect in these individuals may be different from that in cases characterized by a familial pattern. Certain differences in the clinical picture of some of these patients (e.g. failure to observe rigidity or hyperkalaemia) would support this explanation. In some patients, a defective gene may have been newly formed by mutation. Some of these are possibly due to somatic mutation rather than germinal mutation, since none of their progeny have yet been known to be affected. However, since there is reduced penetrance, and since recognition of the deviation cannot always be guaranteed, some cases counted as sporadic may in fact be hereditary. On the other hand a recent report in the *British Medical Journal* mentioning the appearance of hyperpyrexia of five unrelated patients in one hospital in one week makes it likely that environmental factors are of significance in at least some cases.[20]

DISCUSSION

Age of onset

To date this syndrome has never been observed in infancy. Several patients known to be affected have had previous general anaesthetics during infancy without ill effect. The failure of the trait to manifest itself during infancy should not be surprising since it is well known that the effects of many genes do not become apparent until some specific time during development, as for example the juvenile diabetes or Huntington's chorea gene.

Distinction from myotonia

The failure to observe the syndrome in older individuals could have several explanations. Cody[21] has suggested that malignant hyperthermia may actually be an early manifestation of undiagnosed mytonia dystrophica, a condition known to be hereditary. The lack of a hyperthermic response in the older individual could thus be explained on the basis of lack of a sufficient volume of muscle tissue to cause a significant amount of heat production. However, the complete failure to observe myotonia in any family members of whatever age, and the failure to observe prolonged rigidity (of longer duration than the normal duration of action

of succinylcholine) or fever after the administration of succinylcholine to patients with known myotonia[34,35] renders this theory somewhat unlikely. Another explanation could be simply that affected individuals die during general anaesthesia before they have the opportunity to reach an advanced age.

Mitochondrial inheritance

It has been suggested that this condition may be a true mitochondrial disease, with uncoupling of oxidative phosphorylation within the mitochondria being a possible causative factor.[36–40] This postulation brings to mind some rather fascinating questions about the semiautonomous nature of the mitochondria within the cell.[41] Not only can mitochondria carry out most of their native functions when isolated from the cell, but they even appear to replicate independently. Furthermore, when abnormal mutant mitochondria are injected into normal cells, the normal cells take on the characteristics of the mutant strain. Apparently then mitochondria are capable of a form of inheritance that is carried on without the nuclear gene. It has been theorized that mitochondria, in fact, may be specialized forms of bacteria that at some time in the past may have migrated into a rather more primitive cell, and then both evolved together.[42] Thus, inherited mitochondrial disease would be due, not to an abnormal nuclear gene, but to a mutant strain of mitochondria which is perpetuated from generation to generation independently of the nuclear chromosomes. In such inherited mitochondrial diseases the proportion of affected members that one would expect to find in an involved sibship is as yet unknown. One could postulate that the severity and incidence of affliction would progressively decrease over succeeding generations due to the mixture of normal and abnormal mitochondria, because of contributions from both sperm and ovum. However, the possibility that the abnormal mitochondria might in some way inhibit the normal mitochondria cannot be ruled out.

For malignant hyperthermia the risk in an involved sibship is 50 per cent and neither the risk nor the severity of affliction varies from one generation to the next. Thus for this syndrome the inheritance appears to be genetic and not mitochondrial.

SUMMARY

Malignant hyperthermia is a genetically inherited condition in many cases. The pattern of inheritance appears to be that of autosomal dominance with reduced penetrance and variable expressivity. The condition is not manifested in infancy or old age. The possible association with musculo-skeletal disease requires further investigation, although a large family tree did not support previously collected evidence in favour of this association.

RÉSUMÉ

Souvent l'hyperthermie maligne est héréditaire. Le mode de transmission semble être à prédominance autosomique avec infiltration limitée et des manifestations variables. Cette condition ne se manifeste pas dans l'enfance ni dans la vieillesse.

Pour l'associer à une maladie musculosquelettique, il faudrait de plus amples renseignements; cependant une étude généalogique importante n'a pas confirmé des preuves préalablement recueillies en faveur de cette association.

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