MALIGNANT HYPERPYREXIA OCCURRING IN A SECOND JOHANNESBURG FAMILY

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SUMMARY
A further family carrying the abnormality for malignant hyperpyrexia has been studied over four generations. The carriers with one exception have been identified by creatine phosphokinase estimations. In one branch of this family two grandchildren exhibit multiple musculoskeletal abnormalities and in addition a high creatine phosphokinase. The rest of the family was clinically normal though many carried the predisposing tendency for malignant hyperpyrexia as shown by elevated creatine phosphokinase levels. The case of a member of this family who survived two malignant hyperpyrexial episodes is presented.

During the past six years increasing numbers of cases of malignant hyperpyrexia (MH) occurring during or following anaesthesia have been published. There is little doubt that many more cases are still either unrecognized or not reported.

As it is now established that this syndrome is familial (Denborough et al., 1962; Britt, Locher and Kalow, 1969; Isaacs and Barlow, 1970b), it has become vitally important to be able to have some indication as to which members of a family are liable to be triggered into a malignant hyperpyrexial reaction whilst undergoing general anaesthesia. The exact cause of death under anaesthesia is often not known and if, in the case of a person undergoing anaesthesia, there is a family history of death under anaesthesia it should then be suspected that the patient and his family are at risk.

The family described here is of interest in that two members in one branch of the family show multiple musculoskeletal abnormalities, a deceased aunt had similar abnormalities but the other branches of the family are clinically normal. The disease was established in this family when one of the members survived two malignant hyperpyrexial reactions following on general anaesthetics for the surgical correction of dislocated patellae.

CASE REPORT
In November 1968, an emergency reduction of a dislocated patella was attempted on a 14-year-old white male (fig. 1). He was anaesthetized using thiopentone, nitrous oxide and halothane. The anaesthetic lasted 5 minutes and was completely uneventful.

Six months later he was readmitted for a bilateral Hauser procedure. The anaesthesia was induced with ketamine hydrochloride followed by nitrous oxide, oxygen and halothane. At the termination of the operation, which lasted 1 hour 40 minutes, his temperature was found to be 40°C (104°F). He was cooled with fans and ice; within 30 minutes his temperature had returned to normal and he made an uneventful recovery. At the time the ketamine hydrochloride was blamed for the episode by the unsuspecting anaesthetist as this was a new drug and little was known about it.

One week after this episode he was presented for operation on the second leg. Anaesthesia was induced with propanidid and maintained with nitrous oxide, halothane and methoxyflurane. After 20 minutes his temperature rose to 40°C and examination revealed tachycardia, tachypnoea and carpopedal spasm. The limb occluded by the tourniquet remained flaccid. The anaesthetic was stopped and immediate skin cooling was commenced, but the temperature rose to 40.2°C (106°F) before it started to fall. Half an hour later the temperature was normal, the patient was conscious and though he suffered from generalized muscular weakness for several weeks he made a complete recovery. The musculoskeletal abnormalities of the patient included ptosis, pes cavus, genu valgum, underdevelopment of the lateral condyles of the femurs and kyphoscoliosis.

After this second febrile episode the nature of the reaction was realized and it was then discovered that a maternal aunt had died 15 years previously from malignant hyperpyrexia whilst undergoing tonsillectomy; the anaesthetic agents used were di-vinyl ether and di-ethyl ether. It was established that she suffered from ptosis and strabismus.

A muscle biopsy was carried out a week after the last pyrexial episode and showed widespread destruction of muscle fibres. The fibres had lost their striations, showed marked swelling and various stages of disintegration and lymphocyte infiltration. Electromyography carried out by H.I. two months later showed reduction of motor unit potential amplitude, the durations were shortened and abnormally polyphasic. A recent electromyogram has...
shown a slight increase in polyphasic activity. The polyphasic units on this occasion being of above average voltage and prolonged duration suggest a degree of denervation with reinnervation. As the patient was about to undergo further surgery he has been subjected to a repeat biopsy for histological and histochemical study, the details of which are presented by Isaacs, Frere and Mitchell (1973).

![Fig. 1. Photograph of patient (reproduced by courtesy of his parents).](image)

**INVESTIGATION**

Isaacs and Barlow (1970b) have previously shown that serum creatine phosphokinase levels provide a simple and reliable screening test for detecting the muscle abnormality in most asymptomatic carriers. It was therefore considered obligatory that this patient and his family be investigated in this manner so that the carriers could be detected and warned of the anaesthetic hazard. The estimations were carried out at the South African Institute for Medical Research by Professor I. Bersohn. The normal values are 0–30 units for females and 0–50 units for males. Since blood was taken from ambulatory patients at various times of the day, the upper limits of normal were extended to 65 units for males and 45 units for females respectively. This may in time prove to be an unnecessary and perhaps a misleading precaution; however, we regard all borderline cases as suspect and in these the presence or absence of the disease is being confirmed by muscle histochemistry.

The creatine phosphokinase study once again proved to be a simple, rapid and useful screening test which enabled us to identify most of the members of the family who we believe might develop malignant hyperpyrexia.

The mode of inheritance of the abnormally high creatine phosphokinase level was again shown to be autosomal dominant (figs. 2, 3, 4). The proband of this family has been identified as the patient's grandmother who has a creatine phosphokinase level of 139 units. Of her 50 descendants, 45 have been investigated and of these 18 were found to have abnormally high levels. Both sexes were found to be equally affected. The study was extended over four generations as shown in figure 3. Three of the offspring of the propositus were found to have normal values and estimations in their children and, in some instances, grandchildren remained normal. Four of the children had elevated levels and the abnormality was detected in approximately half of their children and again in half of the grandchildren. In one of the families, a daughter of the propositus was found to have a creatine phosphokinase level at the upper limit of normal (44 units) but investigation of her children and grandchildren revealed that she had carried the abnormality and passed this on to the other members of her family (fig. 3).

One second generation daughter had previously died as a result of malignant hyperpyrexia and it was established that this daughter had musculoskeletal abnormalities, specifically ptosis and strabismus, whilst another daughter with no obvious clinical abnormalities and an elevated creatine phosphokinase level of 100 units produced (fig. 2) two sons with musculoskeletal abnormalities which include ptosis, kyphoscoliosis and under-developed dislocating patellae.

**DISCUSSION**

The severity of the malignant hyperpyrexial reaction seems to vary from family to family. The patient described in this paper survived two episodes of malignant hyperpyrexia in short succession without the use of any specific therapy. He also exhibited potentiation of the reaction brought about presumably by sensitization of the muscle by the previous anaesthetic. This sensitization has been encountered frequently in anaesthetic practice and adds to the
MALIGNANT HYPERPYREXIA IN A SECOND JOHANNESBURG FAMILY

KEY

MALE
FEMALE

SERUM CREATINE PHOSPHOKINASE (C.P.K.) NORMAL

C.P.K. FEMALES 45 AND OVER
MALES 65 AND OVER

SURVIVED MALIGNANT HYPERPYREXIA

DIED OF MALIGNANT HYPERPYREXIA

DIED OF NATURAL CAUSES

MUSCULOSKELETAL ABNORMALITIES

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FIG. 2. K.N. family, generation II.

FIG. 3. A.E.C. family, generation II.

FIG. 4. G.C. family, generation II.
difficulty in identifying cases at risk in that it cannot be assumed that because a patient has uneventfully survived one anaesthetic he will do so a second or third time (Britt and Kalow, 1970). No precise information is available on this increased susceptibility but it may well relate to damage to various components of the muscle cell caused by the previous anaesthetic, which has not been detected clinically and only becomes obvious with the challenge of the next anaesthetic.

A high incidence of malignant hyperpyrexia has been noted in patients with certain musculoskeletal problems. The commoner abnormalities which have shown this association are ptosis, strabismus, cleft palate, dislocated patellae, kyphoscoliosis, high arched palate, hernias in young people, and dislocated shoulder joints (Britt and Kalow, 1970). The presence of any of these abnormalities should serve to alert the anaesthetist to the possibility of a malignant hyperpyrexial reaction and we suggest that the creatine phosphokinase level should always be available before surgery. A normal value, however, is no guarantee that malignant hyperpyrexia will not develop, but a high value would call for a total modification of the anaesthetic procedure. The precise link between the various musculoskeletal abnormalities and the susceptibility to develop malignant hyperpyrexia is yet to be established because it is obvious from total studies of such families that the bulk of the members at risk have no evidence of musculoskeletal abnormalities (Britt, Locher and Kalow, 1969; Isaacs and Barlow, 1970b). It also goes without saying that one cannot take the absence of such abnormalities as an indication of freedom from risk nor can one assume that all cases with musculoskeletal abnormalities in these families carry the susceptibility to develop malignant hyperpyrexia.

We maintain that the presence of an elevated creatine phosphokinase is an indication of abnormal muscle. This is a non-specific test and the level may be elevated when muscle is damaged or diseased and, as such, covers a wide spectrum of disorders including, for example, conditions ranging from ischaemic necrosis to Duchenne muscular dystrophy. It is not, therefore, the enzyme itself which signifies a tendency to malignant hyperpyrexia but the unexplained elevation which is associated with the occurrence of malignant hyperpyrexia in other members of the family. Many of the well-known neuromuscular diseases such as myotonia dystrophica and Duchenne dystrophy, the latter characterized by grossly elevated creatine phosphokinase levels, have not in our experience been associated with malignant hyperpyrexia.

It was postulated (Isaacs and Barlow, 1970a) that carriers of the trait for malignant hyperpyrexia have a myopathy, which in the vast majority of cases remains subclinical, and that it was some function of the myopathic abnormality which reacted to the challenge of anaesthetic agents by producing the abnormal amount of heat. Since this time the existence of a subclinical myopathy has been confirmed by histological and histochemical studies (Isaacs, Frere and Mitchell, 1973); the myopathic changes have been found in those subjects indentified as carriers by creatine phosphokinase estimations. Furthermore, the histochemical evidence has been shown to favour a neurological basis for the myopathic changes as was originally postulated by la Cour, Juul-Jensen and Reske-Nielsen (1973).

This enzyme screening procedure has also helped to identify those branches of the family who were free of risk and we have assumed that when creatine phosphokinase levels have been normal in a family extending over three generations the disease is absent. We regard these members as normal anaesthetic risks but would still tend to avoid suxamethonium and halothane until more is known of this disorder.

In those carriers in whom the disease has failed to cause an elevation of the creatine phosphokinase, but who nevertheless have been identified by finding elevated levels in their offspring, the abnormality can and has been confirmed by histological, histochemical and electron-microscopic examination. The sensitivity of affected muscle to specific substances such as halothane and suxamethonium can further be demonstrated by the techniques of Harrison and associates (1969) who demonstrated a fall in ATP and by Ellis and associates (1972) who demonstrated contraction of muscle fibres in vitro when the muscle was experimentally exposed to these agents. These or similar tests may provide the ultimate confirmation of the presence of the abnormal trait though a combination of offending agents may have to be used. It remains for a procedure such as described by Ellis and associates (1970) to be standardized in this respect and also to be shown to be reliable in all affected families, as differences will be found to exist between one and the next involved family.

All members of families who carry the genetically determined predisposition (trait) of malignant hyperpyrexia with or without clinical evidence of musculoskeletal disease, should be warned about their condi-
tion and the associated risks. It should be stressed that each new generation must have serum or histological studies and until either the creatine phosphokinase level has been found to be normal over three generations or muscle biopsy has been found to be negative, these patients must be treated as anaesthetic risks. As far as anaesthesia is concerned in those patients in whom the creatine phosphokinase level is abnormal, halothane and methoxyflurane must be avoided and depolarizing relaxants such as suxamethonium must not be used; local anaesthetic techniques should be used whenever possible or, failing this, a combination of fentanyl, nitrous oxide and a non-depolarizing relaxant.

It is of interest that Hall, Trim and Woolf (1972) have stated recently that the new intravenous steroid anaesthetic Althesin protects susceptible pigs from malignant hyperpyrexia and it may well be that this anaesthetic agent may prove suitable for human patients.

We stress once again that the temperature must be monitored during all anaesthetic procedures, as it is only by early detection of this syndrome that lives will be saved. Once the reaction has developed the régime of Britt and Kalow (1971) should be followed together with the administration of procaine as outlined by Harrison (1971). We further suggest that copies of these procedures and supplies of procaine be available in all operating theatres.

ADDENDUM

This patient has since undergone further surgery. Althesin was used and there was no evidence of malignant hyperpyrexia.

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REFERENCES


HYPERPYREXIE MALIGNE SURVENANT CHEZ UNE SECONDE FAMILLE DE JOHANNESBURG

SUMMAIRE

Une autre famille, porteur de l’anomalie d’hyperpyrexie maligne, a été étudiée sur quatre générations. Les porteurs ont tous, à l’exception d’un seul, été identifiés par les déterminations de la créatinine phosphokinase. Deux petits-enfants d’une branche de cette famille manifestent des anomalies musculosquelettiques, en adition à une créatinine phosphokinase élevée. Le reste de la famille était cliniquement normale mais de nombreux membres présentaient la tendance prédisposante à l’hyperpyrexie maligne, indiquée par l’existence de taux élevés de créatine phosphokinase. Les auteurs presentent le cas d’un membre de cette famille qui a survécu à deux épisodes d’hyperpyrexie maligne.

ÜBER FÄLLE MALIGNER HYPERPYREXIE BEI EINER ZWEITEN JOHANNESBURGER FAMILIE

ZUSAMMENFASSUNG

praedisponierende Neigung für eine maligne Hyperpyrexie besaßen. Dies ergab sich aus der Erhöhung der Kreatinphosphokinasespiegel. Es wird über einen Fall eines Mitgliedes dieser Familie berichtet, welches zwei Episoden von maligner Hyperpyrexie überlebte.

HIPERPIREXIA MALIGNA PRESENTADA EN UNA SEGUNDA FAMILIA DE JOHANNESBURGO

RESUMEN

Se ha estudiado en cuatro generaciones una nueva familia portadora de la anomalía de hiperpirexia maligna. Con una excepción, los portadores han sido identificados por la determinación de la creatinfosfoquinasa. En una rama de esta familia, dos nietos presentaban múltiples anomalías musculoesqueléticas, además de una elevada creatinfosfoquinasa. El resto de la familia era clínicamente normal, aunque muchos miembros de la misma presentaban una tendencia predisponente a la hiperpirexia maligna, como se apreció por los niveles altos de creatinfosfoquinasa. Se presenta el caso de un miembro de esta familia, que sobrevivió después de dos episodios de hiperpirexia maligna.

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1973

SATURDAY, OCTOBER 27. Combined Meeting with Glasgow and West of Scotland Society of Anaesthetists in Glasgow Royal Infirmary at 5 p.m. “Infections of the nervous system”, Dr P. McKenzie, Regional Adviser in Infectious Diseases, Glasgow.

A Sherry Reception and Dinner will follow the Meeting.


1974


TUESDAY, FEBRUARY 12. “Modes of action, critical and incidental, of general anaesthetics”, Professor R. A. Millar, University of Glasgow.

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