TEN CASES OF MALIGNANT HYPERTHERMIA IN NORWAY

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Since 1967 ten cases of malignant hyperthermia (MH) have been reported at the annual meetings of the Norwegian anaesthesiologists. The present paper is a condensed report of these cases with a discussion of the presented data.

The data have been presented in four tables. The patients are numbered from one to ten in chronological order. The MH incidents occurred over a ten-year period, with the first case in 1965 and the last in 1975. New features like creatine phosphokinase (CPK) determinations and procaine infusions therefore only appear in the more recent cases.

Discussion of the Data

Age and sex related to mortality

Eight of our ten patients were between 11 and 20 years of age (Table I). The series of MH victims published by other authors also have the highest incidence in the second decade of life.[1-3] In comparing the age of mortality Gjengstø[2] found a mortality in the second decade almost double that in the first decade. This indicates a dramatic change in the severity of the condition with puberty and our series seems to support the view that such a change occurs. Of our eight teen-aged patients, only one (number 9) survived. Both our prepuberty patients, however, were resuscitated. This increase in mortality with puberty, is not often mentioned in the literature.

The genetic defect in MH is a dominant autosomal trait.[4] This might seem strange in view of the fact that in all the published series of MH victims there is a surplus of males.[1-3] This is also the case in our series which has a ratio of males/females of 8:2. It must be remembered, however, that an autosomal trait might depend on hormonal factors for its penetrance. Such, for instance, is the case with baldness, another autosomal genetic defect which only becomes manifest under the influence of androgens. The genetic defect in MH might also be facilitated in its penetrance by androgens. This hypothesis is supported by the male preponderance of the MH victims as well as by the fact that the severity of the syndrome in the male increases with puberty. In our series all seven fatal cases were males who had reached sexual maturity.

The possible facilitation of the MH syndrome by androgens is of interest in connection with the occurrence of MH in one of our patients (number 7) afflicted with the adrenogenital syndrome. The infrequency of the MH complication (1:1,400),[1] and the even more rare adrenogenital syndrome (1:67,000),[5] makes a coincidence by chance very unlikely. A possible explanation is that the excessive

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TABLE I

AGE, SEX, CPK VALUES, FAMILY DATA AND PREVIOUS ANAESTHETICS

Case number	Age	Sex	CPK values of patient	Family history CPK values	Previous anaesthetics
1	18	Male	Unknown	Healthy family	None
2	19	Male	Unknown	Father pes equinovarus	Uncomplicated gas-ether two years previously
3	15	Male	Unknown	Healthy family	Uncomplicated ether two years previously
4	13	Male	Unknown	Healthy family	None
5	17	Male	Unknown	Mother CPK = 250 Brother CPK = 125	Five days previously halothane-suxamethonium six blood transfusions. No reactions
6	15	Male	Unknown	Parents and brother normal CPK	Three years before stiffness and myoglobinuria after 10 minute halothane anaesthesia
7	4½	Female (pseudo-hermaphrodite)	CPK = 200	Parents not related. Sister also adrenogenital syndr.	The patient and sister uncomplicated N_2O+ halothane at the age of two.
8	16		Unknown	Healthy family Mother CPK = 64 Sister CPK = 74	None
9	15	Male	CPK = 45	Brother CPK = 75	Uneventful ether at the age of seven
10	10	Female	CPK = 100	Healthy family Mother CPK = 40 Sister CPK = 55	None

Upper normal limits for CPK. Males: 35. Females: 20. Children: 20.

formation of androgens in patients with the adrenogenital syndrome acts as a predisposing factor for the MH complication. This is also in agreement with the uncomplicated anaesthesia in our patient number 7 at the age of two years, because at that age excessive secretions of androgens had not yet started. We have not found any previous reports in the literature of MH occurring in patients with the adrenogenital syndrome. It is possible that this rare coincidence occurred because excessive androgen secretion facilitates the manifestation of the MH syndrome. The importance of androgens for the porcine MH cannot readily be determined because most pigs are castrated at an early age. It has been suggested, however, that the MH-prone Pietrain pigs represent a race with androgenic overactivity.[6]

CPK determinations

This was done on the near relatives of the last six patients. Borderline values as well as values well above the normal were found for several of the relatives, although some of them had been subjected previously to anaesthetics without complications. This confirms the report that general anaesthesia may not produce

TABLE II

CONDITIONS REQUIRING SURGERY AND SURGERY PERFORMED

Case number	Conditions requiring surgery	Surgery performed or intended
1	Finger injury 2 weeks previously	Plastic finger surgery intended
2	Traffic accident with nasal fracture 6 days previously	Reduction of nasal fracture intended
3	Elbow fracture 2 weeks previously	Open reduction of elbow fracture intended
4	Femoral bone cyst, congenital, causing symptoms	Angiography followed by operation was intended
5	Traffic accident with shock five days previously	Reduction and fixation of leg fracture intended
6	Cryptorchidism	Orchidopexy intended
7	Adrenogenital syndrome type I. Salt loser. Penile clitoris	Clitoris extirpation intended but only partly performed
8	Appendicitis acute	Appendectomy performed
9	Fracture-dislocation of tibial tuberosity two days previously	Open reduction and fixation performed
10	Cold appendicitis. Suffered appendicitis with peritonitis three months previously	Appendectomy intended

adverse effects in individuals with CPK values above normal limits. In the three patients who survived, the CPK levels rose 15 to 100 times their normal values in the first days after the MH incidents. After a week, the CPK fell to normal limits in one patient while in the other two it remained above normal. This confirms the general opinion expressed by Britt in 1974[8] that CPK determinations are unreliable as a diagnostic indicator.

Indications for surgery

Indications for elective orthopedic surgery were present in six of our patients (Table II). Also in other series orthopedic surgery was the most frequent type of operation to be performed.[1] One of our patients was treated for cryptorchidism, an indication for surgery present in five of the 18 MH-victims reported by King, *et al.*[3] This condition was also present bilaterally in a patient suffering two episodes of MH on different occasions, reported by Katz.[9] Genital surgery was performed on the 4½-year-old pseudohermaphrodite girl in our series. It is possible that young people due to undergo genital surgery are potential victims for MH. Such conditions are frequently congenital and congenital abnormalities were present in 30 per cent, 25 per cent and 50 per cent of previously reported series.[1–3] Among our orthopedic cases patient number 2 had a congenital patellar luxation and pes equinovarus like his father and therefore belongs to this category. The same may apply to our patient number 4 who had a congenital femoral bone cyst which was to be opened and filled with bone.

It is quite possible that some of the pathological conditions requiring surgery among our patients increased the sensitivity to suxamethonium. Such could be the case with five of our orthopedic patients who had suffered traumatic injuries only

TABLE III

PREOPERATIVE CONDITION, PREMEDICATION, ANAESTHESIA INDUCTION AND MAINTENANCE

Case number	Preoperative Temperature	Condition	Premedication (one hour preop.)	Anaesthesia induction	Anaesthesia maintenance
1	37.1° C	Good	Morphine 10 mg Scopolam 0.4 mg	Thiopentone Suxamethonium Jaw stiffness	N_2O + Halothane
2	37° C	Good	Meperidine 50 mg Atropine 0.6 mg	Thiopentone Suxamethonium	N_2O + Halothane
3	37.1° C	Good	Meperidine 50 mg Atropine 0.5 mg Phenergan 25 mg	Thiopentone Halothane	N_2O + Halothane
4	36.6° C	Good	Meperidine 50 mg Atropine 0.6 mg Phenergan 25 mg	Thiopentone Suxamethonium Halothane	N_2O + Halothane
5	37° C	Good	Meperidine 35 mg Atropine 0.5 mg	Hexobarbital Suxamethonium Jaw stiffness	N_2O + Halothane
6	37° C	Good	Meperidine 50 mg Atropine 0.5 mg	Hexobarbital N_2O + Halothane	N_2O + Halothane
7	37.7° C	Good	Atropine 0.5 mg Cortisone 75 mg	N_2O + Halothane	N_2O + Halothane
8	38.7° C	Good	Meperidine 50 mg Atropine 0.5 mg	Thiopentone N_2O + Halothane	N_2O + Halothane
9	37.2° C	Good	Diazepam 12.5 mg Atropine 0.5 mg	Thiopentone Suxamethonium Jaw stiffness	N_2O + Halothane
10	36.9° C	Good	Atropine 0.5 mg	Hexobarbital Suxamethonium Jaw stiffness Temp. 38.1° C	100% O_2 ventilation

a few days previously. Several workers have shown that trauma sensitizes the muscles to suxamethonium.[10-12] Also the planned appendectomy in our patient number 10 who had suffered an attack of appendicitis with fever and peritonitis three months previously might belong to this category. It has recently been reported that after febrile illnesses with sepsis or peritonitis, the patients react to suxamethonium with excessive muscle stiffness and potassium liberation.[13] The rigidity, hyperpyrexia and rise in CPK in our patient number 10 after 100 mg suxamethonium indicates an excessive sensitivity to this drug which might have been induced by the previous attack of appendicitis. Thanks to early diagnosis and prompt treatment, this patient was saved.

Premedication and anaesthetics used

All our patients had received anticholinergic premedication, atropine in nine cases and scopolamine in one (Table II). Rigidity appeared in all our patients except one (number 2). The high percentage of rigidity in our series (90 per cent) supports the original finding that anticholinergic premedication increases the tendency to rigidity.[1] Later, however, it has been suggested that the combination of atropine-suxamethonium was the cause of the high frequency of rigidity.[14] This

does not quite agree with our series as three of our patients (numbers 6, 7 and 8) received no suxamethonium and nevertheless displayed frank rigidity. This rigidity must have been caused by either N_2O or halothane which was given in combination in our patients. Halothane was shown originally to trigger porcine MH[15] and has been shown later to cause contracture of isolated muscle strips obtained from MH victims.[16] N_2O was regarded as innocent up to 1974 when Ellis, *et al.*[17] described a patient developing MH on two occasions after being given only N_2O and oxygen. As nitrous oxide has been used in almost all cases so far reported and regarded as innocent, all the previously made statements and conclusions are open to question. Our patient number 6 must have been permanently and excessively sensitive to one or both of these inhalation agents. During the fatal anaesthesia he breathed these agents for only 15 minutes. Three years previously, he had developed muscle stiffness and red urine (myoglobin) for two days following a 10-minute inhalation of the same agents. This incident had been duly recorded in the case history but passed unnoticed because of language difficulties, as the anaesthetist was of foreign nationality.

Suxamethonium rigidity in the jaw muscles during induction is important as a warning signal to end anaesthesia at once.[18] This sign occurred in numbers 1, 5, 9 and 10 of our patients, but it was only in the last patient that the anaesthetist took notice and cancelled further work, a decision which probably saved the patient's life. A similar aborted MH case has recently been described.[19] This shows that jaw stiffness during induction is a sign which should be taken seriously by the anaesthetist.

Management of the cases

In all our cases anaesthesia was terminated as soon as the diagnosis was made, cooling by various means was started and hyperventilation with pure oxygen performed. Intravenous infusions of various solutions were set up, such as bicarbonate, THAM, lactated Ringer's solution, mannitol, saline and plasma expanders. In addition, various drugs were given (Table IV).

The drug therapy of the three survivors is of some interest. Patient number 7, the 4½-year-old girl with the adrenogenital syndrome, received hydrocortisone and chlorpromazine 5 mg together with bicarbonate infusion. This reduced the rigidity and lowered the temperature so procaine infusion was omitted. Patient number 9, a 15-year-old boy, received hydrocortisone 200 mg and lanatocid 0.8 mg intravenously together with bicarbonate and lactated Ringer's infusion. This raised the blood pressure from shock levels to 100 mm Hg, but pyrexia, rigidity and tachycardia with arrythmia persisted. Procaine 3.5 g was therefore infused over 60 minutes, resulting in disappearance of the rigidity and normalization of cardiac rate, rhythm and temperature without fall in blood pressure. Patient number 10, a 10-year-old girl, received hexobarbitone 500 mg followed by halothane 2 per cent for two minutes and then suxamethonium 100 mg. Intubation, however, was abandoned because of jaw rigidity and anaesthesia was terminated. Less than 10 minutes had elapsed from the time of the barbiturate injection until a diagnosis of MH was made, based on jaw stiffness and hyperpyrexia (temperature 38.1° C). Hyperventilation prevented the development of acidosis but did not prevent body

TABLE IV

FIRST SYMPTOMS, COURSE AND TREATMENT AND FINAL OUTCOME

Case number	Time after induction for first symptoms	Course and treatment	Final outcome
1	After 20 min rigidity, temp. 39.4° C, tachycardia arrythmia	pH 6.8 in arterial blood. Cooling, bicarb., defibrillation	Declared dead 60 min after induction. General rigidity
2	After 60 min tachycardia, hypertension, temp. = 42° C. No rigid.	Cardiac arrest. THAM cooling, mannitol	Declared dead six hours after induction. No rigidity
3	After 20 min cardiac arrest, temp. = 40.6° C. No rigidity	Cooling, calcium, defibrillation, arrythmia, lidocaine, rigidity	Declared dead 36 hours after induction with myoglobinuria, haemolysis, hyperkalaemia, rigidity
4	After 60 min rigidity, respiratory arrest, temp. = 42° C, tachycardia	Ventricular fibrillation, bicarbonate, defibrillation	Declared dead 90 min after induction with general rigidity
5	After 20 min rigidity, temp. = 42° C. Cyanosis	Bradycardia, ventricular fibrillation, defibrillation	Declared dead 50 min after induction with general rigidity
6	After 15 min rigidity, hyperventilation, temp. = 42.5° C. Cardiac arrest	Cooling, cortisone bicarbonate, dextran bradycardia, isoprenaline	Declared dead 90 min after induction with general rigidity
7	After 30 min hyperventilation, rigidity, cyanosis, tachycardia, temp. = 42° C	Cooling, bicarbonate, hydrocortisone, chlorpromazine	Patient survived after a period of hypothermia
8	After 40 min hyperventilation, tachycardia, rigidity, temp. = 42° C	Convulsions, cardiac arrest during cooling and bicarbonate infusion	Declared dead 2½ hours after induction with general rigidity
9	After 30 min tachycardia arrythmia, temp. = 40° C rigidity, collapse	Cooling, bicarbonate, Ringer, hydrocortisone procaine 3.5 g i.v.	Patient survived after a period with hypothermia
10	After 2 min jaw stiffness. Anaesthesia ended 10 min after start	Temp. reached 41.3° C. Cooling and hyperventilation with oxygen. Procaine 1 g	Patient survived after a period with hypothermia

temperature from rising to 41.3° C. Immersion in ice water caused the temperature to fall. Persistence of rigidity was also treated in this case with procaine 1 g intravenously without fall in blood pressure.

Procaine therapy

Procaine therapy was first suggested by Harrison[20] followed by Moulds and Denborough.[2] The clinical effects of procaine reported in the literature seems to be variable. A good effect on both rigidity and temperature was found by two groups of workers,[22,23] while a third found no effect on temperature.[24] Fatal hypotension occurred after only 600 mg of procaine in a patient recently reported.[25] In this case procaine was given initially before correction of acidosis. This is contrary to Harrison's[20] original routine, although other workers have proposed to start procaine initially.[26] Our patient number 9 tolerated procaine 3.5 g, a very

large dose. The absence of blood pressure fall might be due to the fact that acidosis had been corrected before the infusion.

Steroid therapy

Hydrocortisone 100 mg together with chlorpromazine 5 mg appeared to be effective in patient number 7. Dexamethasone was shown by Ellis, *et al.*[17] to work very effectively on two occasions in the same patient. Our patient number 9 also received hydrocortisone 200 mg, which appeared to arrest the temperature rise and raise the blood pressure. The persisting rigidity and tachycardia, however, responded to procaine. Also in patient number 10 residual rigidity subsided with procaine.

Our experience would therefore indicate that procaine should be reserved until other measures, such as cooling, correction of acidosis and steroid therapy have been tried. Incidentally, this conclusion reached from clinical experience is in agreement with conclusions reached experimentally.[27] It has been suggested that the beneficial role played by procaine at this stage is due to inhibition of catecholamine release and block of the adrenergic alpha-receptors.[28] This role, however, may be played by other agents.

Summary

Data are presented on ten cases of anaesthesia-induced malignant hyperthermia in Norway. Seven of the patients died, three recovered. The fatal cases were all boys in the age group 11–20 years. This age and sex distribution suggests that puberty with the increase in androgens is a precipitating factor in malignant hyperthermia. One of the victims who survived was a 4½-year-old pseudohermaphrodite girl with the adrenogenital syndrome. The coincidence of malignant hyperthermia in a patient with such a rare syndrome points to the excessive formation of androgens in patients with this syndrome as a predisposing factor.

The indications for surgery were traumatic injuries in five cases, congenital abnormalities in three and appendicitis in two cases. These conditions in themselves may cause an increased sensitivity to suxamethonium.

One patient received only hexobarbitone, halothane and suxamethonium. After the last drug jaw rigidity and temperature rise to 41.3° C prompted the anaesthetist to end the anaesthetic. The fact that the patient survived proves that suxamethonium induced jaw rigidity is valuable as a warning.

The absence of cardiovascular depression after procaine 3.5 g in one patient is ascribed to the correction of acidosis at the time of infusion of this drug. It is suggested that procaine should be withheld until other measures such as cooling, correction of acidosis and steroid therapy have been tried.

Résumé

Dix cas d'hyperthermie maligne survenus en Norvège sont rapportés et discutés. Sept des dix patients sont morts et trois ont survécu. Tous les décès sont survenus chez des garçons âgés de onze à vingt ans, ce qui suggère que la période de puberté

qui s'accompagne d'une augmentation des androgènes peut représenter un facteur déclenchant. L'un des survivantes, une petite fille de quatre ans et demi, présentait un pseudo-hermaphrodisme avec syndrome adrénogénital. Le fait d'observer une hyperthermie maligne chez une patiente présentant déjà une pathologie aussi rare nous semble indiquer que la formation excessive d'hormones androgènes que l'on retrouve dans ces cas peut agir comme facteur déclenchant de l'hyperthermie.

Cinq des patients furent opérés pour traumatismes, trois pour des malformations congénitales et deux pour appendicite. Ces trois pathologies sont en soi susceptibles d'augmenter la sensibilité à la Succinylcholine.

L'un des patients reçut seulement de l'Hexobarbitone, de l'Halothane et du Suxa methanium. A la suite de l'injection de Suxamethanium, on observa une rigidité du maxillaire et la température s'éleva à 41.3 degrés Centigrade. L'anesthésie fut arrêtée. La survie du malade illustre que la rigidité du maxillaire observée après l'injection de Suxamethanium est un signe très fiable.

On attribue à la correction préalable d'une acidose métabolique chez un malade, l'absence de dépression cardio-respiratoire notée après une dose de 3.5 grammes de Procaine. Les auteurs suggèrent de corriger l'acidose, d'administrer des Stéroides et de tenter de refroidir, avant denvenir à la Procaine.

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