ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN — POLONIA
VOL. LI, 35 SECTIO D 1996

Katedra i Klinika Anestezjologii i Intensywnej Terapii Akademii Medycznej w Lublinie
Kierownik: prof. dr hab. Andrzej Nestorowicz
Katedra i Klinika Neurologii Akademii Medycznej w Lublinie
Kierownik: prof. dr hab. Zbigniew Stelmasiak

MAREK PSUJEK, HALINA BARTOSIK-PSUJEK,
JOANNA WOJCZAL

Pathogenesis and Clinical Aspects of Malignant Hyperpyrexia (MH)

Patogeneza i kliniczne aspekty gorączki złośliwej (MH)

Great progress in anaesthetic techniques has resulted in elimination or significant reduction of complications connected with the disease, operation technique or anaesthesia. However, sometimes a rapid increase in systemic metabolism occurs immediately after induction of anaesthesia and it may end in the patient's death. This syndrome defined as malignant hyperpyrexia (MH) was described for the first time by Denborough and Lovell (2). They reported 10 deaths of this type in one family. Later it was noticed that some patients may develop MH after inhalation anaesthetics or suxametonium. MH was observed more frequently in several groups of patients. It occurs rarely — 1 to 15,000 cases after anaesthesia in children and 1 to 50,000 cases after anaesthesia in adults, but its sudden and rapid development becomes a great clinical problem.

The disease is caused by genetically determined mutation of ryanodynic receptor (RYDR), which in physiological circumstances is responsible for the correct transport and distribution of intracellular calcium in a striate muscle cell. The genetic defect is localized in chromosome 19 q 12—13. This results in structural changes of the receptor and also disturbs its functional activity and mode of action. The essence of these changes has not been fully explained yet (8).

Changes in intracellular calcium are pivotal in etiopathogenesis, however, the importance and effects of mutation of receptor RYDR are also emphasized. A lot of data indicate that MH is not a homogeneous disorder. Other structures responsible for calcium flow are also involved in pathomechanism of changes. In MH an uncontrolled release of

calcium from sarcoplasmic reticulum occurs and this results in a significant increase of calcium level in sarcoplasma. The altered permeability of cytolemma and intracellular membranes affects the metabolism of calcium. It may modulate rate and direction of biochemical reactions. The altered function of both receptor and plasma membranes become evident and amplifies after inhalation anaestetics and depolarizing muscle relaxants (9, 10).

The following disorders predispose to develop MH: 1) myotonia and occult myotonia, 2) myoglobinuria, 3) benign myopathy with a high level of creatinine phosphokinase (CPK), 4) abnormalities of skeletal system (scoliosis, chest deformity) often with cryptorchism and with normal activity of creatinine phosphokinase, 5) "central core" myopathy (5, 6).

Lambert et al. have reported the development of MH in patients with familial periodic paralysis (7).

At present, "central core" myopathy with both structural and nonstructural "core" in morphological picture is considered to be the disease which is the most predisposing to intraoperative MH development, because the genetic mutation of the disease is localized in chromosome 19 in the neighbourhood of the gene responsible for MH (3).

A rapid increase in hypercapnia because of hypermetabolism and production of CO_2 in glycolysis process, tachycardia, with consequent different types of dysrhythmias are the earliest clinical and metabolic signs of MH. These are followed by profuse sweating, skin flush, immediate growth in temperature of the body (1—2 centigrades every 5 min), rapid arterial pressure rise and muscular rigidity. At the same time metabolic disorders are observed, such as respiratory and metabolic acidosis, increased level of lactic and pyruvic acid in blood, hyperkalemia, increased activity of creatinine phosphokinase and myoglobin in blood and urine. A significant rise in epinephrine and norepinephrine and sometimes hyperglicaemia were noticed (10).

Sometimes masseter muscles rigidity may be the first sign of MH, and it makes intubation difficult or impossible. It happens more often after suxamethonium admininistration (1).

When MH develops during operation, administration of anaestetic triggering MH should be immediately stopped and the operation should be finished as quickly as it is possible. Artificial hyperventilation

with pure inspired oxygen, physical and pharmacological cooling should be applied. Sodium bicarbonate should be administered in a dose 1—2 mEq/kg b.m. under blood pH monitoring. At the same time sodium dantrolen should be given in a dose 2—3 mg/kg b.m., repeating intravenous injections every 5—10 min up to the maximum dose of 10 mg/kg b.m. as the need arises. This drug reduces calcium level. Adequate diuresis should be maintained by proper fluid supply along with furosemid or mannitol administration. Hyperkaliemia may be reduced by infusion of 50 ml of 50% glucose with 10 u. of crystalline insulin. The patient should be admitted to an intensive care unit, where he must be observed and monitored in detail. After the acute phase of the disease some complications may occur, such as: renal failure caused by myoglobinuria, disseminated intravascular clotting or recurrence of the syndrome. We prevent this last complication by administration of dantrolen in a dose 1 mg/kg b.m. every 6 hrs for 72 hrs since the onset of the disease (1).

Preoperative diagnostics of MH is very difficult because of unexplained etiopathogenesis and lack of simple and univocal biochemical tests. Determination of creatinine phosphokinase activity before anaesthesia is not entirely sufficient. No direct relationship was found between preoperative creatinine phosphokinase activity and MH occurrence. There were case reports of patients with normal CPK before anaesthesia, who developed MH (5). But when clinical signs of MH appear during operation and activity of CPK determined at the time exceeds 20,000 u., the diagnosis of the syndrome is confirmed univocally (1). Therefore the proper, pre-operative preparation of susceptible patients, in whom anamnesis and family history indicate the possibility of MH development is of the greatest importance in practice of anaesthesia.

In such patients the following prophylactic procedures should be performed:

1. Reduction of exercise and mental effort — stress may intensify hyperthermia.

2. Determination of creatinine phosphokinase activity in blood.

3. Harriman and colleagues (4) postulate to make thin-needle biopsy and test for susceptibility including *in vitro* muscle contractions when exposed to halothane, suxamethonium and ketamine.

4. Administration of so-called "safe anaesthetics", which do not produce MH. These are: intravenous anaesthetics: barbiturates and bezodiazepines; local anaesthetics: ester and amide derivates; analgesic drugs: opiates.

After normal premedication, intravenous dantrolene should be administered in a dose 2.5 mg/kg b.m., body temperature should be monitored and capnograph should be used, because the increase in CO_2 pressure in the end-expired air is earliest sign of MH (1).

It must be clear that lack of complications during operation in a patient does not warrant that he will not develop MH during the next one.

With the introduction of dantrolene to the treatment, the mortality caused by MH has been reduced to 3—5% of the cases. But susceptible patients may still develop it and expecially inhalation anaesthetics, such as: halothane, isoflurane, enflurane, diethyl ether, methoxyflurane, trichloroethylene, cyclopropane, fluoroxem may trigger it off.

REFERENCES

1. Barash P. G. et al.: Podręcznik anestezjologii klinicznej, PZWL, Warszawa 1995.
2. Denborough M. A., Lovell R. R. H.: Anesthetic deaths in a family. Lancet, 2,45, 1960.
3. Friend K. L., Mulley J. C.: Assignment of the gene for central core disease to chromosome 19. Human Genetics, 86, 187, 1990.
4. Harriman D. G. F. et al.: Second International Symposium on Malignant Hyperthermia. Grune and Straton, 67, New York 1978.
5. Hausmanowa-Petrusewicz J.: Choroby mięśni, PWN, Warszawa 1993.
6. Iaizzo P. A., Lehmann-Horn F.: Anesthetic complications in muscle disorders. Anesthesiology, 5, 82, 1093, 1995.
7. Reyford H., Pinand M.: Malignant hyperthermia in a patient with hypokalemic periodic paralysis. Anaesth. Analg., 5, 1012, 1994.
8. Levitt R. C. et al.: Molecular genetics and malignant hyperthermia. Anesthesiology, 75, 1, 1991.
9. Mayzner-Zawadzka E.: Śródoperacyjna hipertermia złośliwa — etiopatogeneza i wybrane zagadnienia kliniczne. Anestezjologia i Intensywna terapia, 25, 39, 1993.
10. Steele A. P. et al.: Malignant hyperthermia and compartment syndrome. Br. J. Anaesth., 75, 3, 369, 1995.

STRESZCZENIE

Ostatnie lata wniosły dużo nowych elementów i bardzo rozszerzyły wiedzę na temat etiologii i patogenezy gorączki złośliwej (MH), zespołu zaburzeń występujących w bezpośrednim związku przyczynowym z anestezją. Autorzy przedstawili aktualne ustalenia na temat etiopatogenezy MH. Szczególną uwagę zwrócono na sposób postępowania podczas śródoperacyjnego wystąpienia gorączki złośliwej.