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*Short communication*

# Fulminant-type malignant hyperthermia in Japan: cumulative analysis of 383 cases

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**Abstract**
We investigated the transition of clinical signs of fulminant-type malignant hyperthermia (f-MH) by analyzing a database consisting of 383 cumulative cases of f-MH from 1961 to 2004. The cases were divided by time period into group 1 (1961–1984), group 2 (1985–1994), and group 3 (1995–2004). The variables considered were age, sex, type of agents used (succinylcholine and volatile anesthetics), dantrolene administration, clinical signs, laboratory data, and mortality. The level of statistical significance was considered to be less than 5%. Groups 1, 2, and 3 consisted of 196, 127, and 60 cases, respectively. In groups 1, 2, and 3, the rates of dantrolene administration were 18.4%, 93.6%, and 86.7%; the rates of occurrence of ventricular arrhythmia were: 75.2%, 55.6%, and 35.0%; and the rates of generalized muscle rigidity were 64.7%, 60.9%, and 23.9%, respectively. The mortality rate decreased over time, from 42.3% in group 1, to 15.0% in group 2 and group 3. We considered that this decrease occurred because of the increased use of dantrolene and the early diagnosis of malignant hyperthermia in the latter two groups.

**Key words** Malignant hyperthermia · Investigation · Dantrolene

## Introduction

Malignant hyperthermia (MH) is a life-threatening disease that occurs during general anesthesia following exposure to a depolarizing muscle relaxant, such as succinylcholine (SCh) and volatile anesthetics. MH, an inherited autosomal dominant disease, is characterized by abnormalities in intracellular calcium metabolism caused by a variety of genetic mutations of the sarcoplasmic reticulum (SR) in skeletal muscle [1–4]. Signs of MH are, approximately, divided into three categories, i.e., early, succeeding, and late, according to time of onset [2]. Early MH signs include masseter muscle rigidity (MMR) just after the administration of SCh; a rise in endtidal $CO_2$ ($E_TCO_2$); acidosis; and unexpected tachycardia due to hypermetabolism. Succeeding signs include increased body temperature, which is the origin of the term "MH", and ventricular arrhythmia. As late signs, continuous muscle contractions may provoke generalized muscle rigidity, which is typically followed by rhabdomyolysis when inappropriately treated. Late signs also include cardiac arrest with hyperpotassemia, cola-colored urine, and a rise in creatine kinase (CK). These changes may lead to fatal renal failure, disseminated intravascular coagulation, and brain edema [1–3,5].

Since 1961, we have been keeping records of fulminant MH (f-MH) cases, diagnosed according to Morio's clinical criteria for MH [6], and we have established a database. The purpose of the present study was to investigate charges in the clinical appearances of f-MH.

## Patients and methods

We investigated MH cases in Japan by referring to reports that appeared at academic meetings, published documents, and personal communications. In this study, f-MH cases that were consistent with Morio's clinical criteria [6] were adopted by excluding abortive MH (a-MH) and postoperative MH cases.

We analyzed 383 f-MH cases in our database (accumulated from 1961 to 2004) and we divided them into three groups according to time periods. Cases reported from 1961 to 1984 were assigned to group 1, those reported from 1985 to 1994 were assigned to group 2, and those reported from 1995 to 2004 were assigned to group 3. Related factors investigated were age, sex, type of agents (SCh and volatile anesthetics), administration of dantrolene, clinical signs, laboratory data, and mor-

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tality. We also analyzed initially noted signs in relation to mortality. There were missing data, especially in group 1, because of the lack of an institutional laboratory examination system and delayed laboratory examination results in that era (1961–1984).

For this study, the maximal values in each case were adopted for the analysis. A one-way analysis of variance (ANOVA) and Kruskal-Wallis test were used to compare date among the three groups. If a significant difference was found, statistical comparisons were performed between the groups using Fisher's protected least significant difference test or a Mann-Whitney test, with a $\chi^2$ test for independence used for correlation. The level of significance was considered to be less than 5%.

## Results

There were 196 cases in group 1, 127 in group 2, and 60 in group 3, with the lowest annual frequency shown in group 3. There were no differences in age or sex ratios among the groups (Table 1). The frequency of SCh administration was 88.4%, 62.9%, and 33.3% in groups 1, 2, and 3, respectively, which demonstrated a significant decrease over time. Different types of volatile anesthetics were utilized in the three groups, mainly halothane in group 1, with sevoflurane and isoflurane being equally common in group 3 (Fig. 1). There was no case of MH triggered by intravenous anesthetics alone in any of the groups. Dantrolene was given to 18.4%, 93.6%, and 86.7% of the patients in groups 1, 2, and 3, respectively. The occurrence of MMR in group 3 was significantly lower than that in groups 1 and 2, while there was no significant difference in tachycardia among the groups. The maximum body temperature was significantly higher in group 1 than in the other two groups. The incidence of ventricular arrhythmia and the frequency of cola-colored urine and were significantly lower in group 3 than in group 2, and the frequency of generalized muscle rigidity in group 3 was significantly lower than that in the other two groups. As serum CK values were missing in many cases, we could not assess CK changes, though there were statistically significant differences among the groups. Further, mortality in the two most groups was recent significantly reduced compared with mortality in group 1 (Table 2).

The most frequently noted initial clinical sign in group 1 was MMR, while it was tachycardia in group 2, and a rise in $E_TCO_2$ in group 3 (Table 3). The mortality rate was 11% when MH was anticipated by a rise in $E_TCO_2$ and approximately 30% when MH was anticipated by the other signs (Table 4).

## Discussion

There were many notable changes in the environment of clinical anesthesia during the era of our analysis—from 1961 to 2004. In particular, pharmaceutical changes, such as the use of new anesthetics and muscle relaxants, could have affected the occurrence of MH.

**Table 1.** Patient characteristics

| Group | 1 | 2 | 3 | |
|---|---|---|---|---|
| Period | 1961–1984 | 1985–1994 | 1995–2004 | |
| No. of patients | 196 | 127 | 60 | *P* |
| Frequency (/year)[a] | 8.2 | 12.7* | 6.0** | 0.0037 |
| Age (years) | 22 (17) | 25 (18) | 26 (19) | NS |
| Sex ratio (male/female) | 8:2 | 7.4:2.6 | 8:2 | NS |

* $P < 0.05$ vs group 1; ** $P < 0.05$ vs group 2
Values are shown as means (SD)
NS, not significant
[a] Frequency of f-MH

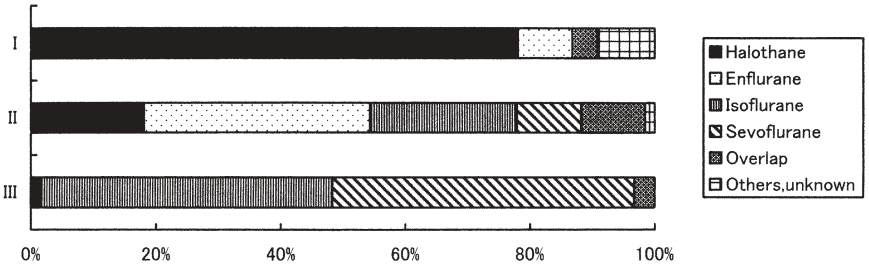


**Fig. 1.** Types of anesthetics utilized in each group. *Overlap*, two types of anesthetics used; *others*, other than the anesthetics listed in the Fig., e.g. ether

**Table 2.** Clinical features and laboratory data

| Group | 1 | 2 | 3 |
|---|---|---|---|
| Frequency of MMR (%) | 49.7 | 44.9 | 17.6*,** |
| Maximal $Pa_{CO_2}$ (mmHg) | 67.8 (31.5) | 82.9 (33.9)* | 79.8 (36.0)* |
| Maximal pH | 7.10 | 7.09 | 7.11 |
| Maximal base excess ($mmol \cdot l^{-1}$) | –11.2 | –9.9 | –7.7*,** |
| Frequency of tachycardia (%) | 95.1 | 96.3 | 88.5 |
| BT (°C) | 41.0 (1.3) | 40.5 (1.4)* | 40.4 (1.5)* |
| Rise of BT (°C/15 min) | 1.2 | 1.1 | 0.9* |
| Frequency of VA (%) | 75.2 | 55.6* | 35.0*,** |
| Frequency of muscle rigidity (%) | 64.7 | 60.9 | 23.9*,** |
| CK (IU) | 13194 (27011) | 25544 (48533)* | 27807 (50623)* |
| Cola-colored urine (%) | 71.3 | 55.1* | 31.8*,** |
| Mortality (%) | 42.3 | 15.0* | 15.0* |

* $P < 0.05$ vs group 1; ** $P < 0.05$ vs group 2
Values are shown as means, with SD in parentheses
MMR, masseter muscle rigidity; BT, body temperature; VA, ventricular arrhythm

**Table 3.** Order of observation of clinical signs and frequency noted initially

| Group | 1 | 2 | 3 |
|---|---|---|---|
| First (%) | MMR (25.0) | Tachycardia (27.6) | Rise in $E_TCO_2$ (46.7) |
| Second (%) | Rise in BT (19.4) | MMR (22.0) | Rise in BT (31.7) |
| Third (%) | MR (18.2) | Rise in $E_TCO_2$ (12.6) | Tachycardia (10.0)<br>MMR (10.0) |

Figures in parentheses are percentages
MMR, masseter muscle rigidity; BT, body temperature; MR, generalized muscle rigidity

**Table 4.** Correlations between first noted clinical signs and survival rate

| | MMR | Rise in $E_TCO_2$ | Tachycardia | Rise in BT | MR | VA |
|---|---|---|---|---|---|---|
| Survived (%) | 62 (75) | 40 (89) | 46 (69) | 49 (69) | 33 (73) | 8 (67) |
| Died (%) | 21 (25) | 5 (11) | 21 (31) | 22 (31) | 12 (27) | 4 (33) |
| Total | 83 | 45 | 67 | 71 | 45 | 12 |

Data from 60 patients are missing. Percentages are shown in parentheses
MMR, masseter muscle rigidity; BT, body temperature; MR, generalized muscle rigidity; VA, ventricular arrhythmia

New volatile inhaled anesthetics and short-acting nondepolarizing muscle relaxants were released for the first time. Then dantrolene, a specific remedy for MH, became commercially available, and the widespread use of $E_TCO_2$ monitors, which are useful to detect MH earlier, could have affected the clinical appearance of MH.

In this study, the frequency of administration of SCh decreased significantly over time. The types and amounts of volatile anesthetics used were different among the three groups. Consequently, we could not directly compare the rates of occurrence of MH in relation to volatile anesthetics. It was also difficult to obtain information from pharmaceutical companies regarding the total sales of volatile anesthetics, with this information being necessary to estimate the occurrence rate as a denominator. It is known that volatile anesthetics promote Ca-induced Ca release (CICR) and may provoke a hypermetabolic crisis. It has been reported that the enhancing effect of isoflurane on CICR was 2.5 times that of sevoflurane in experimental guinea pigs [7]. Therefore, it is suggested that sevoflurane triggers fewer MH reactions than isoflurane.

In terms of the clinical signs, the succeeding and late signs marked decreased rather than the early signs, because MH-associated signs were noted earlier in the later time periods than in the first time period. $E_TCO_2$ monitoring became increasingly popular in the 1990s; thus, MH is now readily anticipated. In group 3, a rise in $E_TCO_2$ was the most frequent initially noted sign. In the most recent era, early diagnosis and prompt treatment, with discontinuation of the triggering agent, were done at the same time. When MH is anticipated by observing a rise in $E_TCO_2$, the mortality rate can be lowered.

Statistics compiled by the Japanese Society of Anesthesiologists suggest that the number of patients receiving general anesthesia has increased, while the numbers of patients with f-MH have decreased. This is because both anesthesiologists and surgeons are highly aware that MH is lethal during general anesthesia, and they examine patients in preoperative interviews in order to take preventive measures when there are suspicions that MH could occur. Further, some f-MH cases may have been miscounted as abortive MH, because early diagnosis and treatment may have modified its clinical appearance. Another reason for the reduced number of f-MH cases is the reduced frequency of usage of both SCh and volatile anesthetics that may trigger MH, because total intravenous anesthesia has gradually been getting more common since the initial release of propofol in 1995.

Concerning the mortality rate, it decreased from group 1 to group 2 following the release of dantrolene (1985), which is still a mainstay of MH treatment. Dantrolene immediately alleviates hypermetabolic crisis by inhibiting the release of $Ca^{2+}$ from the sarcoplasmic reticulum in skeletal muscle. Of note, at present the mortality rate in Japan is greater than that in Europe and North America, which is reported to be less than 5% [1]. We have to consider that two important issues should be addressed. Firstly, the administration of dantrolene is apt to be delayed due to remote storage and difficulties in dissolving the agent [8]. The dosage of dantrolene given in Japan is lower than the doses given in Europe and North America [8,9]. We should further reconsider the adequacy of the initial dose of dantrolene, the total dose, and the most beneficial time period from the onset of MH to dantrolene administration. Secondly, the MH criteria used in Europe are relatively mild as compared with those used in Japan [2,5,10]. Thus, the mortality rate for Japanese patients with MH is higher than that in Europe.

In conclusion, we showed that the succeeding and late signs of MH have decreased significantly over the past two decades in Japan, and this has reduced the mortality rate. This decrease may be related to detection in the early stage of MH and the widespread use of dantrolene. However, additional studies are required to reduce the high mortality rate in Japan as compared to that in Europe and North America.

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