Malignant hyperthermia-like reactions in Duchenne or Becker muscular dystrophy: review and hypothesis

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Abstract: Adverse reactions to general anesthesia, which partly resembled malignant hyperthermia (MII), were more frequent in muscular dystrophy than in controls. In the present study, 35 cases so far reported in Duchenne or Becker muscular dystrophy (DMD or BMD) were analyzed and their pathogenesis was discussed. Cardiac involvements were sole manifestations in 7 cases. In other 28 cases, the acute rhabdomyolysis was the most prevailing manifestation. About 60% of myolysis cases were associated with muscle contracture (rigidity) or other hypermetabolic signs such as hypercapnia, hyperthermia and metabolic acidosis. Cases with BMD were more hyperthermic than with DMD. These results suggest Ca ion-induced hypermetabolic reactions are also present in dystrophinopathy, which have been assumed as core syndromes of the classical (gene-defined) MH. However, question whether the abnormal Ca ion is from the extracellular or intracellular stores is still unclear. Circumstantial evidences suggest that the Ca-induced Ca release (CICR) mechanism might also be involved. Endogenous redox modulators such as nitric oxide or reactive oxygen species in the dystrophic muscle might contribute to the perturbed Ca ion homeostasis.

Key words: malignant hyperthermia, dystrophinopathy, calcium ion, ryanodine receptor, redox modulators

Cobham and Davies firstly reviewed adverse reactions to general anesthesia in patients with various types of muscular dystrophy\textsuperscript{1}. Although similar complications prevailed in other neuromuscular diseases, our concern was limited to Duchenne or Becker muscular dystrophy (DMD or BMD, or dystrophinopathy) in the present study. It was because this problem was mostly referred and biochemical abnormalities were clearly defined in dystrophinopathy. According to Worthen et al, the prevalence of risk for untoward reactions was more than 1 in 200 in patients with DMD\textsuperscript{2}. In another report, three episodes resembling malignant hyperthermia (MII) were complicated in 84 courses of general anesthesia of DMD patients\textsuperscript{3}. The incidence of MII in general population is less than 0.01%\textsuperscript{4} and it seems much higher in dystrophinopathy. In the present study, clinical and laboratory data were analyzed on cases so far reported. Among these adverse reactions, the acute rhabdomyolysis seemed to constitute a major syndrome. The muscular rigidity or hypermetabolic states, which were pathognomonic signs of MIH, were associated in about 60% cases. Causes of these abnormal reactions were discussed in relation to the pathophysiology of Ca ion homeostasis in the skeletal muscle.

Methods

Clinical data of 28 patients with DMD, 6 with BMD and a carrier of dystrophinopathy in 24 papers, in two of which the authors had participated, were reviewed\textsuperscript{5,6}. Patients age was distributed between 4 months and 13 years (mean: 5.3 years) for DMD and between 8 and 22 years for BMD (mean: 14.5 years). A carrier was 1.5 year old. Following items were listed when available: cardiac complications, body temperature, muscular symptoms, myoglobinuria, serum potassium and CK, and arterial blood gas (pH, PaCO\textsubscript{2}, bicarbonate, base excess). Influences of succinylcholine or dantrolene sodium were also examined. A special attention was paid on muscular symptoms and signs of hypermetabolism such as hyperthermia, hypercapnia, or metabolic acidosis. When the acute rhabdomyolysis was associated with muscular rigidity and/or hypermetabolism, complications were classed as MH-like reactions.
Results

1. Classification of adverse reactions

Cardiac involvements were sole complications in 7 cases. In cardiac involvements, tachycardia, tachyarrhythmia or bradycardia appeared initially and ventricular flutter and then fibrillation developed, which terminated in asystole. In other 28 cases, the acute rhabdomyolysis or other muscular symptoms were observed. In these 28 cases, associated abnormalities were classified (Table 1). Cardiac complications were associated in 93%, Myoglobinuria, increased serum CK and metabolic acidosis were observed in 96, 95 and 80%, respectively. The body temperature elevated in 63% and muscular rigidity appeared in 59%, of which 4 cases (27%) presented only a masseter spasm[19/23/26].

2. Muscular rigidity and hypermetabolism (Table 2)

Among various abnormalities, muscular rigidity, hyperthermia, hypercapnia and acidosis were focussed. In 28 cases of the acute rhabdomyolysis, 8 cases lacked these signs. Nine cases presented 3 of them and one presented all 4 signs.

3. Pharmacological aspects

Succinylcholine was applied in 21 cases (61%). When succinylcholine was infused, adverse reactions appeared immediately or within 10 minutes after infusion in 7 cases. However, in cases without succinylcholine, their appearances protracted. In these instances, adverse reactions happened often in a postoperative recovery room (Table 3). Dantrocene sodium was administered in 7 patients, in two of whom the agent seemed effective. In other cases, the effect of dantrocene was not described.

4. Comparison between DMD and BMD (Table 4)

Various clinical and laboratory parameters were compared between DMD and BMD. Among parameters listed in Table 4, only the maximum body temperature was significantly higher in BMD. Muscular rigidity presented in 61% of DMD cases and 67% of BMD (P = 0.78). Myoglobinuria was detected in 57% of DMD cases and 40% of BMD (P = 0.51).

Discussion

In the present study, following questions were asked: had adverse reactions of dystrophinopathy any common pathomechanism with the classical MH? In another word, derangements of Ca ion homeostasis was responsible for adverse reactions? Then, whether did the elevated Ca ion originate from the extracellular space or intracellular stores? For these purposes, clinical and laboratory parameters were analyzed. Especially, we focussed on the acute rhabdomyolysis associated with muscular rigidity or hypermetabolic parameters. As hypermetabolic parameters, hyperthermia, hypercapnia and metabolic acidosis were counted. Although they were not necessarily hypermetabolic signs, these were pathognomonic for the classical MH and were attributed to the uncontrolled Ca ion release mechanism[29].

Cardiac failure had occurred without any other systemic involvement[27]. This was attributed to the subclinical cardiomyopathy in dystrophinopathy, which could not stand hemo-
Table 3  The time interval between noticing adverse reactions and application of succinylcholine or other agents. Succinylcholine was applied in 19 and not applied in 16 cases.

<table>
<thead>
<tr>
<th></th>
<th>with succinylcholine</th>
<th>without succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>immediate — 10 minutes</td>
<td>7 cases</td>
<td>1 case</td>
</tr>
<tr>
<td>between 11 and 60 minutes</td>
<td>4 cases</td>
<td>1</td>
</tr>
<tr>
<td>after 60 minutes</td>
<td>1 case</td>
<td>3</td>
</tr>
<tr>
<td>postoperative period</td>
<td>1 case</td>
<td>9</td>
</tr>
<tr>
<td>2nd day</td>
<td>1 case</td>
<td>1</td>
</tr>
<tr>
<td>No information</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4  Comparison of clinical parameters between DMD and BMD during adverse anesthetic reactions.

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>S.E.</th>
<th>range (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum potassium (mEq)</td>
<td>6.9</td>
<td>0.6</td>
<td>4.2-10.4 (12)</td>
<td>—</td>
</tr>
<tr>
<td>DMD</td>
<td>5.8</td>
<td>0.8</td>
<td>4.2-6.9 (3)</td>
<td>0.41</td>
</tr>
<tr>
<td>serum CK (IU/L)</td>
<td>64,000</td>
<td>11,000</td>
<td>17,000-125,000 (15)</td>
<td>—</td>
</tr>
<tr>
<td>DMD</td>
<td>92,000</td>
<td>34,000</td>
<td>37,000-252,000 (9)</td>
<td>0.34</td>
</tr>
<tr>
<td>BMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>body temperature (℃)</td>
<td>37.2</td>
<td>0.2</td>
<td>36-38.6 (17)</td>
<td>—</td>
</tr>
<tr>
<td>DMD</td>
<td>38.9</td>
<td>1.4</td>
<td>36-40.6 (4)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arterial blood pH</td>
<td>7.11</td>
<td>0.11</td>
<td>6.85-7.40 (10)</td>
<td>—</td>
</tr>
<tr>
<td>DMD</td>
<td>6.91</td>
<td>0.12</td>
<td>6.60-7.17 (5)</td>
<td>0.33</td>
</tr>
<tr>
<td>BMD</td>
<td></td>
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</table>

dynamic stresses. In cases of the rhabdomyolysis complicated with cardiac events, the pathophysiological discussion seemed more complicated, because the rhabdomyolysis itself could cause cardiac complications or they might be involved simultaneously. Among 28 cases of the acute rhabdomyolysis, 19 cases were associated with one or more hypermetabolic signs. Two cases seemed inseparable from the classical MH in their presentations\(^{20,21}\). In this context, these 19 cases were classified as MH-like and suggested that homeostasis of the intracellular Ca ion might be disturbed as in the classical MH.

When adverse reactions were compared between DMD and BMD, incidence or extent of most clinical parameters were the same except body temperature. The maximum body temperature was significantly higher in BMD cases. This might reflect the fact that BMD patients were elder and retained more skeletal muscle mass, which produced excessive heat during adverse events.

It has been speculated that dystrophic plasma membrane is more vulnerable to volatile anesthetics and subject to the rhabdomyolysis and subsequent events\(^{20,21}\). Actually, the metabolic acidosis is well delineated as a sequela of acute rhabdomyolysis. This might be the case, but a fundamental question concerning roles of dystrophin for this vulnerability still remains unsolved. Supporting evidences for this hypothesis seem inconclusive.

In 39% of cases, complications developed without application of succinylcholine. In these instances, progress of the syndrome was rather protracted and mostly appeared in the postoperative period. This protracted course might suggest involvements of a gradual and self-activating process rather than a direct breakdown of the plasma membrane on exposure to agents. Succinylcholine might accelerate the process by the depolarization. In a few cases, dantrolene seemed effective for ameliorating the syndrome. It is well known that the site of action of dantrolene sodium is limited to the ryanodine receptor (RYR)\(^{21}\). Concerning the source of elevated Ca ion, we are yet short of definite evidences and a possible activation of the CICR might remain as a candidate.

In the huge RYR type 1 gene, more than 100 kind of mutations are detected, presenting at least two or more different phenotypes\(^{22,23}\). In the gene-defined MH, mutations has been clustered in 3 domains of the RYR. These mutations could cause interdomain interaction, enhancing the CICR mechanism\(^{24}\). On the other hand, the RYR contains a number of highly reactive SH groups, which are amenable to redox reactions. Endogenous, physiological redox modulators, such as nitric oxide (NO), reactive oxygen species (ROS), glutathione
disulfide and oxygen tension, could cause oxidation of thiols, enhancing the CICR. In dystrophic muscle, the NO synthase was distributed and up-regulated in the cytoplasm.

In dystrophinopathy, cytochrome residues of proteins seemed more susceptible to ROS, but exact targets of ROS were not specified and they might be multiple. Roles of these modulators need to be studied in relation to the pathogenesis of MH-like reactions in muscular dystrophy.

In the present study, results of the in vitro contracture test (IVCT) was not included in the discussion. In previous study, it was shown that response to caffeine differed from normal controls in the contractile system of dystrophic muscle. This phenomenon was probably due to abundance of regenerating fibers of dystrophic muscle, influencing sensitivity and specificity of the IVCT.

References

26) Kleopa KA, Rosenberg H, Heiman-Patterson T: Malignant hyperthermia-like episode in Becker muscular dystrophy. Anesthesiology 2000; 93: 1535—1537
33) Wu S, Ibarra CA, Malicdan MCV, et al: Central core disease is due to RYR1 mutations in more than 90% of patients. Brain 2006; 129: 1470—1480