placement over the ensuing six days before her symptoms finally abated.

**DISCUSSION**

The use of epidural blood placement, despite its documented efficacy, has been associated with considerable controversy. There has been concern that patients would be refractory to subsequent epidural anesthesia. Follow-up studies, however, suggest that this does not occur. The efficacy of epidural blood placement has been questioned because of the absence of comparative studies, including comparison with placebo epidural needle placement. Placebo treatment may be scientifically sound, but in this circumstance, we did not feel it would be clinically justified. With a comparative study, we felt our patients were not offered a treatment with little likelihood of success.

In our study, epidural placement of saline solution has success rates at 24 hours of 60 per cent for 25-gauge dural punctures and 0 per cent for 17-gauge dural punctures. These success rates are somewhat lower than those reported by other investigators. There was, however, a 100 per cent success rate when evaluation was made shortly after treatment. Our epidural blood placement had success rates of 100 per cent for 25-gauge punctures and 73 per cent for 17-gauge punctures. These rates are also somewhat lower than those reported by others. The prospective randomized nature of our study, however, permitted us to demonstrate that blood placement is more efficacious than placement of saline solution. This superior efficacy was most apparent in the population having 17-gauge dural punctures.

**REFERENCES**


**Morphologic Abnormalities in a Case of Malignant Hyperthermia**

**MEREDITH T. HULL, M.D.,* JANS MULLER, M.D.,† WILLARD H. ALBRECHT, M.D.‡**

Malignant hyperthermia is an inherited, metabolic disease of obscure etiology and pathogenesis. Since 1960, in Australia, saw no fewer than ten deaths in one family due to anesthesia, much attention has been devoted to this disease. Frequency is estimated at one per 14,000 anesthetic events. Brit reported a mortality rate of 64 per cent. Denborough established the genetics: autosomal dominance with incomplete penetrance. Recently, investigators have suggested that malignant hyperthermia is associated with a subclinical myopathy that often is manifested by elevated resting creatine phosphokinase (CPK) levels in susceptible individuals. Extramuscular abnor-

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mortality has been found in the form of decreased activity in erythrocyte ATPase preparations.\textsuperscript{8} Virtually all general anesthetic agents have been implicated as "trigger agents," which set in motion a complex array of metabolic changes, initially manifested as a release of calcium into the myoplasm from storage membranes within the muscle fibers.\textsuperscript{5} This, in turn, leads to an uncoupling of oxidation–phosphorylation, inhibition of troponin, and activation of phosphorylase kinase and myosin ATPase.\textsuperscript{8} The result is a self-perpetuating, hypermetabolic, exothermic state.

There have been few reports describing the ultrastructural and light microscopic findings in muscle tissue of patients who have experienced malignant hyperthermia.\textsuperscript{2,9–14} These accounts are confusing, and at times contradictory.

The following is a report of a case of malignant hyperthermia in a patient who subsequently underwent muscle biopsy for electron and light microscopic evaluation.

Methods and Materials

An 8-year-old white boy experienced an episode of malignant hyperthermia during general anesthesia for tonsillectomy. Premedication consisted of meperidine and atropine, im, with halothane, nitrous oxide, and oxygen anesthesia. Following succinylcholine, iv, the patient experienced marked, generalized muscle rigidity, which was not relieved by two additional doses of succinylcholine. His normal sinus rhythm progressed to bigeminy. Anesthetic gases were discontinued, and the rhythm reverted to normal sinus rhythm. During this period of 40 minutes the temperature rose 3.4 degrees F.

The patient's past medical and family histories were unremarkable, and he was clinically free of neuromuscular disease. After anesthesia, he had normal serum electrolytes and coagulation test results. Serum calcium and phosphorus were normal. Serum free hemoglobin was elevated to 27.9 mg/dl. Urine was positive for protein, hemoglobin, and erythrocytes 24

<table>
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<tr>
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<th>1 Hour after Anesthesia (mU/ml)</th>
<th>24 Hours after Anesthesia (mU/ml)</th>
<th>7 Days after Anesthesia (mU/ml)</th>
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<tr>
<td>LDH (normal 90–210)</td>
<td>31.8</td>
<td>1,258</td>
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<tr>
<td>CPK (normal 50–180)</td>
<td>2816</td>
<td>27,000</td>
<td>172</td>
</tr>
<tr>
<td>SGOT (normal 8–30)</td>
<td>135</td>
<td>764</td>
<td>42</td>
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hours after anesthesia, but negative a week after anesthesia. Twenty-four hours after anesthesia lactic dehydrogenase (LHD), creatine phosphokinase (CPK), and glutamine oxaloacetic transaminase (SGOT) were markedly elevated, but corresponding values were significantly decreased a week after anesthesia (table 1).

Sixty-six days after anesthesia the patient returned for a muscle biopsy. Local anesthesia with lidocaine was used for the procedure. Skeletal muscle was obtained from the right vastus lateralis. The muscle tissue was clamped in situ in an isometric device, then fixed in the device in cold buffered glutaraldehyde (6 per cent), postfixed in osmium tetroxide, embedded in Epon, and examined with a Siemens Elmiskop I. Additional tissue was submitted for routine light microscopy.

RESULTS

Electron microscopic examination revealed normal nuclei, contractile material, tubular structures, and basal lamina. However, mitochondria were enlarged, irregular in shape, and increased in numbers. Also, some mitochondria contained incomplete cristae, with their remaining volumes filled with a finely granular matrix (figs. 1 and 2). Additionally, muscle fibers contained increased numbers of lipofuscin bodies and lysosomes (fig. 3). Finally, myelin-like bodies were present throughout the sections (fig. 4, A).

Paraffin-embedded sections stained with hematoxylin and eosin and trichrome demonstrated greater than normal variability in cross-sectional fiber size and abnormally large numbers of internally located nuclei (fig. 4B). All other morphologic features observed by light microscopy were normal.

DISCUSSION

Clinically, this case illustrates the need for constant awareness of malignant hyperthermia as a possible complication of anesthesia, even in those cases where the personal and family anesthetic histories are unremarkable.

In the current case, a paradoxical
reaction to succinylcholine together with cardiac arrhythmias and an increase in body temperature led to early withdrawal of anesthesia. Furthermore, the patient was successfully treated primarily by early discontinuance of administration of the anesthetic agent, demonstrating that survival is related to the speed with which the syndrome is identified and the anesthetic agent eliminated. In general, treatment should be directed at this, ventilation with 100 per cent oxygen, reversal of metabolic acidosis, cooling, and iv procaainamide and steroids. Recently a patient was treated successfully with emergency cardiopulmonary bypass, perhaps impractical under routine circumstances. Following immediate treatment, careful monitoring of serum electrolytes and calcium levels, and evaluation of coagulation status, are indicated during the ensuing 24 to 48 hours. Finally, the patient and patient's family should be counseled regarding the possible danger of future anesthesia. When possible, future procedures should be accomplished by local or regional techniques, with tested agents, procaine or tetracaine. When general anesthesia is necessary, nitrous oxide, narcotics, neuroleptanalgesia, and barbiturates appear to be the safest alternatives at this time.

Recently, the biochemical aspects of malignant hyperthermia have been the subject of much investigation; however, there are few reports of the morphologic changes in the skeletal muscle of such patients. In 16 patients the muscle has been examined for ultrastructural changes.

Carpenter reported biopsy results from three patients; the skeletal muscle was normal by routine light microscopy and showed mitochondrial degeneration with formation of lipid globules by electron microscopy. Reske-Nielsen, in muscle of one patient, found thinned I-bands containing abnormal Z-discs, giant vacuolated mitochondria, distended sarcoplasmic reticulum, and folded, thickened basement lamina. Schiller and Mair studied muscle biopsies from five patients. In specimens from three patients, electron microscopic sections were normal, while in two specimens ultrastructural abnormalities were found: ruptured mitochondria, dilated sarcoplasmic reticulum, decreased glycogen, increased sarcoplasmic fluid, and crystalline inclusions in many muscle fibers. Two of the patients whose muscle specimens had normal ultrastructure showed decreased activity in the ATPase preparation at pH 4.3 to 4.6. Britt and Kalow presented three patients who underwent
muscle biopsy subsequent to malignant hyperthermia; these biopsies were normal by light and electron microscopy. Gullatto and Helpap presented three patients whose skeletal muscles showed acute focal necrosis of fibers by light microscopy. One biopsy specimen obtained two days after anesthesia showed ultrastructural changes, including dilatation of cisterns, proliferation and reduplication of the sarcoplasmic reticulum, and a single mitochondria with a crystalline inclusion. Finally, Wade reported results from a biopsy of a patient also two days after an acute episode. His findings included normal myofibrils and mitochondria but distended sarcoplasmic reticulum.

These reports share little common ground; also, many of the changes described are nonspecific. Some could even be artifactual. For example, mitochondrial degeneration can assume a spectrum of morphologic forms and can be seen in a host of unrelated disease processes in all tissues of the body. In fact, mitochondrial degeneration is one of the earliest artifactual changes to appear in poorly preserved tissue. Also, thickened, reduplicated basement laminae, as described by Reske-Nielsen, have been studied recently in a variety of diseases and are believed to represent a nonspecific response to cellular injury. Abnormalities of the sarcoplasmic reticulum are found in numerous myopathies. Greater than normal variations in fiber size and abnormally large numbers of internally located nuclei, as in this case, are found in many apparently unrelated myopathies. While the mitochondrial changes seen in the skeletal muscle of our patient are not pathognomonic of a particular disease, they are of somewhat greater interest in light of the postulated biochemical abnormalities in mitochondria of patients with malignant hyperthermia. To complicate interpretation of these reports further, biopsies done have been performed at various intervals relative to the acute episodes.

Functional integrity and morphologic integrity of mitochondria have been correlated. Luft et al. described the case of a 35-year-old woman with hypermetabolism of non-thyroid origin together with biochemical and morphologic evidence of abnormal mitochondria. Wijngaarden et al. described a 15-year-old boy with a progressive myopathy and demonstrated loosely coupled oxidation–phosphorylation and morphologic abnormalities in mitochondria. Finally, the presence of an abnormally

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**Fig. 4.** *A,* myelin-like bodies lying between myofibrils and basement lamina. (Uranyl acetate and lead citrate, ×25,600.) *B,* light photomicrograph, showing variability in sizes of muscle fibers and prominent internal nuclei. (Trichrome, ×400.)
large number of lysosomes, increased lipofuscin pigment, and myelin-like bodies are pathologic in this patient, and evidence of cellular degeneration. While there is little agreement as to the definitive nature of the morphologic changes in malignant hyperthermia, all investigators except one have identified definite pathologic, although often nonspecific, changes discernible at an electron and/or light microscopic level in muscle following episodes of malignant hyperthermia. In our patient, muscle changes, including abnormal mitochondria, greater than normal numbers of lipofuscin bodies and lysosomes, myelin-like bodies, and numerous internally located nuclei are pathologic, although at this time not pathognomonic of a specific myopathy. It is hoped that, after sufficient numbers of patients with the disease have been evaluated microscopically and biochemically, a characteristic pattern of pathologic changes can be defined, which would facilitate identification of these patients prior to anesthesia.

**Summary**

An 8-year-old boy underwent general anesthesia and experienced an episode of malignant hyperthermia, characterized by elevated temperature, cardiac arrhythmias, markedly elevated serum enzymes (SGOT, LDH, and CPK), proteinuria, and hemoglobinuria. Sixty-six days after anesthesia a skeletal muscle biopsy was obtained for examination by electron and light microscopy, which showed skeletal muscle cells with abnormally numerous mitochondria, enlarged, and variable in shape. Some contained abnormal cristae. There were more lysosomes than normal, and lipofuscin was increased in quantity. Myelin-like bodies were also present. Previous reports of muscle abnormalities are reviewed and compared with the data in this case.

**References**