

Histomorphologic Examination of Skeletal Muscle Preparations Does Not Differentiate between Malignant Hyperthermia–Susceptible and –Normal Patients

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Background: It has been suggested that malignant hyperthermia (MH) can be diagnosed by specific myopathologic alterations. The purpose of this study was to investigate whether there are characteristic myopathologic changes in skeletal muscles of MH-susceptible (MHS) compared with MH-normal (MHN) patients.

Methods: Four hundred forty patients with clinical suspicion of MH were classified as MHN, MH equivocal (MHE), or MHS by the *in vitro* contracture test with halothane and caffeine. In addition, a small muscle sample excised from each patient was analyzed by histologic, histochemical, immunohistochemical, and computer-aided morphometric methods.

Results: MHN was diagnosed in 243 patients, MHE was diagnosed in 65, and MHS was diagnosed in 132. No myopathologic abnormalities were found in 53.5% of the MHN, 53.9% of the MHE, and 56.1% of the MHS patients. Thirty-five percent of all patients showed one, 9.8% showed two, and only 0.9% showed three different pathologic findings within skeletal muscle preparations. The frequency of pathologic findings did not differ between the MHN and the MHS patients; only fiber type I predominance was observed more often in MHN. MHE patients could not be assigned to a diagnostic group by detection of myopathologic alterations. In six clinically unaffected patients, a former unrecognized myopathy, such as central core disease, was diagnosed. This disease is characterized by a specific alteration (cores).

Conclusions: Histologic differences between MHS and MHN statuses could not be demonstrated in this study. Histopathologic examinations can neither improve the diagnosis of MH nor contribute to a better definition of the MH status. However, histopathologic examinations might be useful to detect formerly unrecognized specific myopathies.

MALIGNANT hyperthermia (MH) is an autosomal-dominantly inherited, genetically heterogenous myopathy that is characterized by a dysregulation of intracellular calcium homeostasis in skeletal muscle.^{1–4} Furthermore, it has been suggested that in skeletal muscle preparations from MH-susceptible (MHS) patients, not only functional⁵ but also in some patients structural abnormalities, indicating a MH-specific myopathy, are present.^{6–8} However, whether characteristic histopathologic changes can be detected in skeletal muscle preparations from

MHS patients is discussed controversially.^{9–11} In studies examining small numbers of patients, no specific histopathology in MH was found. In contrast, a recent investigation with 83 patients presented for the first time specific myopathologic differences between MH-normal (MHN), MH-equivocal (MHE), and MHS patients.¹² Muscle lesions such as muscle fiber hypertrophy, atrophy, necrosis and internal nuclei occurred more often in MHS patients compared with MHN patients. Moreover, the combined occurrence of these lesions enabled discrimination between MHN, MHE, and MHS patients in this study. However, a clear definition for the proposed diagnosis of MH by histopathologic examinations was not given in the article.

In view of these interesting results, we investigated histopathologic changes in a large population of patients with clinical suspicion of MH. The purpose of our study was to detect specific histopathologic properties of MHS muscles and a possible influence of age and sex.

Materials and Methods

Patients

After approval by the local ethics committee (Hamburg, Germany), written informed consent for the different investigations was obtained from the patients or their parents, as appropriate. Four hundred forty patients with clinical suspicion of MH were included between 1991 and 1999 in the study. Patients with known neuromuscular diseases were excluded. Either a patient came from a family with a proven case of MH or the disposition was suspected because of clinical signs in the patient's history. Before the investigation, a complete personal and family history of each patient, with special attention to physical exercise and neuromuscular diseases, was taken. The analysis was performed in all patients but also separately in the subgroups adult patients (aged ≥ 16 yr), children (aged < 16 yr), and female and male patients.

Muscle Biopsies

Adult muscle bundles from the vastus lateralis muscle were excised under regional anesthesia (femoral nerve block) with 40 ml prilocaine (1%). Biopsies in children were obtained during trigger-free general anesthesia. Two or three muscle bundles were excised carefully for a standard *in vitro* contracture test (IVCT).¹³ Apart from these specimens, an additional small muscle sample

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Table 1. Biometric Data of Patients Undergoing *In Vitro* Contracture Testing and Myopathologic Examination

	MHN (n = 243)	MHE (n = 65)	MHS (n = 132)
Age, yr	25.9 ± 18.0 (3–71)	27.3 ± 16.0 (4–62)	28.6 ± 14.4 (5–61)
Weight, kg	55.8 ± 24.6 (12–110)	64.6 ± 23.3 (18–130)	67.1 ± 19.0 (15–108)
Height, cm	156.1 ± 23.2 (98–189)	165.8 ± 20.3 (104–194)	169.5 ± 16.5 (114–196)

Values are presented as mean ± SD; minimum and maximum are given in parentheses.

MHE = malignant hyperthermia equivocal; MHN = malignant hyperthermia normal; MHS = malignant hyperthermia susceptible.

(weight, approximately 250 mg) was taken for evaluation of histomorphology.

Histologic Examinations

Histopathologic Assessment of Muscle Biopsies.

All biopsies were diagnosed in the Institute of Neuropathology, University Hospital Hamburg-Eppendorf (Hamburg, Germany), by two independent neuropathologists who were blinded to the IVCT results. The tissue was processed as follows: Fresh biopsy specimens were directly transferred from the operating room to the Department of Neuropathology and immediately dissected. For semithin and ultrathin sections, one or more 1-mm-thick pieces were cut from the center of the sample to avoid any crush artifacts possibly caused by the surgical excision at the ends of the sample. The pieces were fixed in glutaraldehyde. One of the two end pieces of the biopsy was fixed in Baker solution for paraffin histology; the other was used for frozen sections. To prevent freeze artifacts, the specimen was mounted on a plate of cork with a paste made of gum tragacanth in distilled water, immersed in -80°C precooled 2-methylbutan, and frozen in liquid nitrogen for 1 min.

Conventional Histology and Histochemistry.

Stains included hematoxylin and eosin; Masson-Goldner; and Turnbull for paraffin-embedded material and hematoxylin and eosin; Engel; Sudan black; acid phosphatase; adenosine triphosphatases pH 4.3, pH 4.6, and pH 9.4; lactate dehydrogenase; and PAS (with and without preincubation with diastase) for frozen sections.

Immunohistochemistry. Five-micrometer-thin deparaffinized sections were used for staining procedures. The slides were pretreated in a microwave oven 2×5 min in 10 mM citrate buffer (pH 6.0) for demarcation of the antigen (except for S-100 antigen). Then, 10% goat serum was applied 1 + 1 with antibody diluent reagent solution (Zytomed GmbH, Berlin, Germany) for 30 min to block nonspecific antibody binding. Routinely, the tissue was labeled with antibodies against leukocyte common antigen (DAKO No. M701, 1:100, incubation for 1 h at room temperature; DAKO, Hamburg, Germany) to detect inflammatory alterations. Bound antibodies were visualized by the Strept-ABC method using the DAKO Kit K0492 according to the manufacturer's protocol. Diaminobenzidine (D5637; Sigma, Tauf-

kirchen, Germany) was used as chromogen. The slides were counterstained with alum-hematoxylin.

Semithin and Ultrathin Sections. Glutaraldehyde-fixed specimens were incubated in chrome-osmium according to Dalton for 2 h, dehydrated in ethanol, and embedded in Epon 812 (Serva, Heidelberg, Germany). After polymerization, 1- μm -thin sections were cut, stained with toluidine blue, and examined. Relevant specimens were further processed for electron microscopy by cutting 60- to 80-nm-thin sections, which were contrasted with uranyl-acetate and lead solution.

Computer-aided Morphometry. Morphometry was performed using an Olympus CUE3 system (Hamburg, Germany). When possible, a minimum of 100 type I and 100 type II muscle fibers was assessed. The fiber density, the percentage of type I and type II fibers, and the spectrum of muscle fiber diameters (minimal feret diameters) were evaluated. A *feret* is defined as a diameter drawn through the center of gravity of a given object. A *minimal feret* is defined as the smallest feret running through a muscle fiber.

Statistical Analysis

Statistical evaluation of our data was performed by using a computer-based program (StatView 4.5; Abacus Concepts Inc., Berkeley, CA). The analysis was performed for all patients but also separately for the subgroups adult patients (aged ≥ 16 yr), children (aged < 16 yr), and female and male patients by Kruskal-Wallis test and analysis of variance ($P < 0.05$). Unless otherwise indicated, data are presented as mean \pm SEM.

Results

The biometric data of all patients are presented in table 1. The mean age of all patients was 26.9 ± 16.5 yr. Thirty percent of the investigated patients were children younger than 16 yr, and 17% were younger than 8 yr.

By the IVCT according to the European Malignant Hyperthermia Group protocol,¹³ MHN was diagnosed in 243 patients, MHS was diagnosed in 132, and MHE was diagnosed in 65 (table 2). Among children younger than 16 yr, 93 were characterized as MHN, 18 were characterized as MHE, and 21 were characterized as MHS.

The examinations revealed 20 different myopathologic

Table 2. Age Distribution and the Results of the *In Vitro* Contracture Test

	MHN	MHE	MHS	Total
All patients	243	65	132	440
Aged 0–16 yr	93	18	21	132
Aged > 16 yr	150	47	111	308
Male, Aged > 16 yr	102	15	37	154
Female, Aged > 16 yr	48	32	74	154

MHE = malignant hyperthermia equivocal; MHN = malignant hyperthermia normal; MHS = malignant hyperthermia susceptible.

alterations (table 3). Five nonspecific myopathologic alterations were observed more frequently: Muscle fiber hypertrophy was seen in 14.1%, fiber atrophy in 19.1%, fiber necrosis in 3.2%, internal nuclei in 2.5%, and fiber type I predominance in 18.6% of all biopsies.

No differences in the frequency of muscle fiber hypertrophy, atrophy, and necrosis among the three groups of patients were found (fig. 1). Internal nuclei occurred more often in MHN compared with MHE patients. Fiber type I predominance was seen more frequently in MHN compared with MHS and MHE. The combined occurrence of muscle fiber hypertrophy, atrophy, necrosis, and internal nuclei as indicators for MH susceptibility according to previous studies showed no differences between the MHN, MHE, and MHS muscle samples (fig. 2).¹⁰ Thirty-five percent of all patients showed one, 9.8% showed two, and only 0.9% showed three pathologic findings of the four defined values within skeletal muscle preparations. No muscle sample had four lesions. In 54.3% of all biopsies, no myopathologic alterations were detected.

The data evaluation of all patients aged 16 yr or older revealed no differences between MHS, MHE, and MHN patients. In contrast to results of all investigated patients, fiber type I predominance was not observed more frequently in MHN patients than in MHS patients.

In the subgroup male patients aged 16 yr or older, the occurrence of muscle fiber hypertrophy, atrophy, necrosis, internal nuclei, and fiber type I predominance was not different among MHS, MHE, and MHN patients.

In muscle biopsies of female patients aged 16 yr or older, fiber atrophy was less often observed in MHS (13.5%) than in MHE (33.3%) and MHN (32.3%). There were no differences regarding muscle fiber hypertrophy, necrosis, internal nuclei, and fiber type I predominance. In comparison to male patients aged 16 yr or older, muscle fiber atrophy and fiber type I predominance were more often diagnosed.

One hundred thirty-two children (aged < 16 yr) were investigated in this study. Muscle fiber hypertrophy and fiber atrophy were less often observed in children compared with patients aged 16 yr or older. Fiber type I predominance was more often observed in children. In addition, this alteration was more often seen in MHN (34.4%) than in MHS (4.8%) children.

Overall, in six muscle samples, specific myopathologic alterations were observed (two cases of central core disease, two cases of Duchenne muscular dystrophy, one case of Curschmann-Steinert myotonia dystrophica, one case of myotonia), which were formerly unrecognized (fig. 3). The IVCT in these six patients revealed a MHS or MHE status, respectively.

Table 3. Histopathologic Findings in Patients Undergoing Myopathologic Examinations

	MHN (n = 243)	MHE (n = 65)	MHS (n = 132)
Muscle fiber hypertrophy (types I and II)	31 (12.8%)	8 (12.3%)	23 (17.4%)
Fiber type II hypotrophy	2 (0.8%)	—	—
Muscle fiber atrophy (types I and II)	51 (21.0%)	13 (20.0%)	21 (15.9%)
Necrosis	4 (1.6%)	4 (6.2%)	5 (3.8%)
Internal nuclei	2 (0.8%)	4 (6.2%)	5 (3.8%)
Fiber type I predominance	56 (23.0%)	8 (12.3%)	16 (12.1%)
Fiber type II predominance	2 (0.8%)	1 (1.5%)	4 (3.0%)
Lymphocytic infiltration	16 (6.6%)	1 (1.5%)	6 (4.5%)
Inflammation	2 (0.8%)	—	2 (1.5%)
Fibrosis	1 (0.4%)	1 (1.5%)	1 (0.8%)
Siderosis	7 (2.9%)	—	4 (3.0%)
Clumps and clusters of nuclei	8 (3.3%)	1 (1.5%)	3 (2.3%)
Degeneration	2 (0.8%)	1 (1.5%)	—
Regeneration	2 (0.8%)	1 (1.5%)	2 (1.5%)
Moth-eaten fibers	2 (0.8%)	—	1 (0.8%)
Ragged-red fibers	2 (0.8%)	1 (1.5%)	1 (0.8%)
Alcohol-induced myopathy	1 (0.4%)	1 (1.5%)	2 (1.5%)
Muscle spindle alterations	1 (0.4%)	—	—
Liposis	—	—	2 (1.5%)
Fiber-type grouping	1 (0.4%)	—	2 (1.5%)
Lysosomal activity	2 (0.8%)	—	—

The frequency of the observed alteration in all analyzed samples in a group of patients is given in parentheses.

MHE = malignant hyperthermia equivocal; MHN = malignant hyperthermia normal; MHS = malignant hyperthermia susceptible.

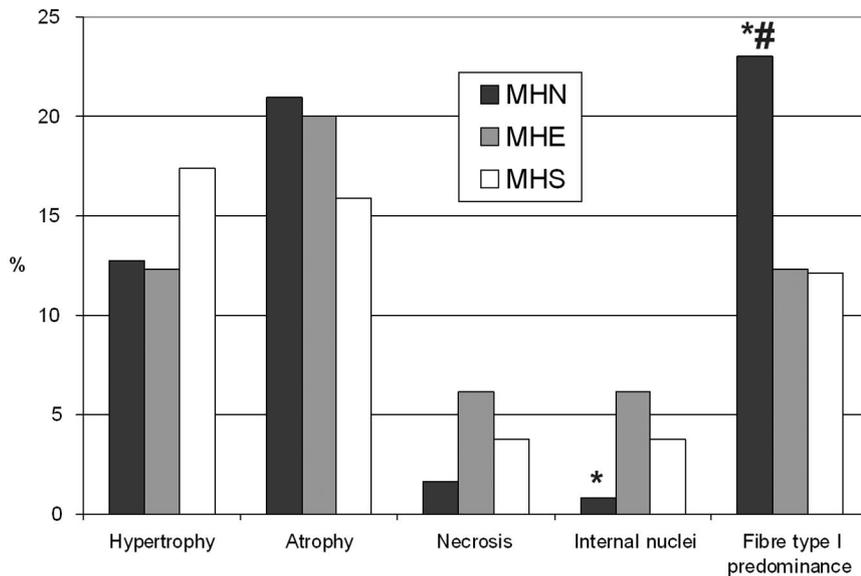


Fig. 1. Frequency of the occurrence of the principal lesions in all muscle biopsies of malignant hyperthermia–normal (MHN), –equivocal (MHE), and –susceptible (MHS) patients. Some patients had more than one type of change. * $P < 0.05$, MHN versus MHE. # $P < 0.05$, MHN versus MHS.

Discussion

The myopathologic examinations of 440 patients with clinical suspicion of MH revealed 20 different nonspecific myopathologic alterations. Among these nonspecific alterations, muscle fiber hypertrophy, muscle fiber atrophy, muscle fiber necrosis, internal nuclei, and fiber type I predominance were more often detected than other parameters. However, MHN and MHS patients did not differ in the frequency of the occurrence of these abnormalities except for fiber type I predominance. This alteration was found more often in MHN patients, but in view of the majority of normal findings, differentiation between MHN and MHS was not possible by histopathologic examination.

Malignant hyperthermia is a myopathy with a functional dysregulation leading to a disturbed calcium ho-

meostasis. Furthermore, it has been suggested that there might be a morphologic defect in the skeletal muscle as well.⁷ However, in one study, 155 patients with clinical suspicion for MH were diagnosed by IVCT as well as histopathologic and histochemical examinations.⁹ The majority of MHN and MHS patients had no or slight myopathologic alterations. Consequently, it has been concluded that most MHS patients do not have a specific myopathy. In another study including 1,400 patients, internal nuclei, moth-eaten fibers, and cores were found more often in MHS patients, and therefore, an MH-specific myopathy was suspected. However, this so-called MH myopathy was only seen in the minority of MHS patients (25%).⁶ In a study of 165 patients, the authors found these alterations less frequently in MHS subjects and concluded that there is no specific MH myopathy.¹¹

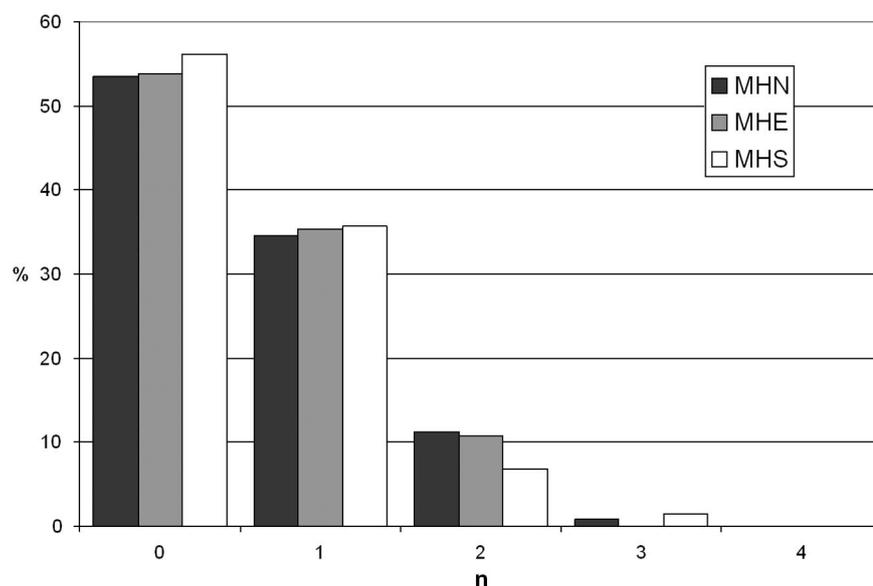


Fig. 2. Number of alterations (n) observed in all patients undergoing myopathologic examinations. The combined occurrence of muscle fiber hypertrophy, muscle fiber atrophy, muscle fiber necrosis, and internal nuclei was not observed more often in malignant hyperthermia–normal (MHN), –equivocal (MHE), or –susceptible (MHS) patients.

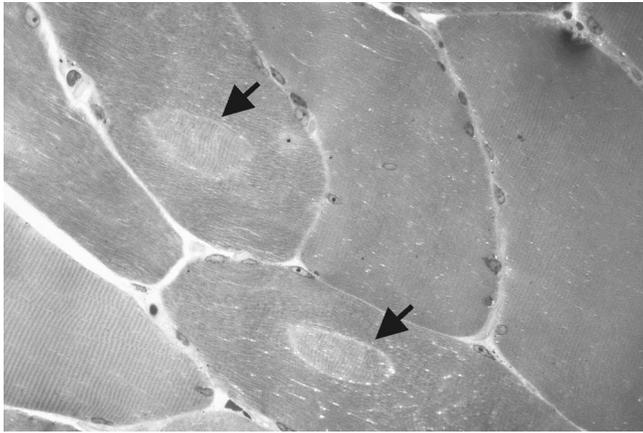


Fig. 3. Central core disease in a 31-yr-old man with moderately elevated creatine kinase (200 U/l). Muscle biopsy revealed a broadened spectrum of fiber diameters, few muscle fiber necroses, and numerous central cores (arrows, semithin section, toluidine blue, original magnification $\times 100$).

All studies mentioned above and some other studies in which only a small number of patients were investigated^{11,14-16} indicate that a histopathologic diagnosis of MH is not possible.

Interestingly, in a recent investigation, a higher incidence of nonspecific histologic alterations in MHS than in MHN patients was found.¹² The frequency of muscle fiber hypertrophy, fiber atrophy, internal nuclei, and necrosis was higher in MHS than in MHE and MHN muscles. Furthermore, the combined occurrence of these alterations enabled discrimination between MHN, MHE, and MHS patients.

Muscle fibers smaller than $36\ \mu\text{m}$ are defined as *atrophic*, and fibers larger than $60\ \mu\text{m}$ are defined as *hypertrophic*.¹⁷ The cross-sectional area is larger in men than in women, and muscle fiber hypertrophy mainly occurs in trained individuals.¹⁸ Muscle fiber atrophy can be caused, among other things, by neuromuscular diseases, malnutrition, treatment with corticosteroids, or denervation. With increasing age, human muscle decrease in volume, mainly because of a reduced number of motor units, muscle fibers, and a muscle fiber type II atrophy.¹⁹ Internal nuclei ($> 3\%$ of all analyzed muscle fibers) are caused by myopathologic alterations and denervation. Muscle fiber necrosis is the response to a variety of pathogenic stimuli. It represents an injury to the entire fiber or a circumscribed region.

The combined occurrence of muscle fiber hypertrophy, atrophy, necrosis, and internal nuclei was seen in the study of Mezin *et al.*¹² in 35% of the MHS but none of the MHE and MHN patients. Three of these nonspecific histopathologic changes were found in 57% of the MHS and in only 4% of the MHN patients and enabled differentiation between MHN, MHE, and MHS biopsies.¹² Therefore, we focused on the combined appearance of these four myopathologic changes as well. In our study, which involved 440 patients, including 132 MHS biop-

ties, no muscle sample had four lesions. A combination of three alterations was only observed in 1.5% of the MHS patients and did not allow us to distinguish between MHN, MHE, and MHS muscles.

Muscle fiber type I predominance was observed more often in MHN patients in our study. An increase of fiber type I in the vastus lateralis muscle (the fiber type composition depends on the analyzed muscle) over 55% is defined as *predominance*. This is a nonspecific alteration and is visible in some myopathies but also can be caused by physical training.²⁰ In the investigation of Staron *et al.*,¹⁷ a wide range in the fiber type distribution in healthy individuals was detected. This might explain the fiber type I predominance in our study.

In this study, myopathologic alterations were studied in children with suspicion of MH for the first time. One hundred thirty-two children were included in our study, and most of them had a diagnosis of MHN ($n = 93$). In accordance with previous studies, muscle fiber hypertrophy and atrophy were less often observed in children compared with adult patients.²¹ During childhood, the muscle fibers are small ($12\text{--}18\ \mu\text{m}$), with no difference between boys and girls. In puberty, the cross-sectional area increases and is $36\text{--}60\ \mu\text{m}$ in adults. Therefore, the analysis of the cross-sectional area must be age corrected. Fiber type I predominance was more often observed in children (aged < 16 yr) than in patients aged 16 yr or older. The fiber type distribution in children older than 1 yr is similar to that of adult patients. There is only a change of fiber type II to fiber type IIb.²²

Muscle fiber hypertrophy, fiber atrophy, necrosis, and internal nuclei were sex independent in our study. Muscle fiber type I predominance was more often observed in MHS than in MHN and MHE women. Adult men showed no difference in the occurrence of fiber type I predominance. The fiber type distribution findings in the literature are inconsistent. Some studies reported a fiber type I predominance in women as compared with men or no difference between women and men. Recent studies suggest that there is no sex difference but that there is a wide range in healthy persons.¹⁷

In the current study, patients with known neuromuscular diseases were excluded, but in six muscle samples, specific myopathologic alterations were observed (two cases of central core disease, two cases of Duchenne dystrophy, one case of Curschmann-Steinert myotonia dystrophica, one case of myotonia). These six patients' IVCT results indicated MHS or MHE. However, in view of the small number of patients with neuromuscular diseases revealed by histopathologic investigation, the economic point of view does not allow routine investigation of all biopsies of MH patients routinely for these alterations, except when there is a clinical hint.

In conclusion, histopathologic examinations can neither improve the diagnosis of MH nor contribute to a better definition of the MH status. However, histopatho-

logic examinations might be helpful to detect an unknown specific myopathy.

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