Canine Malignant Hyperthermia: Diagnosis of Susceptibility in a Breeding Colony

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SUMMARY

Fifteen related dogs were studied for susceptibility to malignant hyperthermia using halothane challenge and caffeine contracture tests. These dogs had hypertrophied muscles, were of a nervous temperament and had rectal temperatures at the upper limit of the normal range. Clinical pathology findings were mild elevations of serum aspartate transaminase and mean corpuscular hemoglobin. *In vitro* caffeine contracture tests were performed on muscle biopsies from five of these dogs. The concentration of caffeine required to increase resting tension by 1 g in biopsy specimens of these dogs was significantly lower than that required for control dogs: 7.6 ± 1.38 ($\bar{x} \pm$ SEM) versus 15.5 ± 2.52 mM ($P < 0.025$), and in the presence of 1% halothane, 3.6 ± 1.44 versus 10.6 ± 2.19 mM ($P < 0.05$). Internal nuclei, fiber caliber variation and fiber hypertrophy were found in histological studies of muscle biopsies. Two other dogs possibly died of a canine stress syndrome analagous to the porcine stress syndrome which occurs in malignant hyperthermia susceptible swine. Eight others of this family were anesthetized with halothane or methoxyflurane. Methoxyflurane did not trigger the syndrome. The first exposure to halothane caused death from malignant hyperthermia in two dogs and a third died on the second exposure to halothane. Postmortem findings were nonspecific. The other three dogs exposed to halothane recovered uneventfully. Inheritance of the defect conforms to a multifactorial pattern, with gradations of susceptibility.

RÉSUMÉ

Hyperthermie maligne canine: diagnostic de la susceptibilité, au sein d'une colonie de reproduction

Cette expérience portait sur 15 chiens apparentés et elle visait à étudier leur susceptibilité à l'endroit de l'hyperthermie maligne. Les auteurs utilisèrent à cette fin l'épreuve de défi à l'halothane et celle de la contracture à la caféine. Ces chiens présentaient une hypertrophie musculaire et un tempérament nerveux; leur température rectale se situait à la limite supérieure de la normale. Des épreuves appropriées révélèrent une faible élévation de l'aspartate-transaminase sérique et de la teneur moyenne des hématies en hémoglobine. On effectua, *in vitro*, l'épreuve de contracture à la caféine, sur des biopsies musculaires prélevées chez cinq des chiens expérimentaux. La concentration de caféine requise pour augmenter de 1 g la tension de repos, dans les biopsies précitées, se révéla sensiblement plus basse que celle qu'exigèrent les biopsies musculaires des témoins: $7,6 \pm 1,38$ ($\bar{x} \pm$ SEM) versus $15,5 \pm 2,52$ mM ($P <$ 0,025), et en présence de 1% d'halothane, $3,6 \pm 1,44$ versus $10,6 \pm 2,19$ mM ($P < 0,05$). L'examen microscopique de ces biopsies révéla que les fibres musculaires présentaient des noyaux internes, de l'irrégularité dans leur diamètre et de l'hypertrophie. Les autres chiens moururent probablement d'un syndrome de stress canin, analogue au syndrome du stress porcin qui se produit chez les porcs sensibles à l'hyperthermie maligne. Huit autres chiens de cette famille subirent l'anesthésie à l'halothane ou au méthoxyflurane; celui-ci ne déclencha pas le syndrome. La première anesthésie à l'halothane causa une hyperthermie maligne fatale, chez deux chiens, tandis qu'un troisième mourut, au cours d'une deuxième anesthésie à l'halothane. La nécropsie de ces chiens ne révéla pas de lésions spécifiques. Les trois autres chiens anesthésiés à l'halothane se réveillèrent normalement. Le mode de transmission héréditaire de cette tare correspond à un modèle multifactoriel qui implique divers degrés de susceptibilité.

INTRODUCTION

Anesthetic induced malignant hyperthermia (MH) has been recognized recently in the dog (1-3) cat (4), horse (5,6) and deer (7). Malignant hyperthermia in man and swine (8-11) has been extensively documented. Malignant hyperthermia is characterized by the peracute development of hypercatabolism and contracture in skeletal muscle. The primary defect in MH is assumed to be in the surface membrane and results in abnormal regulation of myoplasmic Ca^+ (12-14). Triggering agents lead to an uncontrollable elevation in myoplasmic Ca^+ and consequent overstimulation of glycogenolysis and contractile protein activity. Results are: depletion of adenosine triphosphate and glycogen stores, hypoxia and excessive formation of heat, CO_2 and lactic acid. These are followed by: acid-base and electrolyte imbalances and increased sarcolemmal permeability to myoglobin and muscle enzymes. Signs of an approaching MH episode may include tachycardia, cardiac dysrhythmias, hyperpnea, cyanosis, a rise in body

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temperature and muscle rigidity. The course of the syndrome depends on: the intensity and duration of hypermetabolism, and the amount of muscle involved. Fulminating hyperthermia, metabolic and respiratory acidosis, cardiac and respiratory failure, and cerebral, pulmonary and muscle edema usually occur. Disseminated intravascular coagulation, rhabdomyolytic nephrosis, cardiac and skeletal myopathies, and neurological deterioration may also occur in advanced cases (11,15,16). The fatality rate without intravenous (IV) administration of dantrolene[1] and intensive symptomatic therapy (16-20) is 100%. In man and swine dantrolene is reported to be the most effective drug for treatment and prophylaxis (17,21,22). It stabilizes muscle surface membranes and depresses excitation-contraction coupling, thereby decreasing intracellular Ca^+ and reversing the stimulatory effect of the MH triggering agent (12,23,24).

In man and swine, MH may develop in response to potent inhalation anesthetics, quaternary amide muscle relaxants, or severe psychological stress. Factors which predispose genetically susceptible individuals to show MH, include: muscle exertion or trauma, high ambient temperature, fever, hypercalcemia, or drugs such as sympathomimetics and ketamine. Belladonna alkaloids, amide local anesthetics and cardiac glycosides may aggravate a MH episode (9,25).

Susceptibility to MH is inherited in man and swine (26,27). Methods for diagnosing susceptibility in relatives of individuals having a MH episode have been developed (28,29). Presently the only definitive diagnostic test for MH susceptible (MHS) individuals is the *in vitro* caffeine contracture test (CCT). Afflicted muscle has an abnormal sensitivity to caffeine-induced contracture, especially in the presence of halothane. Elevations of serum levels of muscle enzymes, especially after exercise or stress, may occur in MHS individuals but are not diagnostically reliable (9,28).

Fulminating Episodes of Canine Malignant Hyperthermia

Anesthetic induced MH in dogs has been reported sporadically since 1973 (1,18,20,30-32). The incidence of canine MH is unknown, although anesthetic deaths or complications have been estimated to occur at a rate of one in 2000-4000 veterinary anesthesias (2). Sudden, unexplainable tachycardia, tachypnea, hyperthermia and trismus have been characteristic of MH episodes in dogs. Anesthetic machine soda lime is rapidly exhausted and the cannister becomes warm. Generalized rigidity may or may not be present. These signs have not been observed during the first 15 min of halothane anesthesia. The MH protective effects of acetylpromazine (33) and thiamylal (34) used in anesthesia premedication and induction may be partly responsible for the delay in onset of signs. These signs have often been misinterpreted as a lightening from anesthesia and the halothane concentration increased, thereby accelerating the development of the episode. Temperatures have reached maximal values between 42 and 45°C. Elevated Na^+, K^+, H^+ and phosphate are consistently found during the syndrome. Hypoxia and hypercarbia have been revealed by blood gas analysis.

Removal of triggering agents and symptomatic treatment (9) have been ineffectual in reversing MH episodes. Administration of dantrolene IV is usually necessary for survival (30). In man it has been recommended that dantrolene be administered rapidly IV in doses of 1 mg/kg, up to 10 mg/kg, until the clinical signs subside (17,27). In man 2.5 mg/kg (22) and in swine 7.5 mg/kg (35) have produced significant therapeusis. Premedication with oral dantrolene has a preventive effect on the development of intraoperative MH in swine (5 mg/kg, 4 and 24 h before anesthesia; 35). The recommended dose for man (MHS) is 4 mg/kg, in three or four divided doses, in the 24 h prior to anesthesia (37). Use of this drug may cause muscle weakness (17), lead to false negatives in the CCT (38) and has caused liver damage in isolated cases (9).

As in other species, halothane, succinylcholine (1,30) and enflurane (32) have been implicated as triggers of MH in the dog. Methoxyflurane has not been reported as an MH trigger in dogs. In man (39) and in swine (40) it is a weak trigger. Fulminating MH does not always occur during the first halothane anesthesia of susceptible individuals (8,18).

Before diagnosing MH other causes of hyperthermia should be excluded, like: heat stroke, pyrogens, thyrotoxic crisis, pheochromocytoma, hypothalamic defect, drug or transfusion reaction and excessive hair coat or draping.

Fulminating canine MH is similar to human and swine MH with respect to triggering agents, clinical signs, laboratory findings and treatment.

In this paper we describe the diagnosis of malignant hyperthermia susceptibility in a breeding colony of dogs. Three canine cases and a brief review of MH are presented. A MH-related canine stress syndrome is postulated.

MATERIALS AND METHODS

Anesthetic Challenge Trials

A healthy, mature, male, cross-bred Doberman pinscher (X, Figure 1) was acquired from the University of Saskatchewan, Animal Resources Centre for a student surgical laboratory. The dog was given atropine[2] and meperidine.[3] Following induction of anesthesia with thiamylal[4] IV, the animal was intubated and maintained on halothane[5] in oxygen on a semiclosed circle anesthetic machine. After 3.5 h of uneventful anesthesia the dog suddenly developed hyperthermia (41.5°C), tachycardia and tachypnea. Respiratory and cardiac arrest followed despite resuscitative attempts with intermittent positive pressure ventilation (IPPV) and external cardiac massage. Extreme trismus and generalized muscle rigidity occurred immediately after death. Heart failure of undetermined origin was found by

[1]Dantrium IV, Norwich-Eaton Ltd., Paris, Ontario.
[2]Atro-SA, Rafter 8 Serum Ltd., Calgary, Alberta.
[3]Demerol, Winthrop Laboratories, Aurora, Ontario.
[4]Biotal, M.T.C. Pharmaceuticals, Hamilton, Ontario.
[5]Fluothane, Ayerst Laboratories, Montreal, Quebec.

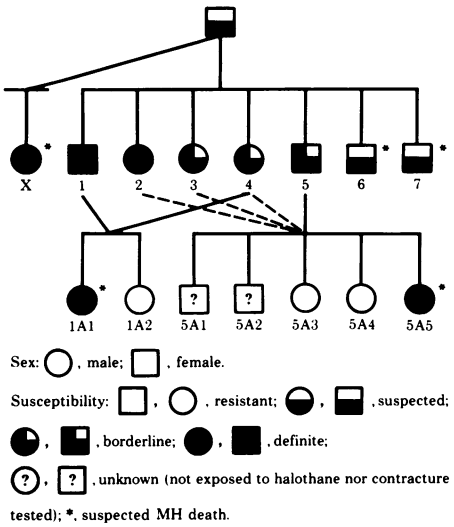

FIGURE 1. Genetic relationships in a breeding colony of malignant hyperthermia (MH) susceptible dogs.

TABLE I
HALOTHANE (H) AND METHOXYFLURANE CHALLENGE TRIALS IN MALIGNANT HYPERTHERMIA SUSCEPTIBLE DOGS

Dog No.	Sex	Weight (kg)	Anesthetic Agent and Duration (min) Trial 1	Trial 2	Trial 3	Trial 4
1A1	M	18.1	80,H[a]	75,H[b]	—	—
1A2	M	25.0	65,H	185,H	75,H	235
5A1	F	13.6	70	165	105,H	140
5A2	F	18.0	40	170	95	165
5A3	M	20.4	80,H	165,H	95,H	195
5A4	M	20.0	45,H	165,H	125,H	195
5A5	M	18.0	70	175	145	45,H[b]
X	M	ND	240,H[b]	—	—	—

[a]Problematic anesthesia.
[b]Malignant hyperthermia death.
ND = Not determined.

postmortem examination to be the cause of death.

The breeder of this dog was found and a litter of seven pups was obtained from the same dam. These were of mixed breed: Doberman pinscher, German shepherd and hound phenotypic features were apparent. At maturity the litter mates (No. 1-5, Figure 1) were allowed to interbreed. The matings resulted in two litters. Mating of F No. 1 with No. 4 resulted in two pups: mating of F No. 5 and No. 2, 3 or 4 resulted in five pups. These seven pups were used, when six to eight months of age, together with 14 unrelated dogs from other sources, in a series of four successive weekly student surgical laboratories. The animals were subjected to anesthesia with either methoxyflurane[6] or halothane on up to four occasions (Table I), after which they were euthanatized. The student anesthetists were unaware that they might be dealing with MHS dogs. Dogs were given 0.04 mg/kg atropine and 0.1 mg/kg acetylpromazine[7] administered subcutaneously. Thiamylal solution was used for induction of general anesthesia (10-15 mg/kg, IV). Following endotracheal intubation anesthesia was maintained with halothane or methoxyflurane, in oxygen using a semi-closed circle system. Ringer's[8] solution was administered throughout the procedures by IV infusion at a rate of 10 mL/kg/h.

Muscle Biopsy Studies

After anesthetic challenge of the offspring, dogs No. 1-5 had semitendinosus muscle biopsies taken under various anesthetic regimes (Table I). The muscle was tested for sensitivity to caffeine and halothane-induced contractures using a procedure already described (28,41). Five clinically normal, unrelated, cross-bred dogs were used as controls. Transverse sections of muscle biopsies from the MHS dogs were analyzed for fiber type (myofibrillar adenosine triphosphatase), fiber diameter and for histopathological changes (hematoxylin and eosin stain).

For contracture studies a semitendinosus muscle strip 30X10X10 mm was excized and maintained in 22°C Ringer's solution. Each of three fascicles 12X3X2 mm was dissected free and mounted in a 30 mL chamber containing carbogenated Krebs-Ringer's solution (28) at 37°C. Resting tension was set[9] at 0.5-1 g. Halothane (1%) was included[10] in one chamber. Every 20 sec, a stimulation[11] of 20 volts for 1 msec was applied. After 30 min equilibration, muscle baths were caffeinated starting at 0.125 mM. The concentration was doubled every 5 min until a concentration of 32 mM was reached. Resting tension was determined[12] 4 min after each addition. The caffeine specific concentration (CSC) is the concentration (mM) required to increase resting isometric tension 1 g and is calculated from dose-response curves. The nonpaired t-test was used for statistical comparisons between the control and experimental groups.

RESULTS

The dogs in this MHS family had mesomorphic somatotypes: they had hypertrophied muscles and greater than normal muscle tone and strength. Most of the dogs were nervous and difficult to handle. Resting body temperatures were high normal or slightly above ($\bar{x}$ = 39.3°C). Preoperative serum aspartate transaminase (SAT) levels and mean corpuscular hemoglobin contents and concentrations were at the upper limit of the normal range or slightly above in many of these dogs (four of eight, six of nine, and five of nine dogs tested, respectively). Of these departures from the normal, the SAT levels in dogs No. 1 and 2 were most conspicuous (46 and 43 respectively, normal range: 18-23

[6]Metothane, Pitman-Moore Ltd., Scarborough, Ontario.
[7]Atravet, Ayerst Laboratories, Montreal, Quebec.
[8]Ringer Solution U.S.P., Baxter Travenol Laboratories, Malton, Ontario.
[9]FT.03.C Grass Force Displacement Transducer, Grass Instrument Co., Quincy, Massachusetts.
[10]Mark III Fluotec Precision Vaporizer, Cyprane Ltd., Keighley, England.
[11]S44B Grass Stimulator, S1U5A Grass Stimulus Isolation Unit, Grass Instrument Co., Quincy, Massachusetts.
[12]Grass Model 5 Polygraph, Grass Instrument Co., Quincy, Massachusetts.

TABLE II
HISTOLOGICAL FINDINGS IN SEMITENDINOSUS MUSCLE OF MALIGNANT HYPERTHERMIA SUSCEPTIBLE DOGS

Dog. No.	Fiber Type	Mean Diameter ($\mu m \pm$ S.D.)	%	% Internal Nuclei[a] (Types I and II)
1	I	60 ± 15.5	6	2.3
	II	54 ± 16.9	94	
2	I	68 ± 14.7	3	4.6
	II	70 ± 18.0	97	
3	I	43 ± 10.8	25	1.2
	II	44 ± 13.2	75	
4	I	55 ± 16.7	8	4.7
	II	45 ± 10.6	92	
5	I	40 ± 12.3	11	0.4
	II	48 ± 11.1	89	

[a] ≥ 1 % is considered abnormal.

I.U./dL). Serum creatine kinase levels were normal.

Dogs No. 6 and 7 died at maturity during a period of stress associated with a change in their housing. Postmortem examinations were not performed on them and the cause of their deaths was undetermined.

Variation in fiber size was noted in the semitendinosus muscle biopsies of MHS dogs. The proportions of type II fibers were high. Mean fiber diameters were larger than reported for most canine muscles. The proportion of fibers with internal nuclei was abnormally high in four of five dogs (Table II). These features were especially prominent in dogs No. 1 and 2.

Anesthetic Challenge Trials[13]

During the first anesthesia of dog 1A1 tachypnea (from 5 to 40 breaths/min) and tachycardia (from 120 to 220 beats/min) developed after 30 min of halothane exposure. These signs were interpreted as a lightening from anesthesia and the halothane was turned from 1.5 to 2%. Heart and respiratory rates decreased to the original values. Anesthesia continued uneventfully for a further 30 min and recovery was normal. During the second anesthesia a similar lightening occurred after 50 min and when the halothane was increased to 2% the signs became more pronounced. Discontinuation of anesthesia, IPPV with oxygen, external and direct cardiac massage failed to revive the dog. Blood taken during the episode had elevated Na^+, K^+ (171 and 10.9 mEq/L) and phosphate (16.6 mg/dL). The rectal temperature was 40.5°C, 30 min after death, and extreme muscle rigidity developed within 45 min of death.

Dog 5A5 underwent methoxyflurane anesthesia uneventfully on three occasions. Maintenance during the fourth anesthesia was with halothane. Tachycardia, hyperthermia (from 39.5 to 43.8°C), severe limb rigidity and trismus developed over a 15 min period commencing 35 min after the onset of halothane administration. The eyes were rolled ventrally and there was no palpebral reflex at the beginning of the episode. The anesthetic machine was noticed to be very warm. Cardiac massage, IPPV with oxygen, IV sodium bicarbonate and cold water baths failed to reverse the syndrome. A blood sample taken during the episode showed elevated Na^+, K^+ (173 and 7.9 mEq/L) and phosphate (14.9 mg/dL). Cardiac arrest occurred 55 min after induction.

Of the six dogs challenged with halothane (13 trials) three died in MH and three did not have reactions. Methoxyflurane did not have observable adverse effects on the six dogs on which it was used (14 trials). An average drop in rectal temperature of 2°C occurred during uneventful anesthesias (23 trials).

Caffeine Contracture Tests

Anesthetic problems were not encountered with the control animals during surgery to obtain the semitendinosus muscle strip. Various complications occurred with the anesthetic protocols of the MHS group (Table III). The two MHS dogs receiving oxymorphone,[14] acetylpromazine, nitrous oxide and thiamylal had stable anesthesia and smooth recovery.

The CSC for the control and MHS dogs were significantly different both in the absence (15.5 verus 7.6 mM) and the presence of 1% halothane (10.6 versus 3.6 mM) (Table IV). Considerable variation in the sensitivity to caffeine and halothane was observed in both groups. Overlap in values between the two groups was minimal in the absence of halothane but in the presence of 1% halothane two controls had CSC in the range for the MHS dogs. Dogs No. 1 especially, and No. 2

TABLE III
ANESTHETIC REGIMES USED FOR MUSCLE BIOPSYING MALIGNANT HYPERTHERMIA SUSCEPTIBLE DOGS

Dog No.	Premedication	Induction	Maintenance	Comments
1,5	Oxymorphone, 0.15, IV Acetylpromazine, 0.1, IV	N_2O, mask	Thiamylal, 5.0, IV N_2O, tube	Uneventful
2	Diazepam[a], 1.5, IM	Pentobarbital[c], 20.0, IV	N_2O, tube	Prolonged recovery
3	Fentanyl[b], 0.024, IV Droperidol[b], 1.2, IV	Diazepam, 1.0, IV N_2O, mask	Diazepam, 0.15, IV Fentanyl[d], 0.03, IV N_2O, tube	Excitement with premedication
4	Meperidine, 5.0, IM	Diazepam, 1.0, IV Thiamylal, 1.4, IV	Meperidine, 2.7, IV Thiamylal, 2.7, IV N_2O, tube	Excitement with diazepam

[a] Valium, Hoffman La Roche Ltd., Vaudreuil, Quebec.
[b] Innovar-Vet, Pitman-Moore, Scarborough, Ontario.
[c] Somnotal, M.T.C. Pharmaceuticals, Hamilton, Ontario.
[d] Sublimaze, McNeil Laboratories, Stouffville, Ontario.
Dosages reported in mg/kg body weights, N_2O administered at 2 L/min with 1 L/min O_2; IM, intramuscular; IV, intravenous.

[13] Preliminary report previously published (42).
[14] Numorphan, Endo Laboratories, Montreal, Quebec.

TABLE IV
CAFFEINE SPECIFIC CONCENTRATIONS (CSC) FOR MUSCLE OF CONTROL AND MALIGNANT HYPERTHERMIA SUSCEPTIBLE (MHS) DOGS

Dog No.	CSC Without Halothane		CSC With 1% Halothane	
	Control	MHS	Control	MHS
1	23.4	2.6	14.3	0.7
2	12.1	6.6	3.6	5.9
3	19.2	10.1	15.0	1.5
4	13.2	9.6	8.8	6.2
5	9.7	9.0	5.5	ND
Mean	15.5	7.6[a]	10.6	3.6[b]
SEM	2.52	1.38	2.19	1.44

Significant at [a]$P < 0.025$ and [b]$P < 0.05$; ND, not determined. The CSC is the concentration (mM) of caffeine required to increase resting isometric tension by 1 g.

had the greatest sensitivity to caffeine. Their CSC were 17% and 43%, respectively, of the mean control CSC in the absence of halothane. Their CSC in the presence of 1% halothane were 7% and 56%, respectively, of the mean control CSC. Muscle from dog No. 3 was abnormally sensitive to caffeine when halothane was present (14% of the mean control CSC). The MHS dogs No. 3, 4, and 5 had CSC near the lower limit of the control range and hence interpretation is equivocal.

The maximal isometric tension to develop was determined from the dose-response curves (data not shown). At 32 mM caffeine, control dog muscle had a mean resting tension of 3.6 g (range 2.5-4.7). Appreciably greater tensions developed at this concentration in two of the MHS dog muscle biopsy samples (10.7 g for No. 1 and 2). At 32 mM caffeine and 1% halothane, mean control tensions were 5.2 g (range 2.3-7.2 g). Values were appreciably greater for No. 1, 2, and 3 (11.8, 14.3 and 10 g respectively).

Necropsy

Intraoperative MH cases from the anesthesia challenge group were necropsied. The first dog (X) had renal hypoplasia, arteriosclerosis, pulmonary edema. metastatic calcification of the thyroid gland and chronic passive congestion of the liver. The pathology diagnoses for dog 1A1 at necropsy were generalized ischemic myopathy, right ventricular dilation and hepatic, splenic and pulmonary congestion. Dog 5A5 showed muscular and central nervous system edema, and splenic and hepatic congestion. The thyroid gland had a wide variation in follicle size with large amounts of stored colloid present. Large distended acini were present and had flattened epithelial linings. In the latter two cases foci of fragmentation, loss of cross-striation and edema in cardiac and skeletal muscle were observed.

DISCUSSION

The clinical course of the three fulminating episodes of MH described in this paper was similar to other reported canine cases (20,32). These dogs verify that MH does not always occur during the first halothane anesthesia of MHS individuals (8,18) and that methoxyfluorane is a less potent trigger of MH than halothane (39,40).

The existence of a canine stress syndrome is postulated because of two stress-associated deaths in this colony. Malignant hyperthermia-like stress syndromes have been reported in MHS swine and humans (43).

Diagnosis of Canine Malignant Hyperthermia Susceptibility

Preoperatively MHS dogs show no distinguishing features although muscularity, nervous temperament and mildly elevated muscle enzymes in serum may be present. Similar observations have been made in MHS swine and people (28,44). Malignant hyperthermia has been associated with various breeds: Greyhound (1,30), St. Bernard (20), Border Collie (32), Pointers (31) and Spaniels (33). In this colony the MHS dogs have German shepherd, Doberman pinscher and hound features. These MH-associated breeds are working, sporting or hound breeds. A sex-associated MH predisposition is not apparent in dogs. Of five previously reported cases two were female. Of 11 dogs (2 F) tested by halothane challenge or CCT in this study, five (1 F) were diagnosed as being unequivocally MHS. The presence of the MH defect in three generations and an approximate 50% frequency of its occurrence are compatible with an autosomal dominant mode of inheritance. The gradations in departure from the normal found in muscle biopsy studies suggests gradations of susceptibility, which is compatible with a polygenic defect (9,17,26). Gradation in susceptibility to halothane anesthesia was found in MHS dogs in this study.

Histopathological features of semitendinosus muscle biopsies of afflicted dogs were nonspecific and included internal nuclei and fiber caliber variation. These alterations have been observed in muscle of MHS people and are believed to be secondary to a biochemical defect (28,45). Fiber hypertrophy and a predominance of fast-twitch fibers were also noted in biopsies from these dogs.

Clinical pathology and necropsy findings were not consistent and interpretation was equivocal, although slight elevations of SAT tended to occur in susceptible dogs. Of the biopsied dogs, No. 1 and 2 had the greatest sensitivity to, and responded the most to caffeine and halothane. These two had the most conspicuous histological changes and the highest SAT levels and resting body temperatures. They were the most nervous. Dogs No. 1 and 2 were considered as unequivocally MHS; dogs No. 3-5 were designated as borderline MHS.

Susceptibility to MH should be suspected in cases where there is a family history of MH or unexplained anesthetic death, or where there is an unexplainable elevation in serum muscle enzymes. For most veterinarians the CCT may not be readily available nor economical. If triggering agents are avoided, then MHS dogs may safely undergo anesthesia. If the patient is continuously monitored for early signs of MH and the anesthetist is prepared for immediate symptomatic and IV dantrolene treatment (until complete recovery from anesthesia, (46) then a full-blown episode may be avoided. Probably a minimum IV dantrolene dose of 5 mg/kg (250 mg) for a large dog should be immediately available, although 0.7 mg/kg has been reported as therapeutically effective in one dog (30).

The technique for performing the CCT must be standardized and have an adequate number of control subjects. The values for caffeine specific concentrations vary between laboratories (9), species (19) and muscle fiber types (47). The biopsy procedure described in this paper required less than 30 min of anesthesia and caused insignificant scarring. No loss of limb function occurred following biopsy.

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