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REPORTS OF ORIGINAL INVESTIGATIONS

Muscular body build and male sex are independently associated with malignant hyperthermia susceptibility

Un corps musclé et le sexe masculin sont associés de façon indépendante à une susceptibilité à l'hyperthermie maligne

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Abstract

Purpose *Malignant hyperthermia susceptibility (MHS) is a disorder of the regulation of calcium in skeletal muscle. Muscular individuals have been shown to have a 13.6-fold increased risk of death during malignant hyperthermia (MH) episodes and are more likely to experience a recurrence after initial treatment. Twenty-five percent of severe MH episodes have occurred in elite athletes. This study investigated the association between MHS and muscular body build.*

Methods *Data were obtained from existing reports in the North American Malignant Hyperthermia Registry, including the Report of Muscle Biopsy and Contracture Testing (caffeine-halothane contracture test [CHCT]) as well as Adverse Metabolic or Muscular Reaction to Anesthesia (AMRA) reports. Malignant hyperthermia susceptible individuals were compared with MH negative individuals with regard to body build and reason for testing. Males were also compared with females. Both the CHCT and the AMRA forms were reviewed for comments.*

Results *Of the 1,292 individuals diagnosed with MHS by CHCT, males were more likely to be diagnosed with the disorder than females (odds ratio [OR], 2.33; 95% confidence interval [CI], 1.99 to 2.7; $P < 0.001$). Muscular individuals were more likely to be diagnosed with MHS than non-muscular individuals (OR, 1.94; 95% CI, 1.51 to 2.49; $P < 0.001$). Males were more likely to be tested after having a possible MH episode (OR, 2.33; 95% CI, 1.45 to 2.1; $P < 0.001$). Logistic regression showed that male sex (OR, 2.28; 95% CI, 1.93 to 2.7; $P < 0.001$) and muscular body build (OR, 2.17; 95% CI, 1.21 to 3.9; $P = 0.01$) were independently predictive of MHS. The interaction between muscular body build and male sex was not significant ($P = 0.13$). Indications for testing, MH episode vs family history of MH, did not differ between muscular and non-muscular individuals ($P = 0.44$). Eight of 839 AMRAs and two reports of CHCT had comments describing athletic abilities. Ryanodine receptor type 1 (RYR1) gene mutations were found in five of these athletes.*

Conclusion *Muscular body build and male sex are strongly associated with MHS.*

Résumé

Objectif *La susceptibilité à l'hyperthermie maligne (SHM) est un trouble de la régulation du calcium dans les muscles squelettiques. Il a été démontré que les personnes musclées couraient un risque 13,6 fois plus élevé de décès pendant des épisodes d'hyperthermie maligne (HM) ainsi qu'un risque plus élevé de récurrence après un premier traitement de la maladie. Vingt-cinq pour cent des épisodes graves d'HM sont survenus chez des athlètes de pointe. Cette étude a examiné l'association entre la SHM et la constitution musculaire.*

Méthode *Des données ont été obtenues à partir de rapports existants dans le Registre nord-américain de l'hyperthermie maligne (North American Malignant Hyperthermia Registry), y compris le Rapport de biopsie musculaire et de test de contracture (Report of Muscle*

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Biopsy and Contracture Testing) (test de contracture à la caféine et à l'halothane [CHCT]) ainsi que les rapports de réactions métaboliques ou musculaires négatives à l'anesthésie (Adverse Metabolic or Muscular Reaction to Anesthesia - AMRA). Les personnes susceptibles à l'hyperthermie maligne ont été comparées aux personnes négatives à l'HM quant à leur constitution physique et à la raison de leur test. On a également fait une comparaison hommes-femmes. Les formulaires de CHCT et d'AMRA ont été passés en revue afin d'en extraire tout commentaire ou remarque.

Résultats *Parmi les 1292 personnes ayant reçu un diagnostic de SHM après avoir passé un test de CHCT, les hommes étaient plus enclins à être diagnostiqués avec ce trouble que les femmes (rapport de cotes [RC], 2,33; intervalle de confiance [IC] 95 %, 1,99 à 2,7; P < 0,001). Les personnes musclées couraient un risque plus élevé de diagnostic de SHM que les personnes non musclées (RC, 1,94; IC 95 %, 1,51 à 2,49; P < 0,001). Les hommes couraient un risque plus élevé de passer un test après avoir subi un possible épisode d'HM (RC, 2,33; IC 95 %, 1,45 à 2,1; P < 0,001). L'analyse de régression logistique a montré que le sexe masculin (RC, 2,28; IC 95 %, 1,93 à 2,7; P < 0,001) et un corps musclé (RC, 2,17; IC 95 %, 1,21 à 3,9; P = 0,01) étaient des prédicteurs indépendants de SHM. L'interaction entre avoir un corps musclé et le sexe masculin n'était pas significative (P = 0,13). Les indications pour envisager un test, prévoir un épisode d'HM vs les antécédents familiaux d'HM ne différaient pas entre les personnes musclées et non musclées (P = 0,44). Huit des 839 AMRA et deux rapports de CHCT comportaient des commentaires décrivant des capacités athlétiques. Des mutations du gène RYR1 (récepteur de ryanodine de type 1) ont été observées chez cinq de ces athlètes.*

Conclusion *Un corps musclé et le sexe masculin sont associés de façon significative à une susceptibilité à l'hyperthermie maligne.*

Malignant hyperthermia (MH) is a disorder of the regulation of calcium in skeletal muscle. In response to certain anesthetic[1,2] agents or other stressors, such as exercise,[3-5] excessive calcium in the muscle cell increases metabolism to the point of producing lethal temperatures. Mutations in the ryanodine receptor type 1 (*RYR1*)[6] gene are the most frequent genetic changes found in individuals with malignant hyperthermia susceptibility (MHS). Mutations in the alpha one subunit of the voltage-gated calcium channel (the dihydropyridine receptor)[7] are less common than *RYR1* mutations.[6,8] The STAC 3 protein has also been found to be associated with MHS in some myopathic patients.[9] There are 35 mutations in the *RYR1* gene and two in the *CACNA1S* gene, encoding the alpha one subunit of the dihydropyridine receptor, that have been shown to be MH causative.[10] Even with an emerging genetic understanding of MHS, the gold standard for a diagnosis of MH risk in North America remains the caffeine-halothane contracture test (CHCT), which is reported to be 97% sensitive and 78% specific.[11]

Muscular individuals have been shown to have a 13.6-fold increased risk of death from MH episodes[12] and are more likely to experience recurrence of MH episodes after initial treatment.[13] Twenty-five percent of severe MH episodes have occurred in elite athletes.[12]

There have also been other reports of athletes suffering MH episodes both with[14,15] and without exposure to anesthesia.[16-18] It was previously noted that three of 25 Danish individuals who experienced MH episodes were elite athletes competing at the international and Olympic levels.[18] Thus, for this study, we looked for more evidence in the North American Malignant Hyperthermia Registry (NAMHR) that muscularity and athleticism were associated with MHS.

Methods

After institutional review board approval, data were obtained from reports existing in the NAMHR from January 1, 1987 to December 31, 2014, including the Report of Muscle Biopsy and Contracture Testing and the Adverse Metabolic or Muscular Reaction to Anesthesia (AMRA) report. The CHCT is completed by physicians in the MH diagnostic testing centres, and the AMRA is completed by the anesthesiologist or other healthcare provider who observed a possible or actual MH event. The CHCT and AMRA contain a check box for body build that includes options for normal, lean, muscular, obese, postpartum, and other. The judgment of body build is subjective on the part of the physician completing the report and not based on objective measurement of fat or muscle. For purposes of analysis, the cases were sorted into categories of muscular and non-muscular, first on the basis of responses to this check box. If comments reported muscular in a text field as well as noting body build other than muscular in the check box, the case was put into the muscular group for analysis. All forms contain a section for comments. Since 2002, forms include a check box for "regular regimen of physical activity". The CHCT form contains the question "What was the reason for MH diagnostic muscle biopsy?" with options for fulminant MH episode, possible MH episode with associated AMRA, possible MH episode without AMRA, family history, control, and other. For the purposes of analysis, fulminant

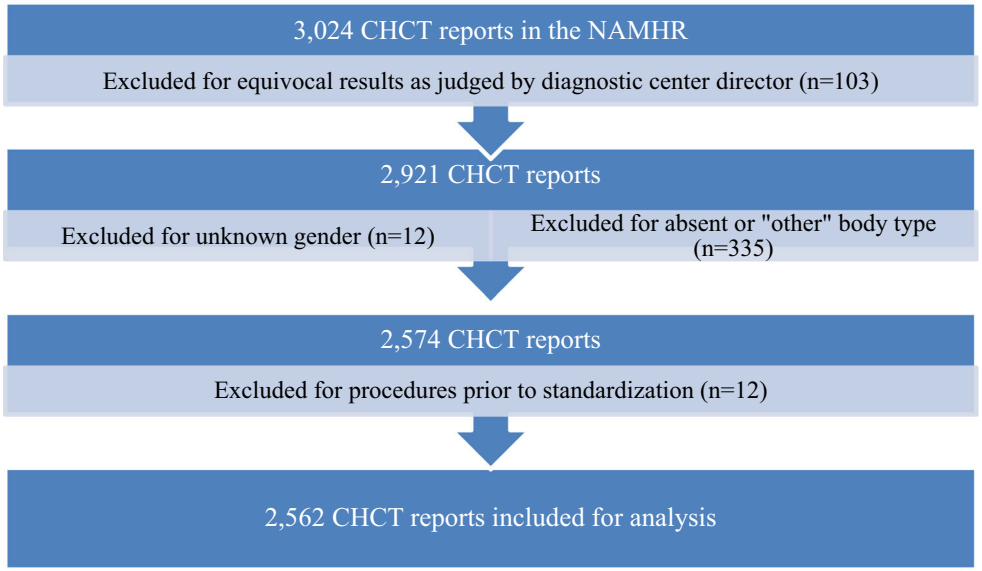

Figure Exclusion algorithm. CHCT = caffeine-halothane contracture test; NAMHR = North American Malignant Hyperthermia Registry

MH episodes and possible MH episodes as the reason for biopsy are grouped together and referred to as possible MH episode. These are the probands.

Three thousand twenty-four CHCT reports from individuals in the USA or Canada were examined. These CHCTs were performed after 1979 and before 2013 and include cases in previously published studies from the NAMHR. We excluded 103 of these reports with equivocal results. At the time of testing, the director of the MH diagnostic centre indicated equivocal result to mean that risk of MHS could not be determined. The magnitude of the contractures in the presence of halothane or caffeine were not evaluated in this report. Reports with unknown sex (12), absent or other body type (335), and 12 reports of CHCT performed prior to standardization[19] were also excluded (Figure). Eight hundred thirty-nine AMRAs were reviewed for comments, and CHCT reports were also reviewed for comments regarding athletic achievement and genetic test results.

Analysis was performed using Fisher's exact test for categorical variables. The associations between CHCT result and body build, CHCT result and body build in male and female sex, body build and indication for testing, as well as sex and CHCT result were examined with Fisher's exact test in SPSS® (versions 22, 23, & 24; IBM, NY, USA). Since muscularity may be associated with being male, we used logistic regression to determine if muscularity was independently predictive of MHS (over and above sex). We used MHS as the dependent variable and muscularity and sex (as well as their interaction) as the independent variables. There was no correction of P values for multiple comparisons.

Results

Results of CHCTs were reported for 1,284 males and 1,278 females. Muscular body build was reported in 194 of 1,292 individuals diagnosed with MHS by CHCT and in 106 of 1,270 individuals diagnosed as not MH susceptible (MHN) by CHCT (Table 1). Thus, those with muscular body build were more likely than those with non-muscular body build to have CHCT results indicate a diagnosis of MHS (odds ratio [OR], 1.94; 95% confidence interval [CI], 1.5 to 2.5; $P < 0.001$). Males were more likely to be diagnosed with MHS by CHCT (OR, 2.33; 95% CI, 1.99 to 2.7) than females ($P < 0.001$). Logistic regression showed that muscularity was indeed predictive of MHS independent of sex. The OR for muscularity (adjusted for sex) was 2.17 (95% CI 1.21 to 3.9; $P = 0.01$), consistent with the unadjusted effect of muscularity on MHS. Being male continued to be predictive of MHS after adjustment for muscularity (OR, 2.28; 95% CI, 1.93 to 2.7; $P < 0.001$). There was no significant interaction ($P = 0.13$) between muscularity and sex, indicating that the effect of muscularity on MHS did not differ appreciably between males and females (or, equivalently, the effect of sex on

Table 1 Percent muscular build and malignant hyperthermia susceptibility

	Male	Female
MHS	166/781 (21.2%)	28/511 (5.5%)
MHN	86/503 (17.1%)	20/767 (2.6%)

MHS = malignant hyperthermia susceptibility; MHN = not malignant hyperthermia susceptible.

Table 2 Logistic regression of sex, muscular body build status, and their interaction

Parameter	Odds ratio	95% Confidence interval	*P* value
Sex	2.28	1.93 to 2.70	< 0.001
Muscular	2.17	1.21 to 3.89	0.01
Muscular by sex interaction	0.6	0.32 to 1.16	0.13

MHS did not differ appreciably between muscular and non-muscular individuals) (Table 2).

With regard to the indication for testing, 458 of 1,091 (42%) males were tested after having a possible MH episode compared with 338 of 1,145 (29.5%) females ($P < 0.001$). There was no difference in the indication for testing between those with and without muscular build ($P = 0.44$). Furthermore, the percentage of muscular probands (those who underwent CHCT because of an episode of suspected MH) was no different from that of muscular individuals who underwent CHCT due to a family history of MH ($P = 0.54$).

Eight of 839 AMRAs, one of which was linked to a CHCT report, and two other CHCT reports included comments describing athletic abilities (Table 3). Four of these individuals had known MH causative mutations in *RYR1*. Two had variants of unproven significance in *RYR1*, one of whom also had an *RYR1* mutation known to be causative of MH.

Discussion

In this report, the CHCT outcome diagnostic of MHS was more strongly related to sex than to report of muscular body build. Our observation that the odds of MHS is more than twice as great in males than in females seems

Table 3 Athletic ability and malignant hyperthermia

Evidence of athleticism In comments	Sex	Body type	*RYR1* finding	MH Episode Chronic issues	Previously published in reference #
Professional athlete	Male	Muscular	N/A	Fulminant MH	12,23
College football player	Male	Muscular	N/A	Fulminant MH	12,15,23
Multiple fractures during sports	Male	Muscular	N/A	Suspected MH	12,23
Olympic athlete	Female	N/A	N/A	Death, Fulminant MH	12,23
College cheerleader, athletic	Female	Non-muscular	p.Gly2434Arg*	Death, Fulminant MH	Larach, 2014
College level volleyball and track to State competition; cheerleader; gymnast reported before MH event at <25 yr of age	Female	Muscular	p.Arg614Cys* & p.Thr3711Arg	Fulminant MH	6, Larach, 2014
Regular regimen of physical activity in mixed martial arts at < 25 yr of age	Male	Muscular	N/A	Fulminant MH	Larach, 2014
Regular bicycling > 20 min·day^{-1} 3 times·wk^{-1} prior to MH event at < 30 yr of age	Male	Muscular	p.Gly2434Arg*	Fulminant MH	12,23
Runs > 6 miles·day^{-1}; bench presses 300 lb when had CHCT at 30 yr of age	Male	Muscular	p.Leu4824Pro	No personal MH; Reported relative died of MH; CCD histology; Intolerant to heat	Sei, 2004
Long distance cyclist; semi-pro hockey player before MH event at ~ 40 yr of age	Male	N/A	p.Gly2434Arg*	Suspected MH; Postop Rhabdomyolysis, max CK 70,000 IU; Exercise-induced rhabdomyolysis and weakness.	6

Reports with evidence of athleticism and sex; most include body type and some include type 1 ryanodine receptor mutation findings.

*Known MH causative mutation

Previously published in this # citation in this report or in Larach *et al*. Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007-2012: A report from the North American MH Registry of MHAUS. Anesth Analg 2014; 119: 1359-66 or in Sei *et al.* Malignant hyperthermia in North America genetic screening of the three hot spots in the type I ryanodine receptor gene. Anesthesiology 2004; 101:824-30

CCD = central core disease; CHCT = caffeine-halothane contracture test; CK = creatine kinase; MH = malignant hyperthermia; MHAUS = Malignant Hyperthermia Association of the United States; N/A = not available; *RYR1*= type 1 ryanodine receptor

contradictory to the understanding of MHS as an autosomal dominant condition. Nevertheless, observation of more males than females with a positive CHCT was first reported in 2007 in 1,407 patients evaluated in Sweden.[20] More recently, a consistent parent-of-origin effect was reported for the transmission of MHS in view of the fact that fathers had more affected sons than daughters.[21] Malignant hyperthermia episodes have been reported more often in males than in females in several different types of studies.[22-24] One might speculate that males experience MH more often than females because of environmental factors. In this report, more males than females presented for a CHCT due to personal experience of an MH event. Nevertheless, in this cohort, there were similar numbers of males and females who underwent CHCT. Sex discrepancy in MH warrants further study.

In the CHCT data in this study, muscular body build was reported in a minority of individuals diagnosed as MHS by CHCT; however, there was a significant association between muscular body build and MHS diagnosed by CHCT. This observation has not been made previously. Logistic regression analysis showed that muscular body build is predictive of MHS independent of sex. There may be ascertainment bias, as a muscular build may be more easily recognized in females than in males. Perhaps many males are subjectively judged to be muscular. Assessment of a larger population with a more objective quantitative measurement of muscularity might yield a different result, as our data may be biased by the subjective nature of the reporting of body build.

The AMRA data, supplemented by a few CHCT reports, show that, although MHS individuals may have mutations in genes encoding proteins involved in the excitation-contraction coupling mechanism in skeletal muscle, some of these individuals perform athletically at high levels. The possibility that an MHS person can be a skilled athlete widens the phenotypic variability of *RYR1* mutations. Myopathies related to the *RYR1* gene, such as King-Denborough syndrome and central core disease, are not the only clinical presentations of MHS in daily life.

The nature of the data acquisition in this study may produce significant bias. Selection bias is present as all reports were submitted voluntarily, and it may be that only the most severe or memorable cases were reported. Specific questions to elicit reporting of athletic accomplishment were recently added (2015) to reports. Testing for mutations in *RYR1* in MHS individuals was experimental until 2005. Also, CHCT is expensive and inconvenient to perform. Patients must travel to only a few available testing centres for muscle biopsy and contracture testing. As a result, our data underrepresent those of lower socioeconomic status. It must be emphasized that all CHCT investigations are done on individuals with an indication, which makes it difficult to apply our results to patients without such medical history.

Conclusion

We report a strong association between muscularity and MHS. Males were more likely to be diagnosed with MHS by muscle contracture testing. Optimistically, as the biology of MH continues to be investigated, the causes of these findings will be elucidated.

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