INTRODUCTION

Malignant hyperthermia (MH) is a potentially fatal pharmacogenetic disorder of skeletal muscle. It is triggered in susceptible people by exposure to commonly used volatile anaesthetics agents such as halothane, isoflurane, enfluorane and sevoflurane or depolarising muscle relaxants such as succinyl choline. A fulminant MH crisis is characterised by any combination of hyperthermia, skeletal muscle rigidity, tachycardia or arrhythmia, and respiratory and metabolic acidosis. Advances in patient monitoring during anaesthesia, intervention on the appearance of early MH indicators and the use of the drug dantrolene sodium (a skeletal muscle relaxant) has reduced the mortality rate in developed countries from 70% to below 10%. Individuals susceptible to MH are not clinically distinguishable from the general population and may present with none, some or all of the classical MH signs with variable intensity on any given exposure to trigger agents. As MH can be avoided by the use of non-triggering anaesthetic agents, knowledge of the susceptibility of individuals prior to anaesthesia is of vital importance for prevention of MH.820

The main accepted and validated test for diagnosing susceptibility to MH is an \textit{in vitro} contracture test (IVCT) performed on skeletal muscle tissue obtained by biopsy from “at risk” cases such as individuals exhibiting unconfirmed MH during anaesthesia and relatives of such probands. The IVCT has been standardised independently by the European and North American Malignant Hyperthermia Groups.821,822 In the test, individuals
whose muscle exhibits hypersensitivity to caffeine and halothane induced contracture are diagnosed as MHS (MH susceptible). Individuals that are not hypersensitive to both agents are classified as MHN (MH normal) while hypersensitivity to either caffeine or halothane is diagnosed as MHE (MH equivocal). Clinically, MHE and MHS individuals are considered susceptible to MH. However, the MHE phenotype is somewhat enigmatic and its biochemical and genetic basis remains to be clarified. The European and North American IVCTs differ in several respects. The former has a sensitivity of 99% and a specificity of 93% while the latter, referred to as the caffeine halothane contracture test (CHCT) has a sensitivity of 92-97% and a specificity of 78%. The diagnostic thresholds are also somewhat different.

Clinical MH is considered autosomal dominant with low penetrance. By contrast, MHS in almost all families is an autosomal dominant pharmacogenetic trait with high penetrance. From a clinical perspective, MH is a relatively rare disorder with an incidence in the region of 1 in 10,000 to 1 in 50,000 administrations of triggering anaesthetic agents. By contrast, epidemiological evidence indicates that the frequency of MHS in the population is on the order of 1% while MHE frequencies are as high as 5%. This suggests that genetic and/or environmental factors have a strong influence on expression of clinical MH.

A syndrome essentially identical to human MH was identified in pigs in the late 1960s. Porcine MH is associated with a high muscle to fat ratio in pigs and has proved to be an invaluable animal model for understanding the biochemical, physiological and genetic basis of human MH. MH like syndromes have also been reported in a number of other species, most notably dogs, where several pedigrees have been described.

MHS has been associated with and/or observed in a variety of other conditions. The clinical congenital myopathy Central Core Disease (CCD) is consistently associated with MH. This disorder is characterised by hypotonia and proximal muscle weakness which presents in infancy and leads to delay of motor milestones. CCD histology shows the presence of amorphous, mitochondria depleted central areas (cores) in type 1 muscle fibres and pathological SR changes. Patients with CCD are at high risk for MH and in almost all cases are diagnosed as MHS by the IVCT. CCD exhibits great variability both clinically and histologically and can range from normal to severe within a single family.