Title : MALIGNANT HYPERTHERMIA: DIAGNOSTIC TESTS AND INHERITANCE

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Introduction. A variety of screening procedures for malignant hyperthermia susceptibility (MHS) in man have been described. One testing procedure involving in vitro contracture response to halothane or caffeine has been used persistently by 3 laboratories and has provided reasonably consistent results within a laboratory. Variations have existed in the exact nature of these contracture test procedures. An International MH Workshop attempted to resolve this problem by establishing uniform testing procedures. Utilizing the recommended procedures, we have performed diagnostic contracture tests on 52 individuals from 24 unrelated families.

Methods. Skeletal muscle biopsy of vastus lateralis was obtained from diagnostic patients after general anesthesia (thiopental/dizepam/fentanyl/$N_2O$). Muscle strips averaging 68mg, 14mm long and 2mm diameter were prepared and tested as described previously.[1] Each muscle strip was placed in a Krebs-Ringer solution in a 37°C thermostated muscle chamber and arranged for isometric contraction measurments using a force transducer. Each muscle was electrically stimulated (0.2 Hz, 1 msec duration) at optimum length-tension settings. At least 2 muscle strips from each patient were exposed to 1 of the following 3 treatments: (1) 3% halothane; (2) cumulative caffeine doses; (3) cumulative caffeine doses in the presence of 1% halothane. Isometric contracture response to these treatments was measured and compared to responses of muscle from 18 elective surgical control patients.

Results. Based on these contracture response comparisons, 2 different classifications of susceptibility appear to exist. One group of susceptible patients referred to as MHS Type H had muscle which produced an abnormally greater contracture response to 3% halothane. Also, the threshold concentration of caffeine with and without 1% halothane for contracture was significantly lower than controls. Another group of patients, some related to the MHS-Type H patients, had contracture response to 3% halothane or to caffeine that did not differ from control responses. However, this group was clearly distinct from controls when the contracture response to caffeine in the presence of 1% halothane was compared. Based on the abnormal contracture response to caffeine plus 1% halothane these patients were diagnosed as susceptible and referred to as MHS Type K. Other elective diagnostic patients had contracture responses to these tests which did not differ from the control group and these were diagnosed negative for MHS. Serum CPK levels were elevated in 67% of MHS Type H patients, in 31% of MHS Type K patients, and in none of the patients with negative diagnoses.

Discussion. Diagnosis of malignant hyperthermia susceptibility remains a difficult problem. The symptoms related to the onset of MH may have other causes, yet to continue surgery and anesthesia in attempts to confirm MH have been associated with higher mortality and morbidity. In the present study, in vitro diagnostic contracture testing has confirmed the occurrance of MH during surgical anesthesia and has identified susceptibility among relatives of these confirmed cases. Results obtained among these MHS diagnostic subjects compares favorably with other laboratories utilizing a similar protocol (Britt, Rosenberg, Anderson, personal communication). Among our data set are subjects who have had a clinically confirmed MH crisis during general anesthesia. Each of these subjects, classified as Type H, have muscle which produced abnormal contracture response to 3% halothane and to caffeine with and without 1% halothane. Based on abnormal contracture responses to caffeine with 1% halothane only, another group of subjects were considered MHS and classified Type K. Some of these subjects are relatives of Type H individuals but the clinical history for MH during anesthesia is equivocal. Among the Type K individuals we have studied, the development of masseter spasm following administration of succinycholine is the only clinical evidence supporting MHS. The data support a basis for diagnosing MHS and provide additional evidence that the genetic determinants predisposing MHS may be multifactoral.

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References.

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