New genetic test promising for malignant hyperthermia

A new noninvasive genetic test looks promising for determining susceptibility to malignant hyperthermia (MH).

A DNA sample for the test can be obtained from buccal cells, white blood cells, muscle cells, or other tissue, according to the June 13 Journal of the American Medical Association.

Malignant hyperthermia is an inherited metabolic disorder of the muscle that ordinarily shows no outward signs. It manifests itself only when a person is exposed to anesthetic triggering agents, such as the volatile inhalational anesthetic gases ether, halothane, and isoflurane as well as succinylcholine.

The onset of MH is heralded by one or more signs of systemic hypermetabolism when the triggering agent is administered. Treatment of MH includes immediately discontinuing the agent and administering dantrolene sodium.

Patients susceptible to MH who need surgery can safely be given regional anesthesia with local anesthetics or general anesthesia with nontriggering agents.

First step

Until now, the only way to test a patient for MH before surgery was a muscle biopsy. A muscle biopsy is expensive and cumbersome because the sample must be analyzed at a specialized diagnostic center.

The new test does not take the place of the muscle biopsy, which remains the gold standard, but is a first step, according to the Malignant Hyperthermia Association of the United States (MHAUS).

Though not a screening test, the new test could identify 50% of those at risk in an MH-susceptible family. MH is inherited in an autosomal dominant pattern, meaning children, parents, and siblings of an MH-susceptible person have a 50% chance of having the susceptibility. Aunts, uncles, and grandchildren have a 25% chance. More distant relatives have a lesser chance.

Mapping mutations

Since MH was first described in 1961, researchers have been looking for a noninvasive test to identify those at risk. Researchers began by mapping mutations within the ryanodine receptor (RYR1) gene, which is responsible for MH susceptibility. So far, they have found RYR1 mutations in at least 25% of known MH-susceptible individuals. The researchers have identified 2 MH susceptibility genes and have mapped 4 to specific chromosomes, but these have not been definitively identified. Those who do not have a known mutation may still be at risk because not all mutations have been identified.

Researchers have associated more than 60 mutations in RYR1 with abnormal muscle biopsy tests or an irrefutable clinical episode of MH. Additional mutations in less investigated regions of the RYR1 or in other genes account for the remainder of MH-susceptible patients. More work is needed to refine the test for those without a family history.

Who should be tested?

To increase the test's sensitivity, MHAUS advises that only the following should consider having the genetic test:

- those who have tested positive by a muscle biopsy
- those who have a mutation causative for MH under research protocol
- relatives of those with a known mutation for MH
• relatives of those who tested positive by a muscle biopsy
• those with a very high likelihood of having had an MH episode.

The cost of RYR1 screening is about $800 unless the patient is a member of a family with a known mutation, and then it is $200. The decision to determine susceptibility is complex and requires guidance of an expert in genetics and MH, MHAUS advises.

MHAUS plans a project to educate insurance companies about the test. In the meantime, MHAUS will provide insurers with information and references on the validity of the genetic test.

There are 6 testing sites in the US and 2 in Canada. A list is at www.mhaus.org. Click on Testing Sites.

Reference