

## **Malignant Hyperthermia – Complex and Insidious**

Dr Kathryn Stowell's update on DNA testing for Malignant Hyperthermia (MH), at the Annual Anaesthetists' Research meeting on July 31, coincided with the publication of Heytens et al excellent article on "The changing face of malignant hyperthermia: less fulminant, more insidious in Anaesthesia and Intensive Care".<sup>1</sup>

As summarized by Heytens et al, modern anaesthetic techniques have resulted in the clinical presentation of MH to be more often indolent and/or insidious than truly fulminant.

Awareness among anaesthetists of this change in presentation is important since the clinical diagnosis is often more doubtful and, if corroborative evidence is not sought, the diagnosis may be delayed or missed altogether. They conclude that the more insidious character is most likely due to the lower triggering potency of modern anaesthetic agents, the mitigating effects of several intravenous drugs including neuromuscular blocking agents, alpha 2 adrenergic receptor agonists and beta-adrenergic blockade or techniques such as neuroaxial blockade, and the routine use of end tidal CO<sub>2</sub> monitoring, leading to the early withdrawal of triggering agents.

The extent to which MH develops is said to be time-weighted with symptoms abating when exposure to the triggering agent ends, even when dantrolene is not administered. There is also evidence that triggering is dose dependent.

Anaesthetists should review this paper and need to be aware of the increasing proportion of insidious presentations. Heytens et al recommend, "in our current practice sufficient attention be paid to the following signs and measures, even when occurring as a sole abnormality:

- Foremost: persistent, unexplained and difficult-to-correct hypercapnia,
- Rapidly increasing and/or inappropriately elevated body temperature,
- Masseter spasm following the administration of succinylcholine and
- Clinical or biochemical evidence of rhabdomyolysis: increased postoperative CK level, voiding of cola coloured urine (myoglobinuria), with or without hyperkalaemia. "

Reactions do still have the potential to be fulminant given enough time.<sup>2</sup> Reports from Japan, which has the highest rate of MH reactions with Sevoflurane show fulminant reactions can occur after over two hours of anaesthesia. For the latest review see: Malignant Hyperthermia: a review. Rosenberg H, Pollock N., Schiemann A., Bulgar T., and Stowell K. Orphanet Journal of Rare Diseases 2015 Vol 10 (1): 93

The "gold standard" diagnosis of MH is by in vitro contracture test of muscle biopsy tissue. This highly invasive test is neither 100% specific nor sensitive. Dr Stowell's group in Palmerston North have sought to genetically and biochemically characterize New Zealand

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<sup>1</sup> Heytens L., Foregt P., Scholtes J.L., Veyckemans F. The changing face of malignant hyperthermia: less fulminant, more insidious. *Anaesth Intensive Care* 2015; 43:4; 506-511

<sup>2</sup> Hoenemann C.W., Halene-Holtgraev T.B., Booke M.M., Delayed onset of malignant hyperthermia in desflurane anaesthesia. *Anesth Analg* 2003; 96 (1): 165-167

families susceptible to MH to replace the *in vitro* test with a simple DNA-based test. They have identified *RYR1* variants in approximately 70% of over 50 New Zealand families susceptible to MH, and one family with a *CACNA1S* variant. Functional analysis has shown that most *RYR1* variants result in hypersensitive channel activity, that correlates with the MH phenotype. Some *RYR1* variants, however, exhibit normal calcium channel activity, while others result in a hypoactive channel.

While DNA testing can be used for diagnosis, it cannot replace the *in vitro* contracture test. A negative DNA test has to be confirmed by a negative muscle biopsy as some families have multiple variants.

MidCentral Health has a pack available to send out for collection of specimens. The testing can only be done at Massey and all specimens would have to be couriered for testing. Following discussion with Dr Neil Pollock the test pack can be available to anaesthetists to send a sample for a battery test, should they suspect a MH reaction or have a patient, such as a child, with a family history of MH.

A battery test, tests for the known 34 causative mutations and examines a few non *RYR1* mutations. The tests are limited, expensive and funding can be a problem. If you have a pack, suspect a reaction then direct discussion with either Neil Pollock or Terasa Bulgar at Mid Central DHB should be undertaken before sending the request. Please contact Neil on 027-449-7170 or Terasa on 021-245-1684.

Having the pack available within anaesthetic departments could assist with the diagnosis of MH, given the often more insidious nature of presentation, and may reduce the need for patients to undertake invasive *in vitro* testing.

I would like to acknowledge the invaluable work undertaken by Neil Pollock, his anaesthetic colleagues and that of Dr Stowell and her team at Massey University in identifying those patients at risk of developing MH in our community.

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