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EDITORIAL

Malignant hyperthermia: new knowledge changing perspectives

Many anesthesiologists may believe that malignant hyperthermia is so rare that most professionals will probably spend their entire lives without facing a case. Nonetheless, we know that the incidence is not as low as initially described.[1] However, since the beginning of the 20th century, cases of increased body temperature related to anesthesia have been observed. The knowledge related to malignant hyperthermia (MH) is intertwined with reports of complications and anesthesia-related deaths, often described as "ether convulsions".[2-4] However, in 1962, Denborough and collaborators described a series of classic cases of malignant hyperthermia that occurred in a single family.[5] A 14-year-old boy from that family underwent correction of a leg fracture and had a typical clinical presentation of tachycardia, cyanosis, increased body temperature, and intense sweating, but he managed to survive. Observing these cases allowed the first association of the syndrome with an autosomal dominant pattern genetic syndrome.

Shortly afterward, another family, this time with 22 cases, 7 of them fatal, helped to further understand the genetic heritage and the variable penetrance pattern, showing that not all carriers of the genetic alteration present the classic syndrome when exposed to anesthetic agents.[6] In this family, the grandmother was a mandatory carrier of the genetic alteration, as 3 of her direct descendants and 19 collateral descendants presented MH episodes. She, however had been submitted to 19 anesthesias with different anesthetic agents known to trigger MH without the clinical presentation. This illustrates that a variable penetrance of the genetic alteration may occur and configure the multiple possible clinical presentations of the disease.[7] Since then, we have increasingly sought to study and better understand the alterations in patients susceptible to malignant hyperthermia.

This issue of BJAN has three articles that provide a new view on patients susceptible to MH, bringing essential information that can help us, as anesthesiologists, to better understand the syndrome and patient characteristics.

De Mello et al retrospectively evaluated the characteristics of 80 patients referred to the halothane/caffeine contraction test due to a personal or family history of malignant hyperthermia between the years 2004 and 2019.[8] Demographic and clinical data, genetic alterations, and responses to *in vitro* contracture tests (IVCT) were assessed. Patients whose Initial Maximum Contraction Test (IMC) was $\geq$ 1 g, or with a contracture after 32 mMoL.L$-$1 (mM) Caffeine (Caf32) $\geq$ 5 g in at least one muscle sample exposed to caffeine, and whose IMC $\geq$ 1 g in at least one sample exposed to halothane, were included. Among the results, we observed agreement with worldwide data on males being a strong predictor of IVCT positivity. Mean patient age in this study can be considered a little higher than that of studies in other countries, given muscle biopsies are not routinely performed on children in Brazil; therefore, many biopsies occurred in older family members. However, age was not a predictor of test positivity. The high positivity rate found in the tests performed can be explained by indication restricted only to highly clinically suspicious cases or even a higher frequency of mutations in Brazil.[9] The presence of RYR1/CACNA1S variants was very similar to what has already been described. However, this sample was minimal among the total number of patients in the study, as genetic tests are not yet widely available in Brazil. One of the most instigating results presented in this article, which had not yet been described, was the absence of muscle weakness as a predictor of IVCT positivity. Another interesting point is that most patients who did not feel susceptible showed weakness and developed atypical reactions to anesthesia that mimicked the clinical presentation of malignant hyperthermia. Therefore, this study reinforces the importance of attention to patients who present suggestive signs of a hypermetabolic syndrome during or after exposure to triggering agents and who do not have a specific phenotype, emphasizing that we need to pay attention to the clinical presentation for diagnosis.

The other two studies in this issue of BJAN seek a different view of patients susceptible to malignant hyperthermia and explore some clinical characteristics to understand

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whether they may be associated with this population, drawing our attention and therefore being able to help us to better understand these patients. Andrade et al conducted a cross-sectional observational study with susceptible and non-susceptible patients and controls to assess the presence of fatigue and other factors that may affect the perception of fatigue, such as depression and physical activity, due to the likelihood that patients with fatigue unconsciously reduce their physical activity.[10] Patients with neurological diseases and chronic medication use were excluded from the study since fatigue may be associated with these other factors. Fatigue has been increasingly studied in the literature, and it leads to a significant deterioration in the quality of life by generating numerous functional limitations. Fatigue has been described in patients with alterations in the RYR1 gene, including patients with malignant hyperthermia.[11] Fatigue deserves a detailed evaluation and general attention, not only due to the global impact on the patient's quality of life, but to be attentive during anesthesia. Albeit a nonspecific finding, together with other clinical and family history information, fatigue can help guide a more in-depth investigation. Interestingly, this study found that physically active susceptible patients had a more significant impact of sleep/rest on fatigue recovery than sedentary patients. This finding reflects more difficulty in recovery and adaptation to exercise in these patients. Fatigue should be valued in the pre-anesthetic evaluation and can be a warning sign of several neurological diseases, although MH patients do not have a higher subjective perception of fatigue, and it may not be perceived during recovery from exercise, which is the time when the difference was observed.

Also in this issue, Rodrigues et al studied the level of knowledge on the syndrome by patients susceptible or in investigation for malignant hyperthermia.[12] Due to the lack of a specific phenotype or frequent symptoms, the syndrome is unknown to most patients who often present for anesthetic-surgical intervention only with a nonspecific family history of complications associated with anesthesia. In addition, the study also explored the impact of suspicion on these patients' lives and their characteristics. We highlight the presence of alterations in the physical/neurological examination in 93% of patients with the syndrome confirmed by IVCT, and in 90% of non-susceptible patients. The patients interviewed did not consider malignant hyperthermia a disease, but a risk. Almost half of the patients evaluated in the study had deformities associated with congenital malformations or osteoarticular diseases, reinforcing worldwide findings.[13,14] One-fifth of the deaths described by members of the families interviewed were related to classic malignant hyperthermia episodes or even unexplained deaths in the perioperative period, stressing the lack of information or of conveying the information within the family itself. In the evaluation of specific knowledge, it was observed that there is still much to be done for the general population that lacks information and clarification. Virtually all patients who tested positive in the IVCT had changes in the physical/neurological examination. This finding should alert all anesthesiologists to an improvement in the physical examination during pre-anesthetic evaluation.

All the studies mentioned in this issue of BJAN provide the anesthesiologist with a view beyond the classic malignant hyperthermia episode. They increasingly underscore the need for anesthesiologists to consider the perioperative period as a whole and be aware of signs and symptoms that have no specific relationship with malignant hyperthermia but which often, when evaluated together, can trigger an alert to in-depth evaluation and even help in the diagnosis of an eventual atypical event in the perioperative period. All current recommendations aim to offer an increasingly safer environment to our patients, with safe anesthesia agents, and adequately evaluate everyone with a suggestive personal or family history.[15] We need to increasingly improve our knowledge on the syndrome and its impact on patients. We hope that in the near future, we will be able to count on greater availability of genetic tests to evaluate suspected patients.[16]

Conflicts of interest

The authors declare no conflicts of interest.

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Cláudia Marquez Simões
Hospital Sírio Libanês, São Paulo, SP, Brazil
E-mail: claudia.simoes@hc.fm.usp.br