A case of rapid progression of postoperative hyperthermia: Dantrolene or not dilemma?

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ABSTRACT
Malignant hyperthermia (MH) is an extremely rare and life-threatening differential diagnosis of postoperative fever. We present an 8-month-old child scheduled for elective outpatient procedure who rapidly developed high fever, tachycardia, and respiratory acidosis shortly after transfer to the postanesthesia care unit. MH hotline expert recommended administering dantrolene, but there was no evidence of hypermetabolism or lactic acidosis. The patient remained clinically stable after admission to the pediatric intensive care unit and was discharged home the next day. The fever was likely due to viral infections as confirmed by a positive result of viral polymerase chain reaction for human metapneumovirus and rhinovirus/enterovirus.

Key Words: Dantrolene, malignant hyperthermia, postoperative fever

INTRODUCTION
Postoperative fever may have various etiologies and lead to different diagnoses. One of the rare but potentially life-threatening possibilities could be malignant hyperthermia (MH). In this report, we present a case with rapidly progressive rise in temperature during emergence from anesthesia in the postanesthesia care unit (PACU), one of the classic but late signs of MH. We discuss the differential diagnosis of immediate postoperative fever, considering a diagnosis of MH and complications of administering dantrolene.

CASE REPORT
An 8-month-old child with baseline gross motor delay, paroxysmal nystagmus, and seizure disorder, was scheduled for elective outpatient nasolacrimal duct probing with stent placement. Her weight was 10.6 kg. The patient’s heart rate was 116, respiratory rate 22 and temperature was 36.8°C in the preoperative area. Following a mask induction with sevoflurane, the anesthetic was maintained with sevoflurane in O₂ and air, through laryngeal mask airway (LMA). The patient received a total of 3 mg morphine intravenous intraoperatively. Total anesthesia time was 1 h and 15 min. The LMA was removed with the patient deeply anesthetized, and she was transported to the PACU. On arrival to the PACU, the patient was still sedated with a heart rate of 130/min, respiratory rate of 11 and temperature of 36.7°C. Over the next 3 h, the heart rate increased to 200/min, respiratory rate to 24 and temperature to 41.2°C [Figure 1]. The temperature measurements were initially made using infrared temporal artery thermometer, and once a Foley catheter was inserted, bladder temperature was continuously measured. External cooling using ice-cold sponges on the face, axillae and chest and acetaminophen 120 mg PR were used to cool the patient. She remained somnolent, and her skin was mottled, especially on the extremities and she was noted to be making jerking movements. The reason for the jerking movement was not clear, but it was not likely to be febrile convulsion, as determined by pediatricians. A venous blood gas
DISCUSSION

Postoperative fever (temperature >38°C) is a relatively common occurrence. Hyperthermia within 48 h after surgery is most likely secondary to surgical stress or infectious cause. Our case is interesting for the rapid progression of very high fever in PACU.

Other less common causes of postoperative fever include exposure to sulfa drugs in susceptible patients, iatrogenic overheating and very rare metabolic syndromes such as mitochondrial myopathy resembling Luft’s disease. Fever due to dehydration is sometimes seen in neonates and infants. Dry mouth and skin, decreased urine output, thirst, cardiovascular, and neurological changes are indicative of dehydration fever in postoperative patients. Infection should be considered when a patient presents with prior symptoms or contact with a known infective source. Investigations may include a chest X-ray, urine analysis, urine and blood culture, complete blood count, and lactate. Our patient did not have any symptoms either pre- or post-operatively suggestive of infection and initial laboratory investigations such as blood counts, lactate levels were within normal limits normal. Fever following drug exposure is most common following antimicrobial therapy and blood products and usually, is accompanied by hypotension and rash. Our patient received neither antibiotics nor blood products and had neither characteristic rash nor hypotension as would be seen in allergic reactions. The patient was anesthetized for the relatively short duration and her fever manifested in the PACU (as opposed to arriving to PACU with fever). Given the rapid progression of fever and with no evidence for other more common sources, MH was suspected.

To improve prediction of MH susceptibility, an international group of MH experts created a multifactor MH clinical grading scale that comprises standardized clinical diagnostic criteria. Use of this scale is recommended as an aid to the objective definition of this disease. According to MH scoring rules, rapidly increasing temperature, equals to score 15 and an inappropriate increase in temperature >38.8°C in the preoperative period equals to score 10. Using this scoring [Table 2], our patient has a score of 15, which means that MH is somewhat less than likely [Table 3].

[Table 1: Summary of postoperative investigations]

| Postoperative time frame | pH  | PaCO₂ | LA  | K  | Urine | U Mgb (nL) | Se Mgb (nL) | CK (nL) | WBC |
|--------------------------|-----|-------|-----|----|-------|------------|------------|--------|-----|
| 2:49                     | 7.19* | 59**  | 2.5* | 3.9 | CL    | <1         | 26         | 78     | 6.1 |
| 3:37                     | 7.40* | 37*   | 0.9* | 3.9 | CL    | 26         | 78         | 6.2    | 10.9|
| 6:07                     | 7.35* | 39*   | 4.2  |    | CL    |            |            |        |     |
| 17:00                    | 7.39* | 28*   | 4.9  |    | CL    |            |            |        |     |

*Arterial, **Venous, LA: Lactic acid, CL: Clear, U Mgb: Urine myoglobin, Se Mgb: Serum myoglobin, CK: Creatine kinase, WBC: White blood cell.
Table 2: Criteria used in the clinical grading scale for malignant hyperthermia

| Process                  | Clinical criteria                        | Points |
|--------------------------|-----------------------------------------|--------|
| Muscle rigidity          | Generalized rigidity                    | 15     |
|                          | Masseter muscle rigidity                | 15     |
| Muscle breakdown         | Creatine kinase > 10,000 units/L        | 15     |
|                          | Cola-colored urine                      | 5      |
|                          | Excess myoglobin in urine or serum K+  | 3      |
|                          | > 6 mEq/L                               |        |
| Respiratory acidosis     | End-tidal CO2 > 55 mmHg;               | 15     |
|                          | PaCO2 > 60 mmHg                         |        |
|                          | Inappropriate tachypnea                 | 10     |
| Temperature increase     | Rapidly increasing temperature          | 15     |
| Cardiac involvement      | Unexplained sinus tachycardia, ventricular | 3    |
|                          | tachycardia, or ventricular fibrillation|        |
| Family history           | MH history in first-degree relative     | 15     |
|                          | MH history in family, not first-degree relative | 5 |

MH: Malignant hyperthermia

Table 3: Malignant hyperthermia rank and qualitative likelihood

| MH rank | Score range | Description of likelihood |
|---------|-------------|---------------------------|
| 1       | 0           | Almost never              |
| 2       | 3-9         | Unlikely                  |
| 3       | 10-19       | Somewhat less than likely |
| 4       | 20-34       | Somewhat greater than likely |
| 5       | 35-49       | Likely                    |
| 6       | 50+         | Almost certain            |

MH: Malignant hyperthermia

In an analysis of postoperative MH cases from the North America MH Registry, Litman et al. reported that postoperative MH is very rare; <2% of reported cases occurred in the postoperative period. No subjects in Litman et al.’s study hyperthermia as the initial presenting sign, instead presenting with tachycardia, tachypnea, hypercapnia, and generalized rigidity. All patients manifested a mix of respiratory and metabolic acidosis. The onset of symptoms was within 0–40 min following surgery. [8]

Although the MH hotline expert thought this was unlikely to be MH, a recommendation was made to administer dantrolene. If we were to administer dantrolene, the patient would have been labeled as MH susceptible and would either have to undergo genetic testing or muscle biopsy to rule out the diagnosis or would undergo trigger free anesthetics in future. Both these options are fraught with additional costs and inconveniences, especially in children. Dantrolene is a skeletal muscle relaxant that decreases intracellular calcium levels and is the only effective therapy in an MH episode. Brandom et al. completed a review of adverse metabolic/musculoskeletal reactions to anesthesia reports to evaluate complications associated following administration of dantrolene. In a dataset of 349 cases, the median total dose administered was 4.7 mg/kg, twice the first quartile dose of 2.5 mg/kg and almost half the third quartile of 8.7 mg/kg. [6]

They reported that complications associated with dantrolene were common but not life-threatening. These complications include muscle weakness (14.6%), phlebitis (9.2%), and gastrointestinal discomfort (4.1%). More serious complications such as respiratory failure, pulmonary edema, and hyperkalemia were also observed. However, through subset analysis, these were likely related to MH episode itself rather than dantrolene therapy. [9]

Our patient had a high fever but no evidence of a hypermetabolic state either by physical exam or laboratory evaluation and the treating team ruled out MH. Positive PCR tests for human metapneumovirus and rhinovirus/enterovirus, complete resolution of symptoms within 24 h helped us to avoid the MH susceptible label to our patient.

CONCLUSION

Hyperthermia in the postoperative period has a long list of differential diagnoses. It is important to rule out MH by clinical assessment and laboratory investigations.

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Conflicts of interest
There are no conflicts of interest.

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