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Letter to Editor

Unusual presentation of G6PD deficiency with isolated hyperthermia: Anesthetic management and key insights

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Dear Editor

Glucose-6-phosphate dehydrogenase (G6PD) insufficiency is an X- linked genetic disorder and the most prevalent enzyme deficiency in humans worldwide. Haemolytic anaemia develops in these people when they are subjected to oxidative stressors, such as infections, fava beans, surgical stress, or the use of specific medications. This case highlights an unusual presentation of G6PD patient, with isolated hyperthermia that lacks the expected symptoms & signs which were insufficient to fulfil the criteria of the differential diagnosis of oxidative stress due to anaesthetic drugs or malignant hyperthermia.

A 4-year-old male child, diagnosed with G6PD deficiency and Autism spectrum disorder (ASD), presented with a complaint of swelling in the lower right molar teeth for the past 4-5 days and was scheduled for pulpectomy and full mouth rehabilitation. A detailed pre-operative history was taken, along with a general and systemic examination, keeping in mind the patient's consent, cooperation, anxiety levels, and the history of febrile seizures for better planning of pre-medication. The examination was unremarkable except for heightened anxiety. The child's past history included neonatal jaundice on day 3 of life, which was managed with exchange transfusion, and seizures on day 3 of life, for which the child was admitted to the NICU for 10 days. During this stay, further investigations led to the diagnosis of G6PD deficiency. Since then, there has been no history of anti-epileptic medications. Currently, the child has no signs of haematuria, pallor, or icterus, and lab values, including CBC, LFT, and reticulocyte count, were within normal limits, ruling out active haemolytic anaemia. Given the child's medical background, special care was taken in selecting medications and planning the dental procedures, particularly considering the risks associated with G6PD deficiency and ensuring anxiety levels are appropriately managed.

The patient was premedicated in the pre-operative area with Injection midazolam 0.1 mg/kg and injection Glycopyrrolate 10 mcg/kg and was shifted to the operation theatre with written informed consent from the parents. ASA standard monitors, including pulse oximetry, NIBP, ECG and skin temperature were attached. Patient was preoxygenated with FiO_2 of 1.0 at 6 LPM Fresh gas flow till ETO_2 is > 90%. Standard IV induction was done with Injection Fentanyl 2mcg/kg and Injection propofol 2mg/kg, after confirming that mask ventilation was easy and possible, muscle relaxation was achieved with Injection atracurium 8 mg.

The patient was intubated orally with an uncuffed PVC endotracheal tube (ETT) of size 5 fixed at 15 cm and position was confirmed with 5-point auscultation and consecutive square waveform capnograms. An oropharyngeal pack was

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placed. Intraoperative anaesthesia was maintained with Inhalational Sevoflurane (2.5%) in oxygen with FiO_2 of 0.6 with Nitrous oxide a maintaining MAC of around 1.0. Ventilation was switched to VCV mode (V_T=110ml, RR=16/min, FiO_2-0.6, PEEP= 4cmH_2O) with baseline $ETCO_2$ 35-40 mmHg. Another IV access secured for anticipated blood loss and the patient was catheterized because of prolonged surgery, monitoring of urine output and haematuria. Injection Paracetamol given as a part of pre-emtive analgesia 15 mg/kg after induction. Pre-operative skin temperature was 37.1°C and decreased 25 minutes after induction to 36.4°C. Patient was covered with forced air warmer blanket with a set temperature of 37.5°C. Almost an hour after starting of surgery temperature started rising from 36.2 to 38°. We immediately turned off air warmer and replace warm fluids with cold IV fluids. All possible causes of oxidative stress taken into consideration inadequate depth of anaesthesia, pain, fever, hypoxia, hypovolemia, electrolyte disturbance, ETT kinking etc.; were checked but temperature continued to rise throughout surgery till 39.5°C (**Figure 1**). $ETCO_2$ was also started rising, the highest value being 50 cm H_2O. Close monitoring for haematuria was done, sample ABG, electrolyte were sent and result was within normal limits. On completion of the surgery of 5 hours, extra drapes sheets were taken off, cold sponging was started. For post-operative analgesia, infra-orbital nerve block, anterior-superior, middle alveolar nerve block was given with 0.125% bupivacaine. The patient was reversed with Injection Glycopyrrolate 10 mcg/kg and Injection Neostigmine 50 mcg/kg and the trachea was extubated (before extubation temperature was 39.9°C). Temperature started decreasing slowly from 40 to 39°C with cold sponging. The patient was shifted to recovery and cold sponging was continued. The fever subsided after 1 hour 30 min, and relevant tests like CBC, urine for haematuria, myoglobin, creatinine and CK-MB were sent and all are within normal limits. The patient was followed post-operatively for 72 hours was watchful for any sign of oxidative stress and discharged on 4th postoperative day. He came for a follow-up in OPD after a month, with good signs of improvement and no signs of late haemolysis.

Figure 1: Images from monitor showing intra-operative rise in temperature over few minutes without a significant change in other parameters

G6PD enzyme catalyses the first step in the Pentose Phosphate Pathway (PPP) or Hexose monophosphate pathway shunt, which is a rate-limiting step, that reduces $NADP^+$ to NADPH, which is necessary to keep Glutathione in its reduced form. Glutathione has potent antioxidant activity and protects the cells from free radical injury and oxidative stress. Though there are multiple pathways, it is the only possible way for RBCs, as RBCs are devoid of nuclei. In G6PD patients, any triggers like Infection, Surgical stress, fava beans, certain drugs (**Table 1**) can lead to oxidative stress with resultant haemolytic crisis.

Table 1: List of drugs which can be safely, controversially discussed about safety (Safe in normal therapeutic doses), and unsafe[3]

Safe	Controversial	Unsafe
Acetaminophen (Paracetamol) in class 2 and 3)	Alfentanil Ascorbic acid Aspirin (low dose) Chloramphenicol Fentanyl Glibenclamide Isoflurane Isoniazid Metamizole Midazolam Nitroprusside Paracetamol Penicillin Prilocaine Remifentanil Sevoflurane Streptomycin Trimethoprim	Acetanilid Acetazolamide (Diamox®) Aspirin (high dose) Co-Trimoxazole* Dapsone Diclofenac Diazepam Gentamicin Lidocaine Methylene blue Metoclopramide Naphthalene Nitrofurantoin Sodium Nitroprusside Penicillin Phenazopyridine Prilocaine, e.g. EMLA® cream Primaquine/ Pamaquine Quinolone antibiotics, e.g. Nalidixic acid, Ciprofloxacin* Rasburicase
Amikacin		
Bupivacaine		
Chloroquine		
Clopidogrel		
Glycopyrrolate		
Halothane		
Heparin		
Ibuprofen		
Ketamine		
Mannitol		
N2O		
Neostigmine		
Parecoxib		
Pethidine		
Phenytoin		
Propofol		
Rocuronium		
Succinylcholine		
Sufentanyl		
Thiopental		

G6PD deficiency patients are categorized into five classes based on the severity of enzyme deficiency. Classes 1 and 2 represent the most severe forms, with Class 1 being associated with chronic haemolytic anaemia and Class 2 with intermittent acute hemolysis. Class 3 is considered moderate, while Classes 4 and 5 are benign, having negligible clinical significance. Our patient belongs to Class 3, indicating a moderate form of G6PD deficiency. Preoperative evaluation involves a detailed history and examination, including an inquiry into neonatal jaundice, previous episodes of haemolytic anaemia, and any history of blood transfusions. Laboratory investigations, including CBC, ALP,

haptoglobin, lactate dehydrogenase, total and unconjugated bilirubin, and reticulocytes, should be performed along with any routine or specific tests relevant to the case. It is essential to rule out any active haemolytic state before proceeding with elective procedures. Additionally, it is recommended to include a list of contraindicated drugs in the patient's medical file to prevent the use of medications that could trigger haemolysis.[1]

The goals of anaesthetic management should be minimizing triggers of oxidative stress, monitoring and treating haemolysis[2] Triggering factors includes fava beans, infections, metabolic conditions such as diabetic ketoacidosis, metabolic acidosis, hyperglycaemia, hypoglycaemia, hypothermia and certain drugs reported previously. Therefore, these patients should have first priority in operation theatres, reduce preoperative stress, strict asepsis and antibiotic prophylaxis, aggressive treatment of hyperglycemia peri-operatively and close temperature control (air warming blankets), effective analgesia management intraoperatively and post- operatively.

The use of few drugs like Midazolam, Paracetamol, and Sevoflurane remains controversial as these have an inhibitory action on NADPH in vivo studies. Still, many cases were reported with no complications or side effects after using those drugs.[2-4] So, we also believe that these drugs are safe to use provided in class 2 and 3 of G-6 PD cases. Lidocaine and prilocaine are not recommended but Bupivacaine is safe to use for regional anaesthesia and nerve blocks for perioperative pain management.[3]

Other than routine monitoring, patients with G6PD deficiency require additional vigilance for potential triggers, such as monitoring for acidosis via ABG, blood sugar levels, and tracking excreted urine for hemoglobinuria during the intra-operative period. Hypothermia is a known trigger for haemolysis in G6PD patients, and given that our patient was a child, we implemented measures to prevent hypothermia, including the use of air-warming blankets and fluid warmers. However, when the patient's temperature began rising noticeably, we suspected malignant hyperthermia (MH). In response, we replaced warm fluids with room-temperature fluids, turned off the air warmer, sent ABG and electrolyte samples for intra-operative analysis, removed the surgical drapes, and performed cold sponging once the surgery was concluded. Singh et al. reported a case involving a 33-year-old male with G6PD deficiency and multiple episodes of severe rhabdomyolysis.[5] Malignant hyperthermia susceptibility (MHS) remains one of the differential diagnosis, with a single case report.[6] The Caffeine Halothane Contracture Test (CCT) is the gold standard for diagnosing MH but has limitations, such as being available only at certain centres and being costly. Molecular genetic testing is often used as a first-line diagnostic tool, especially in families with a known RYR1 mutation.[7] Any family history of MH or prior exposure to triggering anaesthetics is important to note.

In our case, the isolated intra-operative hyperthermia, along with a modest increase in $ETCO_2$, presented an unusual pattern as it did not meet the criteria for oxidative stress or malignant hyperthermia (MH). Since ABG did not show signs of metabolic acidosis or hyperkalaemia, and there were no symptoms of trismus, haematuria, or abnormal lab results such as myoglobin and CK-MB levels, the differential diagnosis of oxidative stress and MH was ruled out. It is worth noting that in MH, a rise in $ETCO_2$ is an early sign, while a temperature increase is typically a late manifestation. Therefore, we managed the patient conservatively with cold sponging, replacing warm fluids with room temperature fluids, removing extra drapes, and providing postoperative analgesia through regional blocks.

Patients with G6PD deficiency who are exposed to triggers often develop signs and symptoms of haemolysis within 24 to 72 hours after exposure.[8] Early signs of haemolysis include cola-coloured or dark urine, pallor, jaundice, fatigue, and tachycardia. Monitoring for a haemolytic crisis and performing laboratory workups are essential in the postoperative period. The treatment for haemolysis involves removing the triggering agent and providing symptomatic management. In our case, all postoperative investigations were within normal limits.

Avoiding oxidative stress and detecting and monitoring haemolysis are key strategies for the successful anaesthetic management of such patients. Given the potential for atypical presentations, a comprehensive understanding of the disease pathophysiology and its differential diagnosis is essential. Anaesthesiologists can effectively mitigate risks and promote optimal patient outcomes by adhering to these principles. This highlights the importance of avoiding triggering agents, vigilant monitoring, and prompt treatment of complications with supportive therapy, antibiotics, effective analgesia, anxiolysis in the peri-operative period.

1. Conflict of Interest

None.

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