Dental Treatment Considerations in Patients With RyR-1 Related Myopathies

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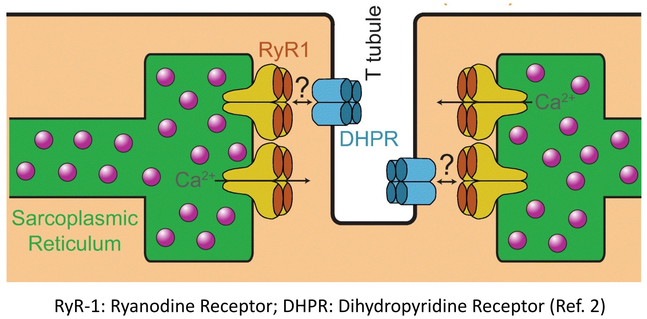
Kids deserve the best.

Ryanodine Receptor-1 Related Myopathy (RyR-1)

Ryanodine Receptor-1 Related Myopathies (RyR1-RM) are a group of skeletal muscle disorders resulting in the most common cause of congenital muscle weakness.
RYR-1 related myopathies are caused by a mutation in the Ryanodine receptors, which act as a gatekeeper for calcium channels in the sarcoplasmic reticulum of skeletal muscle cells. RyR-1 variants can prevent normal calcium release and impair excitation-contraction coupling in skeletal muscles, resulting in myopathy.



RyR-1: Ryanodine Receptor; DHPR: Dihydropyridine Receptor (Ref. 2)

Inheritance:
RYR-1 myopathies can be inherited as autosomal dominant, autosomal recessive or de novo variations. These myopathies are rare and classified as an orphan disease, with an estimated prevalence of 1:90,000 in the US.
Diagnosis:
Genetic testing and muscle biopsy provide most definitive diagnosis.
Treatment:
Currently there are no treatments or cures for RYR-1, and management is based on severity of symptoms.

Clinical Features

A range of symptoms → from almost undetectable to potentially lethal

- Generalized muscle weakness including facial muscles, muscles of respiration, arms and legs
- Long and narrow face, drooping eyelids (ptosis)
- Delays in sitting, walking, running
- Muscle wasting, muscle fatigue and cramps
- Breathing difficulties including sleep apnea
- Malignant hyperthermia
- Rhabdomyolysis

Life expectancy is generally normal in affected individuals and cognitive development is unaffected.

Malignant Hyperthermia (MH)

RYR-1 gene mutations are the most common genetic risk factor for malignant hyperthermia (accounting for >60% of cases).
MH is a potentially fatal reaction which occurs in susceptible individuals following exposure to volatile anesthetics or depolarizing muscle relaxants which trigger a rapid increase in body temperature (hyperthermia) and muscle breakdown (rhabdomyolysis).
MH can result in kidney failure, brain damage, cardiac arrest, failure of additional organs or death.

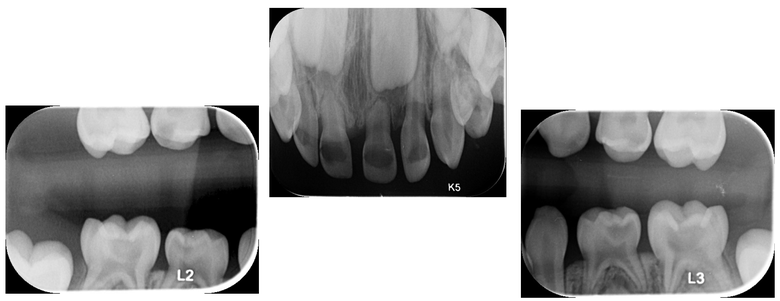
Local anesthesia and nitrous oxide are non-triggering agents for MH.
The emergency treatment drug for MH is Dantrolene.

Patient Presentation at CW Dental Clinic

A 4-year-old male with a rare form of RyR-1 related myopathy presented to Children's Wisconsin Dental Center for routine dental care.
Medical History included Central Core Disease (sub-type of RyR-1 myopathy with weak core muscles and diminished cough reflex), lymphatic malformations, arthrogryposis, dysphagia, obesity and obstructive sleep apnea.
Pertinent Dental History included a cariogenic diet, night-time milk habit (2-3 bottles per night) and recent discontinuation of pacifier habit.
Social History: spends time between both parents' homes.

Clinical and Radiographic Examination revealed :

- Generalized mild gingivitis
- Severe early childhood caries (S-ECC)
- Anterior open-bite (4mm)
- No clinical signs of infection present & parent reports intermittent, mild pain



Behavior: Anxious, required active immobilization for radiographs (papoose contraindicated due to lymphatic malformation)

Treatment Plan:
Given patient's medical complexity, young age, extensive treatment needs and multiple co-morbidities including hypotonia, dysphagia, aspiration risk, obesity and sleep apnea, **dental rehabilitation under general anesthesia was planned.**
Interim measures such as SDF were offered however family declined due to esthetic concerns as well as preference for definitive treatment.

Barriers to Care

Medical complexity and a complicated social situation presented multiple barriers to timely care. Family expressed concerns related to potential complications with general anesthesia, as well as the natural progression of RYR-1 related myopathy and ultimate impact on patient's quality of life given life expectancy.

Consultations and Considerations for Care

June 2021	• Patient presents to CW Dental Clinic for Periodic Exam, Prophylaxis and Radiographs (previous visit was 2 years ago) • Treatment planned under GA • Consultations completed with Neuromuscular Medicine & Anesthesia: "OK to proceed with MH precautions"
August 2021	• Pre-op visit with PMD; chest x-ray recommended
September 2021	• Anesthesia Pre-op visit completed. ASA 3, STBUR score: 5 • Recommended Sleep Medicine evaluation • Dental OR postponed
November 2021	• Non-compliance with Sleep Medicine and Neuromuscular Medicine referrals • Dental OR postponed
February 2021	• Neuromuscular Medicine: "OK to proceed with MH precautions" • Sleep Medicine visit: recommend sleep study; Brodsky 4+ • Sleep study aborted due to patient/family request • Pulmonology consultation: "OK to proceed with precautions; recommend overnight ICU stay post-operatively"
April 2021	• Social work consultation to assess for barriers to care • Dental OR scheduled: "Patient complains of nocturnal pain" • Pre-op Anesthesia and PMD visits • Dental OR postponed due to current URI + bilateral otitis media
June 2021	• Dental OR scheduled

General Anesthesia Recommendations

Given MH susceptibility, volatile anesthetic gases (sevoflurane, desflurane, isoflurane, halothane, enflurane) and depolarizing muscle relaxants (succinylcholine) are contraindicated for use.
Non-MH triggering agents such as Propofol are useful for general anesthesia in susceptible patients.
Parents strongly prefer to avoid Propofol due to previous adverse events. In this situation, oral Versed and Ketamine are recommended along with Dexmeditomidine and Remifentanil infusion for induction and maintenance of general anesthesia.
Overnight hospital stay is recommended for post-operative monitoring.

References:

1. RYR-1 Related Diseases. Rare Disease Database. National Organization for Rare Diseases (NORD)
2. Shishmarev D. Excitation-contraction coupling in skeletal muscle: recent progress and unanswered questions. Biophys Rev, 12: 143-153 (2020)
3. Clinical Care Guidelines: what patients and families need to know about Ryr-1 related diseases. RYR-1 Foundation.