Genetic Disorders of Anesthetic Importance

1st Course
Lecture : 6

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Learning Objectives

- By the end of this lecture, students should be able to:

1. Recognize the role of genetics in anesthesia.
2. Identify major inherited disorders affecting anesthetic management.
3. Understand mechanisms, risks, and prevention of complications.
4. Apply safe anesthesia practice in genetically susceptible patients.

Introduction

Genetic disorders can influence how patients respond to anesthetic agents.
Some defects alter enzyme function, muscle physiology, or drug metabolism — leading to life-threatening reactions if unrecognized.

Classification of Genetic Diseases

1. **Single-gene disorders** (Mendelian)
2. **Chromosomal disorders**
3. **Multifactorial disorders**
4. **Mitochondrial disorders**

➢ Mitochondrial Disorders

- Caused by mutations in mitochondrial DNA (mtDNA).

Only transmitted from the mother.

Common features: muscle weakness, neurological defects.

Why Genetics Matters in Anesthesia?

1. Explains unusual drug reactions.
2. Helps predict complications.
3. Supports personalized anesthetic plans.
4. Improves patient safety.

Basic Concepts

1. **Gene mutation:**

   Permanent change in DNA sequence.

2. **Inheritance:**

   Transmission of traits from parents to offspring.

3. **Pharmacogenetics:**

   Study of how genetic variations affect drug response.

Types of Gene Mutations

1. **Point mutation**
2. **Deletion**
3. **Insertion**
4. **Duplication**
5. **Frameshift mutation**

Patterns of Inheritance

1. **Autosomal dominant**
2. **Autosomal recessive**
3. **X-linked dominant**
4. **X-linked recessive**
5. **Mitochondrial**

Autosomal Dominant Disorders

- Only one copy of the abnormal gene is needed to cause disease.

Examples:

1. Marfan syndrome
2. Huntington’s disease
3. Familial hypercholesterolemia

Autosomal Recessive Disorders

- Two abnormal copies required for expression.

Parents are usually carriers.

Examples:

1. Cystic fibrosis
2. Sickle cell anemia
3. PKU

X-Linked Disorders

- Gene located on the X chromosome.

Males are more affected.

Examples:

1. Hemophilia A
2. Duchenne muscular dystrophy

Pharmacogenetics in Anesthesia

Differences in drug-metabolizing enzymes (like CYP450, pseudocholinesterase) can cause:

1. Delayed recovery from anesthesia.
2. Unusual drug sensitivity or resistance.
3. Unexpected toxicity.

Diagnosis of Genetic Diseases

1. Family history
2. Genetic counseling
3. Karyotyping
4. DNA sequencing
5. Prenatal testing (amniocentesis, chorionic villus sampling)

Importance of Genetic Knowledge in Anesthesia

1. Some genetic diseases alter drug response
2. Certain mutations increase risk of complications during anesthesia
3. Genetic screening can prevent anesthesia-related deaths

Malignant Hyperthermia (MH) – Overview

- A life-threatening hypermetabolic reaction to certain anesthetic agents.
- **Inheritance:** Autosomal dominant.
- **Gene:** RYR1 mutation affecting skeletal muscle calcium release.

Pathophysiology

- Mutation → uncontrolled Ca^{2+} release from sarcoplasmic reticulum → sustained muscle contraction, heat production, and acidosis.
- **MH – Triggers**
- Volatile anesthetic gases (halothane, sevoflurane, desflurane).
- Depolarizing muscle relaxant (succinylcholine).

Clinical Features

1. Sudden rise in body temperature (> 40°C)
2. Muscle rigidity (especially jaw)
3. Tachycardia, tachypnea
4. Hypercapnia (↑ end-tidal CO_2)
5. Acidosis, hyperkalemia, arrhythmia

Management

1. Stop triggering agents immediately.
2. Administer **IV dantrolene sodium** (2.5 mg/kg).
3. Cool the patient, correct acidosis, monitor urine output.
4. Inform family — genetic testing is recommended.

Pseudocholinesterase Deficiency

Overview

- Inherited enzyme deficiency causing prolonged apnea after succinylcholine administration.
  Inheritance:
  Autosomal recessive.

Mechanism

- Lack of plasma cholinesterase → inability to hydrolyze succinylcholine → prolonged neuromuscular blockade → delayed recovery

Pseudocholinesterase Deficiency

Management

1. Avoid succinylcholine and mivacurium.
2. Use non-depolarizing relaxants (e.g., atracurium).
3. Provide mechanical ventilation until recovery.
4. Family testing may be indicated.

Acute Intermittent Porphyria (AIP)

- Overview

Inherited enzyme defect in heme synthesis.

Inheritance:

Autosomal dominant.

Triggered by certain drugs or stress

- Clinical Features

1. Severe abdominal pain
2. Tachycardia, hypertension
3. Peripheral neuropathy, seizures
4. Dark urine

AIP – Anesthetic Precautions

- **Avoid:**

barbiturates, sulfonamides, etomidate, steroids.

Safe:

- propofol, opioids, volatile agents (halothane, isoflurane).
  Maintain carbohydrate intake and hydration.

Methemoglobinemia

Overview

- Excess oxidation of hemoglobin to methemoglobin → reduced oxygen delivery.
  May be **congenital (genetic)** or **acquired (drugs)**.

Clinical Signs

1. Cyanosis unresponsive to oxygen
2. Chocolate-colored blood
3. Low oxygen saturation despite normal PaO_2

- **Treatment:**
  - **Methylene blue 1–2 mg/kg IV** (if not G6PD deficient).

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

- **Inheritance:**

X-linked recessive.
Red blood cells lack protection against oxidative stress → hemolysis.

- **Anesthetic Considerations:**
- **Avoid oxidative drugs:**

1. Sulfa drugs
2. Prilocaine, lidocaine in large doses
3. Methylene blue (can worsen hemolysis)

Use safe agents:

- propofol, sevoflurane, fentanyl.

Duchenne Muscular Dystrophy (DMD)

- X-linked disorder causing progressive muscle weakness.

Risk:

cardiac and respiratory failure during anesthesia.

Avoid succinylcholine and volatile agents (risk of hyperkalemia and rhabdomyolysis).

Mitochondrial Myopathies

- Inherited defects in mitochondrial oxidative metabolism.
  Patients may show poor tolerance to propofol and muscle relaxants.
  Use short-acting agents and monitor oxygenation closely.

Propofol Infusion Syndrome (PRIS)

- Rare but fatal complication in genetically or metabolically susceptible patients.

Features:

metabolic acidosis, rhabdomyolysis, cardiac failure.

Prevention:

avoid prolonged high-dose propofol infusions.

Pharmacogenetic Variations in Drug Metabolism

- Examples:

1. **CYP2D6** polymorphism → altered opioid effect (codeine, tramadol).
2. **NAT2** variation → variable response to local anesthetics.
3. **CYP2C9/CYP3A4** → altered metabolism of midazolam, diazepam.

Pre-operative Evaluation

1. Detailed family history of anesthesia complications.
2. Previous prolonged apnea or fever after surgery.
3. Screening tests for suspected conditions (e.g., caffeine–halothane test for MH).

Prevention and Genetic Testing

1. Genetic counseling for affected families.
2. Document all adverse reactions.
3. Use anesthesia alert cards or bracelets.
4. Choose safe alternative drugs.