- FVL is resistant to inactivation by APC so thrombin generation is allowed to continue and subsequent clot formation.
- FVL paradox describes the higher prevalence of FVL in pts with DVT compared with FVL pts with pulmonary embolism.
- In CPB, FVL pts found to have less blood loss and need less blood transfusion during hospital stay.
- Testing in FVL is the same as other causes of thrombophilia: Venous thrombosis and age <50 y; unusual sites of thrombosis (hepatic, mesenteric, cerebral); recurrent venous thrombosis; venous thrombosis with strong history of thrombotic disease, venous thrombosis in pregnant women taking oral contraceptives, relatives of pts who had venous thrombosis <50 y, MI in female smokers <50 y.
- Screening test: Modified APC resistance functional assay (sensitivity and specificity for FVL close to 100%).
- Confirmation test: DNA test. In liver transplant pts, DNA test positive, plasma FVL negative. In bone marrow transplant pts, DNA test negative, but plasma shows APC resistance.

## Etiology

- SNP 1691 G >A on factor V gene that predicts a single amino acid substitution Arg >Gln.
- The mutated factor V protein is resistant to inactivation by APC.

## Usual Treatment

- Treat acute thrombosis event according to standard guidelines.
- Long-term anticoagulation not recommended for heterozygotes if no prior thrombosis.
- Prophylactic anticoagulation (heparin, warfarin) considered for high-risk clinical setting.
- Newer oral anticoagulants (dabigatran [Pradaxa], rivaroxaban [Xarelto], apixaban [Eliquis]) may be considered for prophylaxis.
- Consider minimizing other risk factors for VTE: Stopping oral contraceptives (progesterone) in women with VTE, encouraging obese pts to lose weight, and minimize extended travel.

## Assessment Points

| System | Effect | Assessment by Hx | PE | Test |
|---|---|---|---|---|
| CNS | Cerebral vein thrombosis | Headache<br>Abnormal vision<br>Seizures | Stroke signs, weakness | CT/MRI with contrast |
| RESP | Pulm embolus | Chest pain<br>Shortness of breath | Tachypnea | ABG, CXR, CT scan |
| HEME | Thrombosis | Pain at site of thrombosis | | Prolonged aPTT, PTT |
| GU | Renal vein thrombosis | Flank or lower back pain | Hematuria, oliguria | Ultrasound, CT scan |
| MS | DVT most common<br>Upper extremity thrombosis | Calf pain | Calf pain with DVT | Venography, compression ultrasound of legs |
| OB | Miscarriage<br>Postpartum thrombosis | Bleeding, spotting | | Ultrasound, FHR (Doppler) |

**Key References:** Kujovich JL: Factor V Leiden thrombophilia, *Genet Med* 13(1):1–16, 2011; Van Cott EM, Khor B, Zehnder JL: Factor V Leiden, *Am J Hematol* 91(1):46–49, 2016.

## Perioperative Implications

### Preoperative Preparation

- Preop screening not recommended if asymptomatic.
- Anticoagulation should follow standard guidelines.
- In FVL heterozygotes, risk of bleed from warfarin is greater (1–3%) than risk of thrombosis (<1%).
- Avoid CVC if possible. FVL heterozygotes have twofold to threefold increase in CVC-related thrombosis.
- Sequential compression devices may decrease incidence of DVT.
- Consider consultation with hematology; may require temporary treatment with anticoagulation during periods of high-risk settings: surgery, cast, immobilization, pregnancy, etc.

### Monitoring

- If arterial line indicated, use cautiously in homozygous pts.

### Airway/Induction/Maintenance/Extubation

- No special precautions

### Postoperative Period

- Standard anticoagulation protocols if no prior history of VTE
- Target INR 2.5 effective anticoagulation even in homozygous pts

## Anticipated Problems/Concerns

- No need to alter periop management if asymptomatic.
- Confirmation test is a genetic test, so implications for pt and family members should be discussed.
- Aprotinin, an inhibitor of APC, has been used safely in FVL pts undergoing cardiac surgery without increased risk of thrombosis, although caution is often advised.

# Familial Dysautonomia (Riley-Day Syndrome)

Thomas J. Ebert | Craig E. Cummings

## Risk

- Autosomal recessive transmission
- Complete penetrance, marked variability in expression
- Predominantly affects Ashkenazi Jewish population (incidence 1:10,000–20,000; carrier frequency 1:27-32)

## Perioperative Risks

- Intraop: Primarily cardiovascular with hemodynamic variability
- Postop: Primarily cyclic vomiting and pulmonary complications

## Worry About

- Paroxysmal dysautonomic crisis triggered by physiologic or psychologic stress characterized by intractable vomiting, Htn, tachycardia, diaphoresis, erythematous macular rash
- Resp status compromised by dysfunctional swallowing, leading to repeated aspiration pneumonias, and restrictive lung disease secondary to scoliosis
- QTc prolongation and dysrhythmias, including bradycardia and asystole
- Insensitivity to hypoxemia and hypercarbia, including apnea to mild hypoxia
- Increased sensitivity to acetylcholine and catecholamines

## Overview

- HSAN type III
- Differentiated from other HSAN types by profound autonomic dysfunction, Htn, orthostatic hypotension, and excessive or decreased sweating
- Characterized by recurrent pulmonary infections, esophageal dysmotility, spinal abnormalities, and thermal dysregulation
- High morbidity and mortality, with only 50% of newborns expected to reach age 40 y

## Etiology

- Mutations of gene coding IKBKAP on chromosome 9q31
- Incomplete neuronal development and progressive neuronal degeneration in the peripheral and autonomic nervous systems
- Symptoms due to denervation of peripheral blood vessels and dysfunctional parasympathetic nervous system, baroreceptors, and chemoreceptors

## Usual Treatment

- Dysautonomic crisis: Benzodiazepines are first-line therapy.
- Hemodynamic instability: Managed with hydration and direct-acting vasoactive therapies.

## Assessment Points

| System | Effect | Assessment by Hx | PE | Diagnostic Test |
|---|---|---|---|---|
| CV | Orthostatic hypotension<br>QTc prolongation<br>Arrhythmias | Dizziness, syncope<br>Palpitations | Orthostatic vital signs | Autonomic function ECG |
| RESP | Pneumonia<br>Bronchiectasis<br>Restrictive lung disease | Pleuritic chest pain<br>Productive cough<br>SOB | Abnormal breath sounds,<br>digital clubbing | CXR<br>Pulm function |
| GI | Poor swallowing<br>Aspiration pneumonia | Drooling, vomiting<br>Paroxysmal crisis | | Swallow study |
| GU | Dehydration<br>Glomerulosclerosis | Nocturia, diaphoresis | Dry mucosa, skin turgor | BMP |
| CNS | Seizure<br>Developmental delay | Seizure | | EEG |
| MS | Scoliosis | | Spinal curvature | Plain films |

**Key References:** Ngai J, Kreynin I, Kim JT, et al.: Anesthesia management of familial dysautonomia, *Paediatr Anaesth* 16(6):611–620, 2006; Weingarten TN, Sprung J, Burgher AH: Perioperative management of familial dysautonomia: a systematic review, *Eur Jour Anaesth* 24(4):309–316, 2007.

### Perioperative Implications

**Preoperative Preparation**

- Consider regional or neuraxial anesthesia as primary anesthetic or combined with general anesthesia to improve analgesia; poor thermal discrimination may affect assessment of blocks.
- Diminished laryngeal reflexes and dysphagia leading to abundant secretions: treat with antisialagogues.
- $H_2$ blockers can decrease gastric volume and acidity.
- Prevent dysautonomic crisis with anxiolytics; treat crisis with benzodiazepines or clonidine.
- Avoid medications that interact with the autonomic nervous system.
- Correct chronic dehydration secondary to dysphagia and emesis to reduce intraop hemodynamic instability. Maintenance requirements may be higher due to increased insensible losses from excessive sweating and drooling.
- Minimize narcotics as premedication because of the impaired ventilatory response to hypoxia and hypercarbia.
- Lines can often be placed without sedation given insensitivity to superficial pain.

**Monitoring**

- Standard monitors.
- Arterial line.
- Consider processed EEG monitor.
- Consider noninvasive cardiac output monitoring.

**Induction**

- Rapid sequence induction.
- Titrate induction agents carefully to minimize risk of hypotension.
- Use of nondepolarizing neuromuscular blocking drugs balanced against risk of postop hypotonia and unpredictable effect of reversal agents on the autonomic nervous system.
- Lubricate eyes to avoid corneal abrasions secondary to alacrima and corneal insensitivity.

**Maintenance**

- Consider mechanical ventilation with lung protective strategies, especially with restrictive lung disease.
- Consider total IV anesthesia.
- Titrate volatile anesthetic using processed EEG monitor plus minimum alveolar concentration to minimize autonomic compromise.
- Fluid management and judicious use of direct acting vasopressors and inotropes guided by noninvasive cardiac output monitoring.
- Aggressively treat blood loss.
- Vigilant temperature monitoring and correction.

**Emergence**

- Titrate analgesics for pain control.
- Spontaneous ventilation may be delayed. Chemoreceptor dysfunction makes $PaCO_2$ levels a poor trigger.
- Unpredictable response to reversal agents due to increased sensitivity to acetylcholine.
- Aggressive pulm toilet to decrease atelectasis and bronchiectasis.

**Postoperative Care**

- Multimodal analgesic regimen. Visceral and peritoneal sensations remain intact despite abolishment of peripheral pain sensation.
- Judicious use of opioids given abnormal ventilator response to hypoxia and hypercarbia.
- First-line treatment for cyclic vomiting with benzodiazepines.
- Optimization of resp function with assisted ventilation, deep suctioning, inhalational therapies, and chest physiotherapy.

# Familial Periodic Paralysis

Oliver Bandschapp

### Risk

- Rare; hyperPP approximately 1:200,000 and hypoPP approximately 1:100,000
- HyperPP with childhood onset; hypoPP with teenage onset

### Perioperative Risks

- In hyperPP, succinylcholine may provoke severe myotonia, provide no relaxation, and cause hyperkalemia (resulting postop muscle weakness over days and rhythm disturbances).
- HypoPP associated with supraventricular or conduction defect-type cardiac arrhythmias; weakness may be enhanced by β-adrenergic blocking drugs, and postop resp muscle weakness may occur.
- Hypermetabolic crises (necessitating dantrolene use) reported in hypoPP pts.

### Worry About

- Cold can trigger attack in both types of PP.
- $K^+$ and glucose have opposite effects in the two disorders; in hyperPP, $K^+$ triggers attacks and glucose is cure, whereas in hypoPP, glucose-induced hypokalemia triggers attacks and $K^+$ is cure.
- Cardiac complications (dysrhythmias) due to severe dyskalemia during attack.
- Respiratory insufficiency during attack.

### Overview

- Channel defects in the sarcolemma lead to aberrant depolarization in the presence of dyskalemia, which inactivates sodium channels and renders muscle fibers inexcitable.
- Autosomal dominant conditions; hypoPP with reduced penetrance in females.
- HyperPP with frequent (daily) episodic attacks for minutes (to hours); episodes of weakness generalized, rarely bulbar and resp muscles involved in severe paralysis; hyperkalemia (in approximately 50%) during attacks; triggered by $K^+$ intake, rest after exercise, or cold; often additional EMG myotonia.
- HypoPP with less frequent but more severe episodic attacks for hours (to days); weakness may be focal or generalized, usually sparing facial and resp muscles; invariably hypokalemia during episode; triggered by carbohydrates, cold, stress, specific medications (e.g., beta-agonists, corticosteroids, insulin); no myotonia.
- Fixed proximal weakness often develops with increasing age in both types.

### Etiology

- HyperPP caused by mutations in the voltage-gated sodium channel $Na_v1.4$ gene (*SCN4A*). Mutant channels (inactivation defect) lead to persistent sodium influx and depolarization, muscle membrane becomes inexcitable.
- HypoPP either caused by mutations in the *CACNAS* gene (encodes $\alpha_{1s}$-subunit of dihydropyridine receptor) (type 1 hypoPP) or in approximately 10% by mutations in the *SCN4A* gene (type 2 hypoPP). Introduction of new accessory ion conduction pathways independent of normal conduction pathways, leads to paradoxical membrane depolarization in low potassium conditions causing inexcitability.

### Usual Treatment

- Both types: In case of prodrome keep moving
- HyperPP: Salbutamol spray, glucose, thiazide diuretics, or carbonic anhydrase inhibitors
- HypoPP: $K^+$ salts, carbonic anhydrase inhibitors, or $K^+$-sparing diuretics