Disorder	Hyperkalemic periodic paralysis	Paramytonia congenita	Myotonia Congenita	Familial hypokalemic periodic paralysis	Andersen-Tawil Syndrome
Inheritance	Autosomal dominant	Autosomal dominant.	Autosomal dominant (Thomsen) or recessive (Becker)	Autosomal dominant	Autosomal dominant
Gene and gene locus	SCN4A on 17q23 Sodium channel	SCNA4A on 17q23 Sodium channel	CLCN on 7q35 Chloride channel	CACNL1A3 on 1q32 Calcium channel	Kir 2.1 (KCNJ2) Potassium channel
Symptoms	Generalized attacks of weakness. Weakness may become gradually permanent.	Muscular stiffness at the beginning of exposure to cold. Muscular weakness on prolonged exposure to cold. Paradoxical myotonia = myotonia worsened by exercise	Stiffness with sudden movement after resting.; warm up phenomenon = decreased myotonia with repeated motion; hypertrophied muscles; lid lag;	Generalized attacks of weakness. Weakness may become gradually permanent	Periodic paralysis (hyper or hypo); cardiac arrhythmia (long QT, ventricular arrhythmia, others); dysmorphic features (microcephaly, clinodactyly, low set ears, others)
First occurrence of symptoms	At the end of the first decade or beginning of the second decade	At birth	Thomsen – early childhood; Becker – 10 years old or later	Usually in the second decade	Variable
Frequency of attacks	A few times per year to daily	On every exposure to a cold environment	Daily	Extremely variable: from one to two attacks in a lifetime to daily	Can be daily
Severity of attacks	Occasionally, generalized paralysis. Frequently moderate weakness, often only in single muscle groups	Stiffness and weakness that become more severe the heavier the work in the cold. The lower the temperature, the more severe the weakness	Legs or generalized	Often, generalized paralysis. Sometimes, moderate weakness (e.g., of the arms or legs)	Often ,generalized paralysis
Duration of attacks	Usually ½ - 1 hour, occasionally several hours	Stiffness only at the beginning of work in a cold environment. Weakness may last for hours after re-warming	Seconds to minutes	Several hours to several days	Minutes to hours
Time of day when symptoms appear	Early to late morning. Occasionally at any time of day	At any time when exposed to cold environment	Any time, esp. after rest	Second half of night. Early morning. Occasionally, late morning.	Any time
Triggering factors	Muscular exercise with subsequent rest (attack 20 – 30 minutes later). Cold. Hunger	Cooling and heavy muscular work, particularly in combination	Sudden noise; forceful movement after rest	Muscle exercise with subsequent rest (attack follows several hours later) Carbohydrate-rich meals. Stress. Cold.	Rest after exercise; carbohydrates; cold
Diagnostic provocation	Muscular exercise (ergometer or running upstairs). Administration of K+	Cooling of lower arm for 30 minutes in water of 12 – 15^{o}C Repeated forceful closure of the fist	Exercise after rest; stair test: rest for 10 minutes in a chair, then climb 10 steps as fast as possible (normal 3 sec., myotonia 30 sec)	Administration of glucose with or without insulin (caution). Muscle exercise and carbohydrate-rich food the evening before the test	Muscular exercise.
Concomitant symptoms at the beginning of an attack	Myotonia, when present, increased. Cases without myotonia might present lid lag. Paresthesias common	Sensations of tension in the muscle	Muscle pain, sometimes	No myotonia. No sensory disturbance. Sometimes, paresthesias	Paresthesias, muscle discomfort
K+ in the serum during an attack	4.5 – 8.0 mM	3.5 – 4.5 mM	3.5 – 5.0 mM (i.e., normal)	2 – 3 mM	Variable (low, normal, or high)
Therapy	Preventive: frequent meals, acetazolamide,	Preventive: keeping the muscles warm, mexiletine. No	Behavior modification; Mexiletine	Preventive: acetazolamide, dichlorophenamide,	Preventative: acetazolamide; dichlorphenamide;

	dihydrochlorithiacide At the beginning of attack: movement, salbutamol spray, injection of calcium gloconate	therapeutic action known for relief of weakness		spironolactine, low-sodium diet. During an attack: continued muscle use can blunt severity of attack, potassium tablets.	depends on associated type of periodic paralysis; +/- pacemaker/defibrillator

While "classical" descriptions of the diseases are found here, individuals commonly can display a wide range of "non-textbook" signs and symptoms.

Disorders:

Familial (aka Primary) Hypokalemic Periodic Paralysis:

presentation: episodic weakness, lasts for minutes to hours

triggers: rest after exercise, high carbohydrate meals, salt

treatment acutely: potassium (orally when possible)

treatment chronically: acetazolamide, dichlorphenamide, eplerenone, spironolactone, triamterene, behavioral modification

Thyrotoxic Hypokalemic Periodic Paralysis:

presentation: episodic weakness, lasts for minutes to hours

triggers: rest after exercise, high carbohydrate meals

treatment acutely: potassium (orally when possible)

treatment chronically: treat hyperthyroidism (often with thyroid ablation); propranalol

Andersen Tawil Syndrome:

presentation: episodic weakness, lasts for minutes to hours; arrhythmia (long QT interval, ventricular arrhythmia, others); dysmorphic features (microcephaly, clinodactyly, low set ears, others)

triggers: rest after exercise, high carbohydrate meals, salt

treatment acutely: potassium normalization (i.e., potassium for hypokalemia, sugar for hyperkalemia)

treatment chronically: acetazolamide, dichlorphenamide, spironolactone, sometimes beta-blockers or pacemaker for heart arrhythmia

Hyperkalemic Periodic Paralysis:

presentation: episodic weakness, lasts for minutes

triggers: rest after exercise, fasting

treatment acutely: sugar ingestion, albuterol, insulin and glucose, calcium gluconate; some experts feel that there is no role for a potassium binding resin (Kayexalate)

treatment chronically: potassium wasting diuretics, such as hydrochlorothiazide, furosemide

Hyperkalemic Periodic Paralysis with Paramyotonia Congenita:

presentation: episodic weakness preceded by stiffness

triggers: rest after exercise, fasting, cold

treatment acutely: sugar ingestion, albuterol, insulin and glucose, calcium gluconate; muscle rewarming; some experts feel that there is no role for a potassium binding resin (Kayexalate)

treatment chronically: potassium wasting diuretics, such as hydrochlorothiazide, furosemide; rarely, mexiletine

Paramyotonia Congenita:

presentation: episodic stiffness that INCREASES with repeated exercise

triggers: cold

treatment acutely: muscle rewarming

treatment chronically: mexiletine

Myotonia Congenita:

presentation: episodic stiffness that DECREASES with repeated exercise

triggers: exercise after rest; sudden noise

treatment acutely: muscle “warm up”

treatment chronically: mexiletine, sometimes

Some Drugs Used in Ion Channelopathies:

Diuretics: agents that cause the kidney to excrete water, often causing salt wasting. Some diuretics spare potassium (i.e., keep potassium in the blood), while others waste potassium (i.e., cause potassium to be spilled into the urine).

Potassium-Sparing Diuretics:

Spironolactone (Aldactone): causes loss of sodium, and thus water, while conserving potassium (blocks aldosterone); *side effects*: breast tenderness in women, gynecomastia (breast enlargement) in men; do not combine with triamterene (two deaths reported)

Epleronone (Inspra): causes loss of sodium, and thus water, while conserving potassium (blocks aldosterone); less side effects than spironolactone; do not combine with triamterene

Triamterene (Dyrenium): causes loss of sodium, and thus water, while conserving potassium (works directly on the kidney); *side effects*: avoid non-steroidal anti-inflammatory drugs (such as indomethacin), can worsen gout; do not combine with spironolactone (two deaths reported)

Amiloride (Midamor): causes mild loss of sodium while conserving potassium

Potassium-Wasting Diuretics:

Acetazolamide (Diamox): for hyperkalemic periodic paralysis, felt to work by wasting potassium; for hypokalemic periodic paralysis, felt to work by making the blood more acidic. When the blood is acidic, it has a lot of hydrogen ions (H+). The muscle buffers excess H+ by absorbing it into muscle. The muscle spits out potassium ions (K+) to the blood in exchange (so that too much + charge does not build up in the muscle).

Dichlorphenamide (Daranide): about five times more potent than acetazolamide, felt to work the same way as acetazolamide

Hydrochlorothiazide (Microzide; Hydrodiuril): a water pill used to waste potassium; *side effects*: lowers blood pressure; does not waste calcium; can increase uric acid and make gout worse

Furosemide (Lasix): a water pill used to waste potassium; *side effects*: low blood pressure; low magnesium; wastes calcium too, so osteoporosis with long term use can be a problem

Other agents:

Potassium Chloride (Klor-Con; K-Dur; others): many forms and types, taken to raise potassium in the blood quickly in the face of attacks of hypokalemic periodic paralysis; some use sustained release preparations for blood level maintenance; *side effects*: diarrhea; stomach upset; stomach lining irritation and ulcer formation

Mexiletine (Mexitil): a heart rhythm drug that acts on sodium channels and helps to prevent myotonia

Clonazepam (Klonopin): a muscle relaxant that may help relieve spasms and myotonia in select cases

Calcium Gluconate Injection: stabilizes heart rhythm in the face of high potassium

Albuterol (Proventil): a "cousin" of epinephrine, it serves to drive potassium from the blood to the muscle by stimulating the Na/K pump

Potassium binding resin (Kayexelate): given as a rectal suppository, absorbs potassium from the gut