Updates in Skeletal Muscle Channelopathies

MDA® Muscular Dystrophy Association

Updates in Skeletal Muscle Channelopathies

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Program Agenda and Objectives

Overview & Diagnostic Approaches

- Recognize symptoms
- Use of laboratory and genetic testing to accurately diagnose ion channel diseases involving muscle

Treatments & Management

- Review evidence-based guidelines and best practices to coordinate care
- Explore current management of patients with ion channel diseases

Resources

- Identify additional tools and resources

Overview of Skeletal Muscle Channelopathies

Etiology

- Inherited mutations in genes coding for ion channels[1,2]

Classification

- Non-dystrophic myotonias[1,2]
- Periodic paralyses[1,2]

Epidemiology: rare diseases

- All channelopathies[1]: 1.12/100,000
- Non-dystrophic myotonia[1]
  - From 0.06 (Na channel myotonia) to 0.52 (myotonia congenita) per 100,000
- Periodic paralysis[2]
  - 1/100,000 (hypokalemic)
  - 1/200,000 (hyperkalemic)
  - 1/1,000,000 (Andersen-Tawil syndrome)

Clinical symptoms

- Fluctuating symptoms including muscle stiffness, spasms, and intermittent weakness with intervening normalcy[2]
  - Relatively common symptoms in the population
  - Need to recognize definite cases
- QoL impacted by muscular symptoms, pain, and fatigue[3,4]
- Normal life expectancy with some exceptions[4]
- Occasionally other acquired and genetic diseases can lead to a similar phenotype[5]

QoL, quality of life.

1. Horga A, et al. *Neurology*. 2013;80(16):1472-1475. 2. Sansone VA. *Continuum (Minneap Minn)*. 2019;25(6):1696-1711. 3. Phillips L, Trivedi JR. *Neurotherapeutics*. 2018;15(4):954-965. 4. Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444. 5. Matthews E, et al. *Pract Neurol*. 2021;21(3):196-205.

Classification – Genotype/Phenotype

	Phenotypes	Genotypes
Non-dystrophic myotonia[1,2]	Myotonia congenita	*CLCN1* mutations (AD/AR)
	Paramyotonia congenita	*SCN4A* mutations (AD)
	Sodium channel myotonia	
Periodic paralysis[1-4]	Hyperkalemic periodic paralysis	*SCN4A* mutations
	Hypokalemic periodic paralysis	*SCN4A* mutations; *CACNA1S* mutations
	Andersen-Tawil syndrome	*KCNJ2* - *KCNJ5* mutations
	Thyrotoxic periodic paralysis	*KCNJ18 (susceptibility)*

AD, autosomal dominant; AR, autosomal recessive.

1. Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444. 2. Matthews E, et al. *Pract Neurol.* 2021;21(3):196-205. 3. Jitpimolmard N, et al. *Curr Treat Options Neurol.* 2020;22(10):34. 4. Maggi L, et al. *Cells*. 2021;10(6):1521.

Overall Diagnostic Approach

Approach[1-3]

1. Identify characteristic phenotype and review typical family history
2. Electrophysiological testing
3. Genetic testing

Myotonia predominant[1-3]

1. Rule out a myotonic dystrophy diagnosis
2. Confirm presence of myotonia by EMG. Perform short exercise test (SET), long exercise test (LET) as needed, cooling studies
3. Consider testing for a comprehensive myotonia gene panel

Episodic weakness predominant[1-3]

1. Confirm muscle inexcitability during episodes of weakness, if possible
2. EMG: look for myotonia, perform LET and cooling studies
3. Consider acquired serum potassium abnormalities: endocrine and renal disease, thyrotoxic
4. Mutation testing for *CACNA1S*, *SCN4A*, and *KCNJ2*

EMG, electromyography.

1. Maggi L, et al. *Cells*. 2021;10(6):1521. 2. Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444. 3. Matthews E, et al. *Pract Neurol.* 2021;21(3):196-204.

Electromyography Guides

Short exercise test (SET)[1] (ADM, APB)

- Obtain supramaximal CMAP and keep stimulating electrode in position
- Set stimulator to repetitive stimulation mode at 1 stimulation every 10 seconds
- Voluntary maximal contraction for 10 seconds and relax
- Switch on stimuli within 2 seconds then 1/10 seconds for 50 seconds, assess CMAPs
- CMAP change in controls: -1- to +20%

Long exercise test (LET)[1] (ADM, TA)

- Obtain supramaximal CMAP
- Exercise muscle maximally for 5 minutes
- Ask the patient to relax the muscle completely
- Obtain supramaximal CMAP every minute for 5 minutes, then every 5 minutes for 40-45 minutes, assess CMAPs

Cooling test[2] (ADM, APB)

- Obtain supramaximal CMAP
- Cool hand in ice cold water, temperature down to 20℃
- Repeat CMAP with SET

Fournier patterns[1]

- Pattern I: SET with post-exercise decline in CMAP, which worsens with repeating exercise
- Pattern II: SET with post-exercise decline in CMAP, which improves with repeating exercise
- Pattern III: SET with no significant changes post exercise
- Pattern IV: LET with immediate increase and then delayed decline in CMAP amplitude
- Pattern V: LET with delayed decrease in CMAP only

ADM, abductor digiti minimi; APB, abductor pollicis brevis; CMAP, compound muscle action potential; TA, transverse abdominals.

1. Fournier E, et al. *Ann Neurol.* 2004;56(5):650-661. 2. Fournier E, et al. *Ann Neurol.* 2006;60(3):356-365.

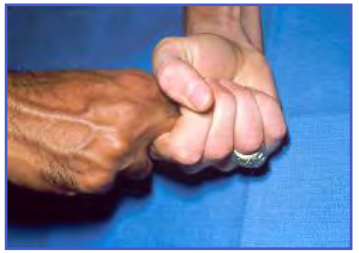
Myotonia Congenita

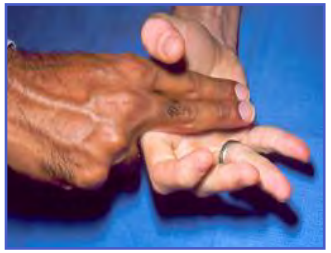
Mutations in the *CLCN1* gene coding for a chloride channel (ClC1)[1]

- Autosomal dominant: Thomsen's disease[1,2]
- Autosomal recessive: Becker myotonia congenita[1,2]

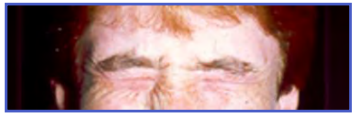
Clinical presentation

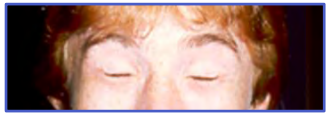
- Onset in childhood, maybe earlier[1,2]
- Stiffness, often generalized, and fluctuating depending on myotonia[1-3]
  - Hands: grip myotonia
  - Percussion myotonia
  - Eye: Eye closure myotonia, lid lag, eye movement (diplopia)
  - Gait problems, unexpected falls
  - Warm up phenomenon
  - Aggravation by cold temperatures[1]
- No progressive atrophy; muscular appearance but poor motor skills[1,2]
- Transitory weakness[1,2,4]
  - Often present at the onset of voluntary activity



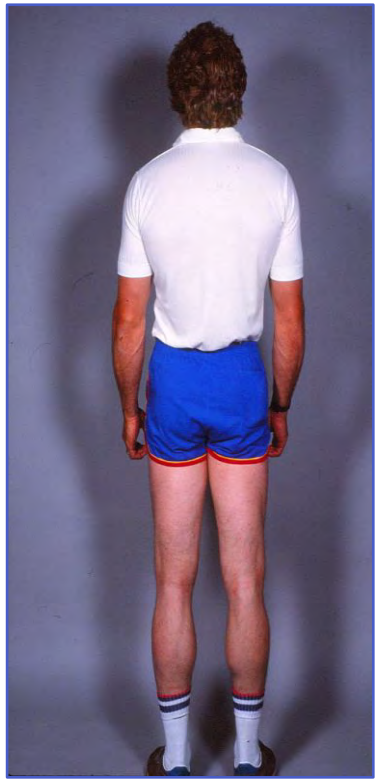


Grip myotonia





Eyelid myotonia



Muscular appearance

Photos courtesy of Dr. Subramony.

1. Maggi L, et al. *Cells*. 2021;10(6):1521. 2. Morales F, Pusch M. *Front Neurol*. 2020;10:1404. 3. Sansone VA. *Continuum (Minneap Minn)*. 2019;25(6):1696-1711.
4. Matthews E, et al. *Pract Neurol.* 2021;21(3):196-204.

Myotonia Congenita – Diagnosis

Electrophysiological testing[1-3]

- No abnormalities in routine SNCS and MNCS data
- Diffuse myotonic potentials and normal motor unit potentials in EMG analysis

Short exercise test (SET)[1-4]

- Immediate decline in CMAP amplitude (by 17% to 90%) with recovery over several seconds in >80% of cases[5]
- Repetitive trials show improvement in CMAP decline
- Cooling and long exercise tests normal but cooling may exacerbate post-exercise CMAP decline

Differential diagnosis[1-3]

- Myotonic dystrophy
- *SCN4A*: sodium channel myotonia, paramyotonia congenita

Targeted mutation testing[1]

EMG trace of myotonic discharges[5]

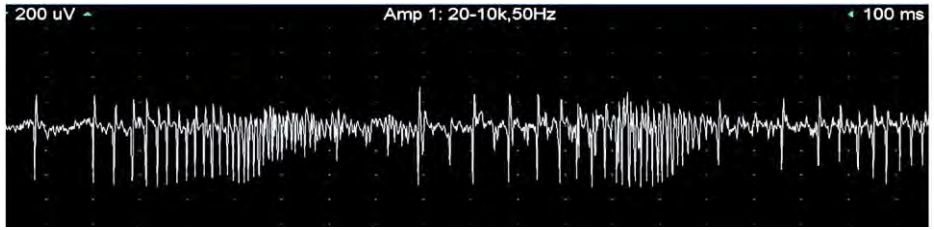


Figure from Jitpimolmard 2020. Open Access (CC-BY-4.0)

SET findings in myotonia congenita

Image courtesy of Dr. Subramony.

CMAP, compound muscle action potential; EMG, electromyography; MNCS, motor nerve conduction study; SNCS, sensory nerve conduction study.

1. Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444. 2. Subramony SH, et al. *Muscle Nerve*. 1983;6(5):374-379. 3. Matthews E, et al. *Pract Neurol.* 2021;21(3):196-204.
4. Phillips L, Trivedi JR. *Neurotherapeutics*. 2018;15(4):954-965. 5. Fournier E, et al. *Ann Neurol.* 2004;56(5):650-661. 6. Jitpimolmard N, et al. *Curr Treat Options Neurol*. 2020;22(10):34.

Sodium Channel Myotonias

Mutations in the *SCN4A* gene coding for a sodium channel (Nav1.4)[1]

- Autosomal dominant

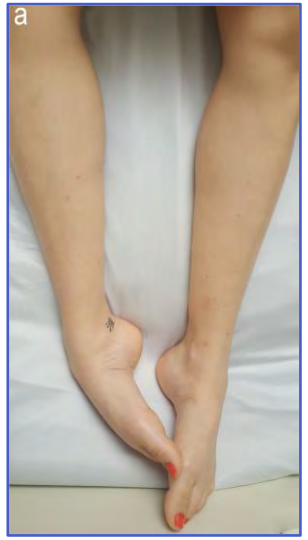
Clinical presentation[1-4]

- Lower mean age at onset than myotonia congenita: 5 vs 10 years of age
  - Severe neonatal episodic laryngospasms can be life threatening
- Resembles myotonia congenita, not paradoxical myotonia
  - Myotonia fluctuans, myotonia permanens, acetazolamide responsive myotonia
  - "Myotonic crisis" or "status myotonicus"
  - Pain, focal features
  - Features often observed in other sodium channel mutations
    - Attacks of weakness lasting hours
    - Cold temperatures and high potassium diet aggravate myotonia and muscle weakness
    - Some degree of permanent weakness
- SET, LET usually normal (Fournier pattern III) but can overlap with paramyotonia congenita or hyperkalemic periodic paralysis patterns

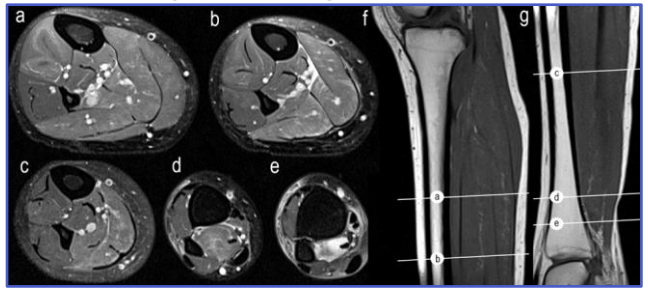
Finger flexor weakness in Na channel myotonia

Photos courtesy of Dr. Subramony.

Fixed, tight contraction of calf muscles and muscle edema[2]



MRI of the right lower leg[2]



Figures from Rempe 2020. Used with permission from Elsevier.

LET, long exercise test; MRI, magnetic resonance imaging; SET, short exercise test.

1. Phillips L, Trivedi JR. *Neurotherapeutics.* 2018;15(4):954-965. 2. Rempe T, Subramony SH. *Neuromuscul Disord*. 2020;30(5):424-426. 3. Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444. 4. Jurkat-Rott K, Lehmann-Horn F. *J Clin Invest*. 2005;115(8):2000-2009.

Paramyotonia Congenita

Mutations in the *SCN4A* gene coding for a sodium channel (Nav1.4)

- Autosomal dominant
- Allelic to sodium channel myotonia and hyperkalemic periodic paralysis

Clinical presentation

- Myotonic symptoms resembling myotonia congenita
- In contrast to warm-up phenomenon in myotonia congenita, myotonia (and muscle dysfunction) worsens with activity (and cooling) (paradoxical myotonia)
- Overlapping features with other sodium channel disorders
  - Potassium aggravates myotonia
  - Attacks of weakness

Phillips L, Trivedi JR. *Neurotherapeutics.* 2018;15(4):954-965.

Clinical Examination

Video courtesy of Dr. Subramony.

Diagnosed at 9 years old with “myotonia congenita”

Onset

Childhood

Symptoms

Stiffness and weakness of the head and limbs

- Stiffness every day
- Weakness occurs a few times every month

Physical examination

- Ptosis, mild eyelid myotonia, worsened by activity
- Grip myotonia
- Facial and neck flexor weakness
- Distal>proximal weakness

Paramyotonia Congenita – Diagnosis

Electrophysiological testing[1]

- No abnormalities in routine SNCS and MNCS data
- Diffuse myotonic potentials and normal motor unit potentials in EMG analysis
- Significant decline in CMAP amplitude with cooling

Short exercise test (SET)[1,2]

- SET similar to myotonia congenita, but repeat test shows worsening defect (Fournier pattern I)
- Muscle cooling aggravates SET abnormality
- Needle EMG can show increase in myotonic potentials followed by electrical silence

Targeted mutation testing[3]

Effect of muscle cooling on CMAP amplitude[1]

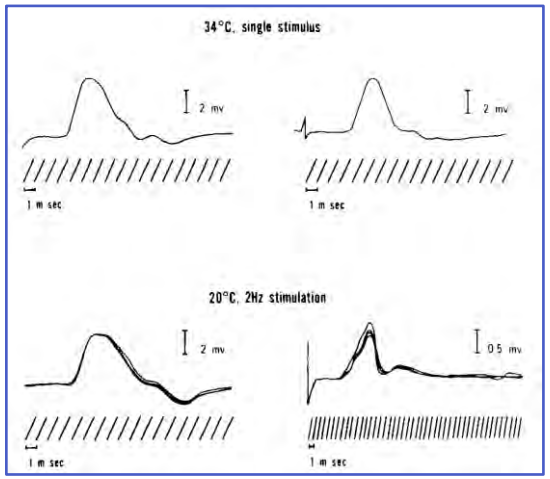


Figure from Subramony 1983. Used with permission from John Willey and Sons.

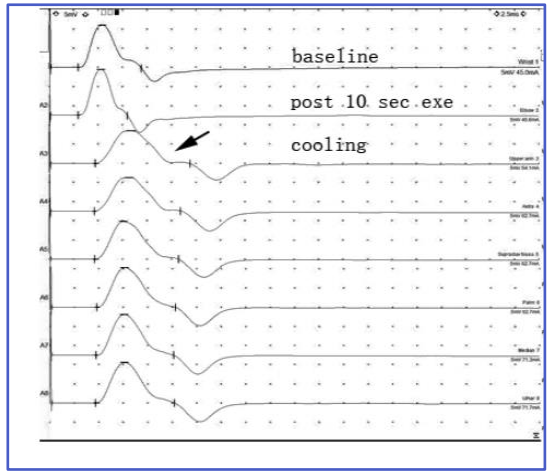


Image courtesy of Dr. Subramony.

CMAP, compound muscle action potential; EMG, electromyography; MNCS, motor nerve conduction study; SET, short exercise test; SNCS, sensory nerve conduction study.

1. Subramony SH, at al. *Muscle Nerve*. 1983;6(5):374-379. 2. Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444. 3. Phillips L, Trivedi JR. *Neurotherapeutics*. 2018;15(4):954-965.

Hyperkalemic Periodic Paralysis

Mutations in the *SCN4A* gene coding for a sodium channel (Nav1.4)[1,2]

- Autosomal dominant

Clinical presentation[1-3]

- Onset in first decade of life
- Episodic muscle weakness evolving over a few minutes to hours associated with hyperkalemia
  - Often focal, but can be generalized, with recovery a few hours later
- Attacks affect different parts of the body in a fluctuating manner
- Gentle activity can abort attacks of weakness
- “Rest after exercise” and high potassium diet may trigger weakness episodes; other triggers include pregnancy, stress, and cold exposure
- Permanent weakness can occur later in life

1. Phillips L, Trivedi JR. *Neurotherapeutics.* 2018;15(4):954-965. 2. Maggi L, et al. *Front Neurol.* 2020;11:646. 3. Morales F, Pusch M. *Front Neurol.* 2020;10:1404.

Hyperkalemic Periodic Paralysis – Diagnosis

During an attack

Laboratory tests[1,2]

- Usually high serum potassium level, but can be normal or even low in different attacks
- CK can be elevated
- Myotonia, often subtle, can be observed

Electromyography[1,3]

- In weak muscle, CMAPs have low amplitude and recover when symptoms resolve
- Needle EMG can show myotonic potentials and fibrillations
  - Reduced or absence of insertional activity in weaker muscles
  - Commensurate decrease in MUP recruitment indicates loss of muscle membrane electrical activity

Interictal period

Physical examination[1,2,4,5]

- Focal weakness can be detected
- Mild myotonia

Electromyography[1,3,5]

- Mild myotonia
- Perform “long exercise test”: CMAP increase right after exercise but then late decline (Fournier pattern IV)

Targeted mutation testing[1,5]

Lid lag from myotonia

Photo courtesy of Dr. Subramony.

LET in periodic paralyses[6]

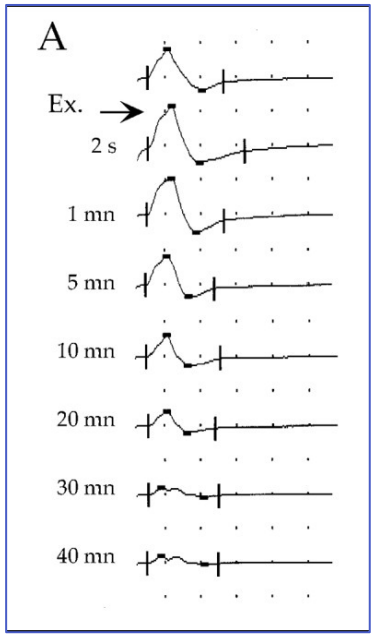


Figure from Fournier 2004. Used with permission from John Willey and Sons.

CK, creatine kinase; CMAP, compound muscle action potential; EMG, electromyography; LET, long exercise test; MUP, motor unit potential.

1. Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444. 2. Matthews E, et al. *Pract Neurol*. 2021;21(3):196-204. 3. Subramony SH, Wee AS. *Neurology*. 1986;36(2):173-177. 4. Maggi L, et al. *Cells*. 2021;10(6):1521. 5. Phillips L, Trivedi JR. *Neurotherapeutics*. 2018;15(4):954-965. 6. Fournier E, et al. *Ann Neurol*. 2004;56:650-661.

Mutations in Non-Dystrophic Myotonia and Periodic Paralysis

Myotonia mechanism[1,2]

Accumulation of K^+ in T-tubules needs to be balanced by Cl^- to prevent recurrent depolarization

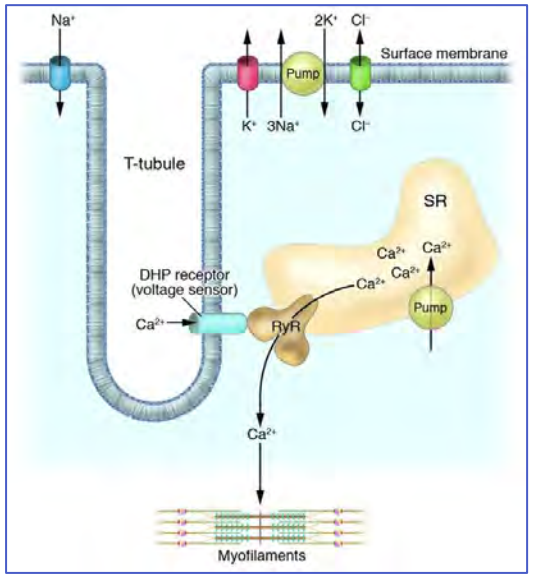


Figure from Jurkat-Rott 2005. Open Access. (CC-BY-4.0)

Paralysis mechanism[1,2]

Importance of *SCN4A*/Nav1.4 mutations

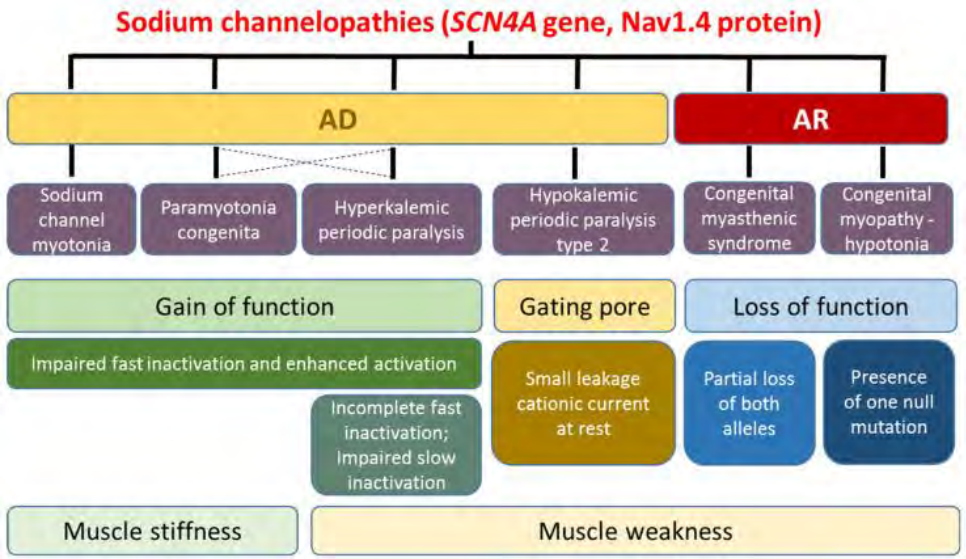


Figure from Maggi 2021. Open Access. (CC-BY-4.0)

- **Gain of function mutations** lead to quicker activation and impaired fast inactivation of Nav1.4 and results in Na leakage and myotonia
  - Impaired slow inactivation causes persistent leak and depolarization block leading to hyperkalemic paralysis
- **Loss of function mutations** lead to CMS or congenital myopathy
- **Mutations creating an aberrant gating pore** lead to hypokalemic periodic paralysis

AD, autosomal dominant; AR, autosomal recessive; CMS, congenital myasthenic syndrome.

1. Jurkat-Rott K, Lehmann-Horn F. *J Clin Invest*. 2005;115(8):2000-2009. 2. Maggi L, et al. *Cells*. 2021;10(6):1521.

Hypokalemic Periodic Paralysis

Mutations in the *CACNA1S* gene coding for a calcium channel (Cav1.1) (60%) or in the *SCN4A* gene coding for a sodium channel (Nav1.4) (20%)[1]

- Autosomal dominant

Clinical presentation[1,2]

- Onset in first and second decade of life
- Episodes of muscle weakness evolve over a few hours
  - Usually generalized with recovery over 1 or 2 days
- Focal attacks are not common
- "Rest after exercise," high carbohydrate/salt diets, and insulin can precipitate attacks
- Permanent weakness can occur later in life, resembling LGMD

LGMD, limb-girdle muscular dystrophy.

1. Maggi L, et al. *Cells*. 2021;10(6):1521. 2. Matthews E, et al. *Pract Neurol.* 2021;21(3):196-204.

Hypokalemic Periodic Paralysis – Diagnosis

During an attack

Laboratory tests[1,2]

- Low serum potassium level (ie, <3.5 mEq/L)
  - If <2 mEq/L, it suggests an acquired hypokalemia
- CK level is usually normal
- No observation of myotonia

Electromyography[1]

- Similar to hyperkalemic periodic paralysis but usually no myotonic discharges

Interictal period

Physical examination usually normal

Electromyography[2,3]

- Normal examination
- Perform “long exercise test”: no CMAP increase right after exercise but shows late decline (Fournier pattern V)
- Less dramatic than hyperkalemic periodic paralysis

Targeted mutation testing[4]

CK, creatine kinase; CMAP, compound muscle action potential.

1. Maggi L, et al. *Cells*. 2021;10(6):1521. 2. Matthews E, et al. *Pract Neurol.* 2021;21(3):196-204. 3. Fournier E, et al. *Ann Neurol.* 2004;56(5):650-661.
4. Phillips L, Trivedi JR. *Neurotherapeutics.* 2018;15(4):954-965.

Andersen-Tawil Syndrome

Mutations in the *KCNJ2* (60%) and *KCNJ5* (15%) genes coding for potassium channels[1-3]

- Autosomal dominant

Clinical presentation[1,2]

- Episode of hypokalemic periodic paralysis
- Cardiac conduction defects
  - Abnormal EKG including abnormal TU morphology, enlarged U waves, prolonged QU intervals and polymorphic ventricular contractions
  - Torsade, long QT, ventricular fibrillation
  - 20% require devices
- Dysmorphic features
  - Micrognathia, low set ears, hypotelorism
  - Short fifth finger, clinodactyly, and syndactyly

Dysmorphias characteristic[4]

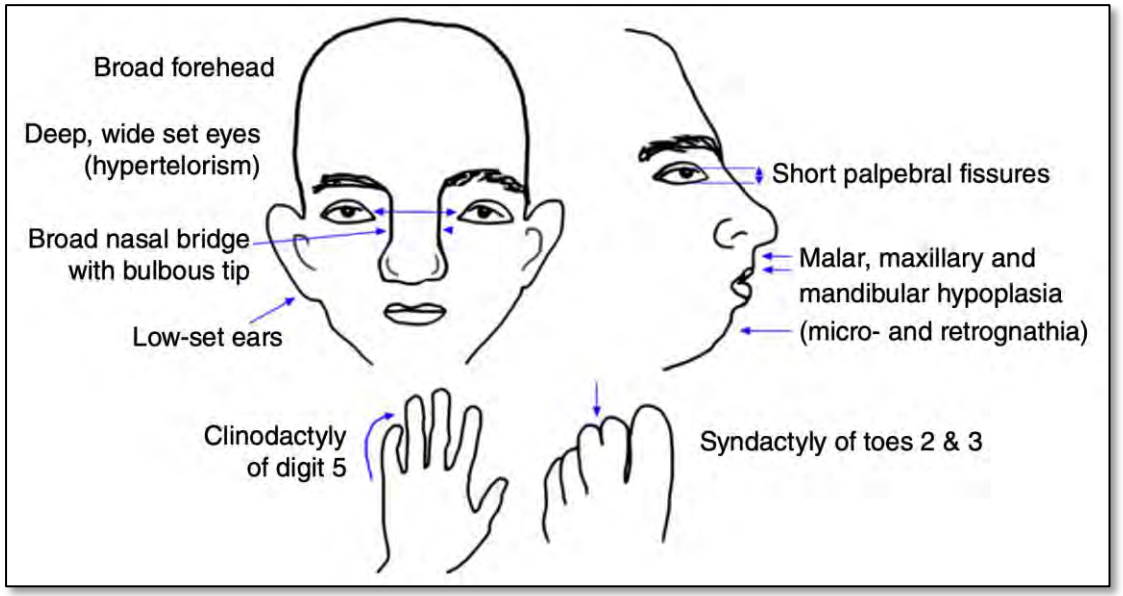


Image from Adams 2016. Reused with permission from The Journal of Physiology © 2016 The Physiological Society.

1. Phillips L, Trivedi JR. *Neurotherapeutics.* 2018;15(4):954-965. 2. Maggi L, et al. *Cells.* 2021;10(6):1521. 3. Pérez-Riera AR, et al. *Cardiol Rev*. 2021;29(4):165-177. 4. Adams DS, et al. *J Physiol.* 2016;15;594(12):3245-3270

Thyrotoxic Periodic Paralysis

No family history but likely genetic factors present[1,2,4]

- No mutations in *CACNA1S* or *SCN4A*
- Association also with mutations in *KCNJ18,* SNPs in *CACNA1S*

1.8%

of Asians with hyperthyroidism[2,3]

0.15% in North American hyperthyroid population

Males > females[2,5]

20+

Age[5]

20 years of age and above

Attacks of weakness similar to hypokalemic periodic paralysis[2,4,5]

Low serum potassium level (ie, <2.0 mEq/L)

SNP, single nucleotide polymorphisms.

1. Phillips L, Trivedi JR. *Neurotherapeutics.* 2018;15(4):954-965. 2. Batch JT, et al. *Cureus.* 2020;12(2):e7041. 3. Kung AWC, J Clin Endocrinol Metab. 2006;91(7):2490-2495. 4. Maggi L, et al. *Cells.* 2021;10(6):1521. 5. Salih M, et al. *Neth J Med.* 2017;75(8):315-320.

Treatments for Ion Channel Disorders

No treatments are currently approved by the FDA and common medications included in guidelines are used for symptoms management[1,2]

Non-dystrophic myotonia[1-4]

Drug	Dose	Level of evidence
Mexiletine	Start 150 mg BID; titration up to 300 mg TID	Level I (RCT) – EMA approval
Lamotrigine	Start 25 mg/day; titration up to 300 mg/day	Level II (RCT)
Acetazolamide	Start 125 mg BID; titration up to 1000 mg/day	Level III and IV (open-label studies)
Ranolazine	Start 0.5 g BID; titration up to 1 g BID	Level III (open-label studies)
Carbamazepine	Start 100 mg BID; titration up to 1.2 g/day	Level III (RCT)

Periodic paralysis[1-3]

Prophylaxis

Drug
Acetazolamide: 125-1000 mg/day
Dichlorphenamide: 50 mg BID; up to 200 mg/day
K^+-sparing diuretics (for hypoPP): eg, triamterene 50-150 mg/day
Thiazide diuretics (for hyperPP): eg, hydrochlorothiazide 25-100 mg/day

Acute treatment

Drug	Conditions
Oral potassium up to 200 mEq/day	Acute hypoPP
IV potassium up to 20 mEq/h, up to 250 mEq/day	
Carbohydrate intake up to 2.0 g/kg	Acute hyperPP
Beta agonists (eg, salbutamol)	

BID, twice daily; EMA, European Medicines Agency; FDA, Food and Drug Administration; hyperPP, hyperkalemic periodic paralysis; hypoPP, hypokalemic periodic paralysis; RCT, randomized controlled trial; TID, three times daily.

1. Jitpimolmard N, et al. *Curr Treat Options Neurol.* 2020;22(10):34. 2. Phillips L, Trivedi JR. *Neurotherapeutics.* 2018;15(4):954-965. 3. Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444. 4. Matthews E, et al. *Pract Neurol.* 2021;21(3):196-205.

Management of Patients With Ion Channel Disorders

Importance of the coordination of care[1,2]

- Cardiac, renal, and hepatic function monitoring for patients with myotonia congenita treated with mexiletine, lamotrigine, or ranolazine
- Cardiac care for patients with Andersen-Tawil syndrome

Lifestyle and activity[1,2]

- Dietary management of potassium, salt, and carbohydrate intake; avoidance of cold temperatures (eg, swimming in cold water)
- Exercise
- Pregnancy and anesthesia issues
- Keep limbs warm (all NDM) and use the warm-up phenomenon (myotonia congenita)

NDM, non-dystrophic myotonia.

1. Matthews E, et al. *Pract Neurol.* 2021;21(3):196-205. *2.* Phillips L, Trivedi JR. *Neurotherapeutics.* 2018;15(4):954-965.

Other Disorders Considered Ion Channel Diseases of Muscles

Congenital myopathic syndromes

- From mutations in *SCN4A* (AR), *RYR1*, *RYR2*, *CACNA1H*, *STAC3*, *ORA1*, *STIM 1*

Scapulo-peroneal syndrome

- From mutations in *TRPV4*

Congenital myasthenic syndrome

- From mutations in *SCN4A* (AR), *AChR*

AR, autosomal recessive.
Maggi L, et al. *Cells.* 2021;10(6):1521.

Resources

Muscular Dystrophy Association	MDA Muscular Dystrophy Association	https://www.mda.org/disease/ion-channel-diseases
Periodic Paralysis Association	PERIODIC PARALYSIS ASSOCIATION	https://periodicparalysis.org/
National Organization for Rare Disorders	NORD 40 YEARS RARE. STRONG. TOGETHER.	https://rarediseases.org/

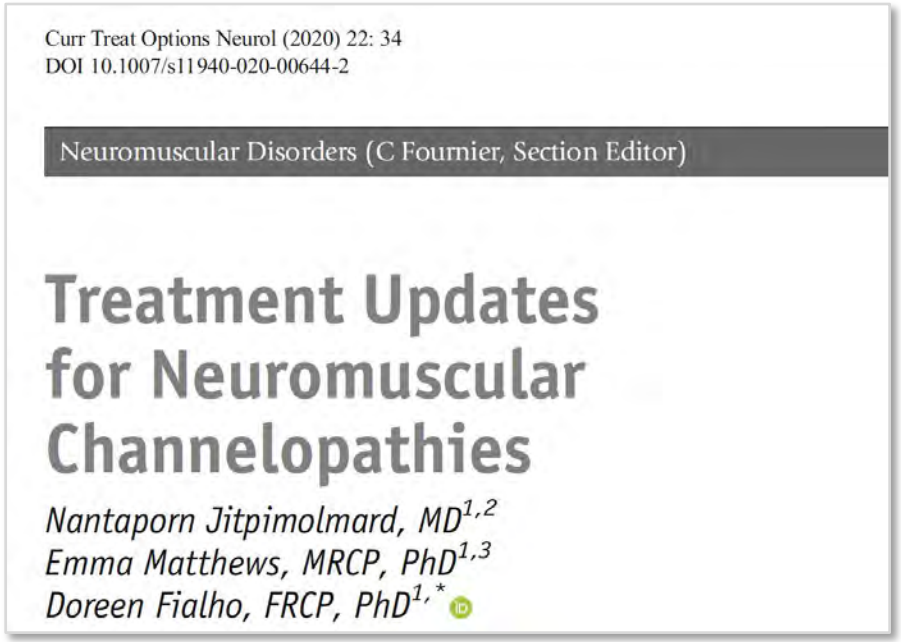
Resources (cont.)


Review

Skeletal muscle channelopathies: a guide to diagnosis and management

Emma Matthews [1,2] Sarah Holmes,[3] Doreen Fialho[2,3,4]

Matthews E, et al. *Pract Neurol.* 2021;21(3):196-205.


Curr Treat Options Neurol (2020) 22: 34
DOI 10.1007/s11940-020-00644-2

Neuromuscular Disorders (C Fournier, Section Editor)

Treatment Updates for Neuromuscular Channelopathies

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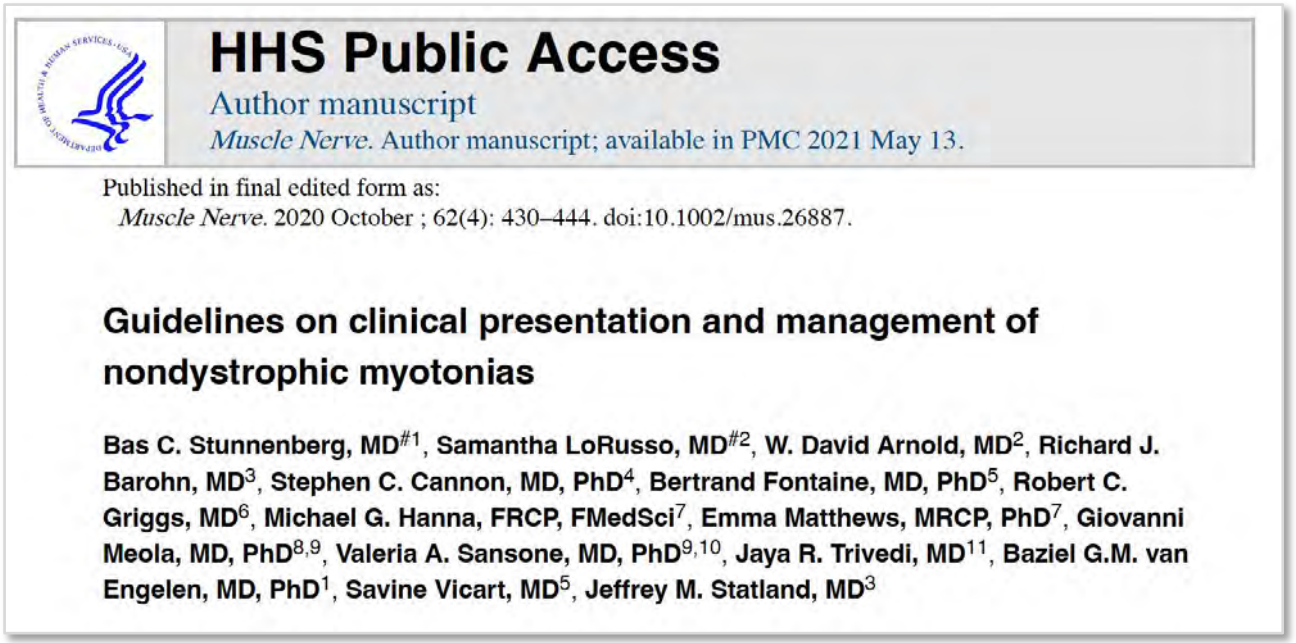
Jitpimolmard N, et al. *Curr Treat Options Neurol.* 2020;22(10):34.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Guidelines on clinical presentation and management of nondystrophic myotonias

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Stunnenberg BC, et al. *Muscle Nerve*. 2020;62(4):430-444.