Motor neuro- and neuronopathies

Björn Falck, MD, PhD
Turku, Finland

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Goals

- Have an understanding of other motor neuronopathies than ALS

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Outline 20 min

- Spinal muscular atrophy (SMA)
- Kennedy syndrome
- Post polio syndrome
- Monomelic spinal atrophy
- Tick borne encephalitis
- Late onset spinal muscular atrophy
- Distal hereditary neuropathies
- Hereditary spastic paraparesis
- Benign fasciculation

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Spinal muscular atrophy (SMA)

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Spinal muscular atrophy

- Hereditary motor neuronopathies
- Proximal > distal

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SMA – General aspects

- 1: 10 000 newborn affected
- Gene carriers 1:50
- Homozygous deletion in the SMN1-gene
- Treatment available!!!!

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SMA genetics

- Chromosome 5q13
- SMN = survival motor neuron gene 1 & 2
- SMN1 in the telomeric part
- Homologous SMN2 in the centromeric part
- SMN1 and SMN2 include 8 exons (1, 2a, 2b, 3-8), stop codon at the end of exon 7
- SMN1 and 2 differ from each other only in exons 7 ja 8 (one base pair in each)

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SMN genes

- SMN1 and SMN2 code survival motor neuron –protein
- SMN1 gene produces 90% of the SMN protein
- SMN2 alone is not capable of producing enough SMN
- 94 % of SMA patients lack lack both SMN1 genes
- SMN2 genes copies
  - 1% no copies
  - 18% 1 copy
  - 47% 2 copies
  - 31 % 3 copies
  - 4% 4 copies

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SMA phenotypes

SMA Type	SMN2 Copies	SMA 5q %	Onset Age	Motor Milestone Achieved	Life Expectancy
SMA 0	1	< 1%	Birth	Never Sit	< 6 mo
SMA 1	2-3	55%	0 - 6 mo	Never Sit	8 to 24 mo
SMA 2	2-4	30%	6 - 18 mo	Sit	2 to 4 decades
SMA 3	3-5	10%	1.5 - 20 yrs	Walk	Normal
SMA 4	3-5	5%	Adult	Walk	Normal

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SMA I (Werdnig-Hoffman)

- Onset usually < 3 months of age, before 6 months
- Sometimes intrauterine onset
- Reduced movements of the fetus
- Symmetric weakness of arms and legs
  - Diffuse or proximal > distal
- Hypotonia, swallowing difficulties, unable to sit
- Fasciculations may be seen
- Lack tendon reflexes
- Weakness of respiratory muscles
- Normal cognitive function
- Without treatment 50% die before 7 months, 95% by 17 months

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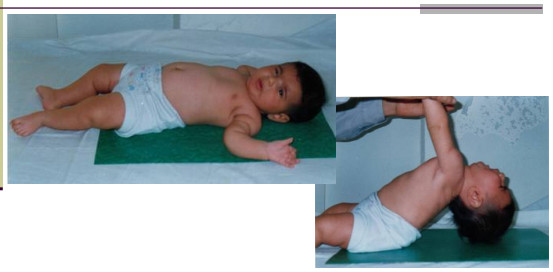
SMA1



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SMA treatments

Features	Drug		
	Nusinersen	Risdiplam	Onasemnogene Abeparvovec-xio
Drug Type	Oligonucleotide, Antisense	Small molecule	Virus (AAV) Gene Delivery
Drug delivery	Intrathecal	Oral	Single intravenous
Mechanism	More splicing of SMN2 gene to full length SMN protein		SMN transgene: Produces full length SMN protein

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SMA treatments

- With earlier treatment better results
- Newborn sreening
  - USA 85% of babies screened
  - Many countries screen
- 11 000 patients so far treated
- Cost high: Nusinersen (Spinraza®)
  - USA $125,000 per injection
  - $750,000 in the first year, annually $375,000

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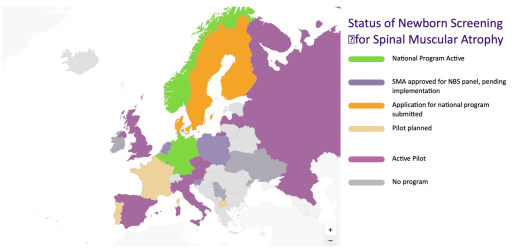
SMA screening in Europe



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Neurophysiology

- EMG
  - Abundant fibrillations in all muscles
  - Often fasciculations
  - MUPs difficult to evaluate
- Neurography
  - Sensory normal (superficial peroneal, radial)
  - Motor: low amplitudes

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SMA II (Intermediate)

- Onset around 6 months, before 18 months
- Learn to sit, never stand
- All muscles weak
- Normal cognitive function

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SMA III (Kugelberg-Welander)

- Onset 2-17 years
- Muscle weakness, proximal > distal
- Some walk
- Good survival

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SMA IV

- Adult onset
- Walk
- Muscle weakness, proximal > distal
- May remain ambulatory
- Normal lifespan

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SMA diagnosis

- Clinical findings
- EMG
- Neurography
- SMN-gene test abnormal in 95 % a deletion
- Muscle biopsy
  - Fiber type grouping and group atrophy
  - SMA I ja II: type 1 hypertrophy
  - SMA III (ja IV): reinnervation

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Bulbo-spinal muscular atrophy

Kennedy syndrome

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Kennedy syndrome

- Described by William Kennedy 1968
- X-chromosomal (Xq12 recessive)
- Androgen receptor located in the cytoplasm
- Accumulation of altered androgen receptor proteins leads to cell degeneration
- CAG repeat
  - Normal 9-39
  - MSMA 40-65
- De novo mutations rare
- Prevalence 1:50 000
- In Scandinavia common founder haplotype
- Female carriers are often also symptomatic
- Diabetes in 10%
- Life expectancy only slightly reduced

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Kennedy syndrome

- Onset 15-75 years, mean 27-43
- Muscle weakness
  - Legs > arms
  - Proximal > distal
  - Symmetric
- Bulbar symptoms
  - Dysphagia
  - Dysarthria
- Muscle cramps
- Sensory abnormalities
  - Distal

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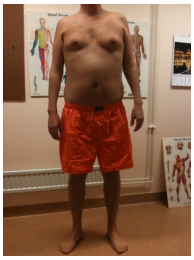
Kennedy syndrome

- Gynecomastia
  - Not always
- Androgen insensitivity
  - Testicular atrophy
  - Infertility
  - Erectile dysfunction
- CK value often high
- Diabetes



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EMG findings

- EMG
  - Neurogenic findings
  - Bulbar muscles affected
  - Fasciculations
- Neurography
  - **Sensory amplitudes reduced or absent**

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Diagnosis

- Clinical picture
- EMG
- DNA analysis

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Treatment

- No disease modifying treatment available
  - Androgen supplement contraindicated
- Supportive
  - Swallowing difficulties
  - Dysarthria

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Acute polio
Post-polio syndrome

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Acute polio

- Poliovirus types 1, 2 & 3
- Incubation times 3-30 days
- Most infections very mild
  - 70% asymptomatic
  - 25% minor illness
  - 1-5% aseptic meningitis
  - 0.1-0.5% develop poliomyelitis

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Acute polio

- 85% paralysis caused by type 1
- High fever, myalgia, nausea, headache
- Flaccid paralysis maximum within 48 hours
- Some recovery
- 1/1000 in children, 1/75 in adults

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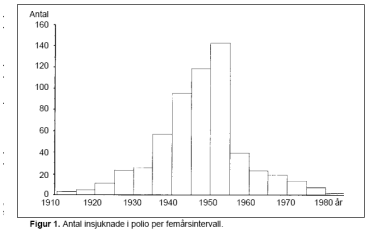
Epidemiology in Sweden



Figur 1. Antal insjuknade i polio per femårsintervall.

Andreasson et al. Rehabilatringsbidrag gav fler… Läkartidningen 1999;96:1999-

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Polio

- Vaccination started 1956
  - Salk trivalent inactivated virus
  - Sabin attenuated live virus
- Dramatic reduction in poliomyelitis
- Polio has practically disappeared
  - Recent cases reported from Ukraine in 2021
  - Central Africa and Pakistan
- Patients with postpolio symptoms
  - European patients born before 1956
  - Immigrants may be born later

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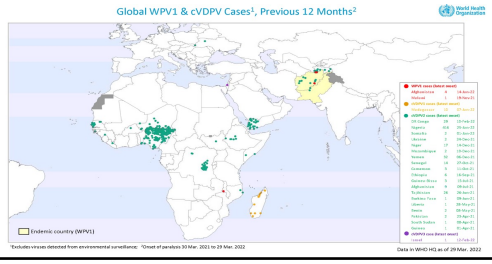
Poliocases in March 2022



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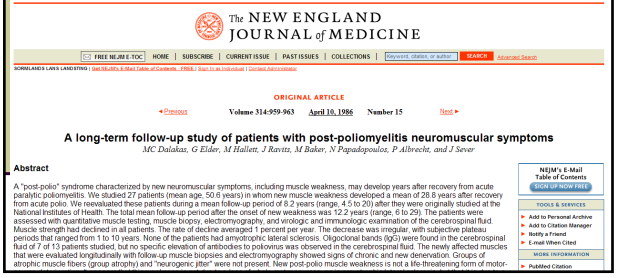
Postpolio syndrome (PPS)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Volume 314:959-963 April 10, 1986 Number 15

A long-term follow-up study of patients with post-poliomyelitis neuromuscular symptoms

MC Dalakas, G Elder, M Hallett, J Ravits, M Baker, N Papadopoulos, P Albrecht, and J Sever

Abstract

A "post-polio" syndrome characterized by new neuromuscular symptoms, including muscle weakness, may develop years after recovery from acute paralytic poliomyelitis. We studied 27 patients (mean age, 50.6 years) in whom new muscle weakness developed a mean of 28.8 years after recovery from acute polio. We reevaluated these patients during a mean follow-up period of 8.2 years (range, 4.5 to 20) after they were originally studied at the National Institutes of Health. The total mean follow-up period after the onset of new weakness was 12.2 years (range, 6 to 29). The patients were assessed with quantitative muscle testing, muscle biopsy, electromyography, and virologic and immunologic examination of the cerebrospinal fluid. Muscle strength had declined in all patients. The rate of decline averaged 1 percent per year. The decrease was irregular, with subjective plateau periods that ranged from 1 to 10 years. None of the patients had amyotrophic lateral sclerosis. Oligoclonal bands (IgG) were found in the cerebrospinal fluid of 7 of 13 patients studied, but no specific elevation of antibodies to poliovirus was observed in the cerebrospinal fluid. The newly affected muscles that were evaluated longitudinally with follow-up muscle biopsies and electromyography showed signs of chronic and new denervation. Groups of atrophic muscle fibers (group atrophy) and "neurogenic jitter" were not present. New post-polio muscle weakness is not a life-threatening form of motor-

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PPS

- Past history of polio
  - Stable period after poliomyelitis
- Development of new impairment
  - Generalized fatigue
  - Weakness
  - Joint and muscle pain

Extremely vague definition!

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PPS

POSTPOLIO MUSCULAR DYSFUNCTION: RELATIONSHIPS BETWEEN MUSCLE ENERGY METABOLISM, SUBJECTIVE SYMPTOMS, MAGNETIC RESONANCE IMAGING, ELECTROMYOGRAPHY, AND MUSCLE STRENGTH

BENGT NORDGREN, MD, PhD,[1*] BJÖRN FALCK, MD, PhD,[2] ERIK STÅLBERG, MD, PhD,[2] GUNNAR RONQUIST, MD, PhD,[3] ANDERS WALDENSTRÖM, MD, PhD,[4] HÅKAN AHLSTRÖM, MD, PhD,[5] and ANDERS HEMMINGSON, MD, PhD[5]

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PPS – macro EMG & MRI

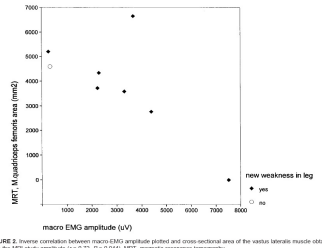

FIGURE 2. Inverse correlation between macro-EMG amplitude plotted and cross-sectional area of the vastus lateralis muscle obtained from the MRI study amplitude ($r = 0.72$, $P = 0.044$). MRT, magnetic resonance tomography.

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PPS – weakness vs strength

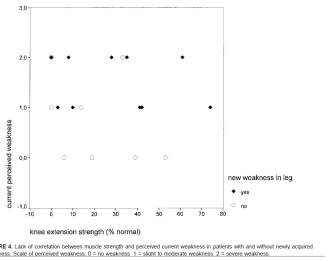

FIGURE 4. Lack of correlation between muscle strength and perceived current weakness in patients with and without newly acquired weakness. Scale of perceived weakness: 0 = no weakness, 1 = slight to moderate weakness, 2 = severe weakness.

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PPS

- No objectively measurable parameter discriminated between stable and unstable
  - EMG
  - Histology
  - Imaging
  - Muscle strength
- Pain correlated with loss of function

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Muscle strength

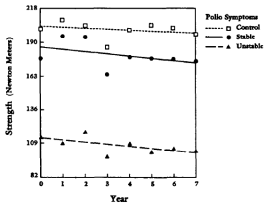

Fig 2. Mean yearly strength (MVC) measurements.

Agre et al. Electromyographic and neuromuscular variables in unstable postpolio subjects…Arch Phys med Rehab 1997;78:986-

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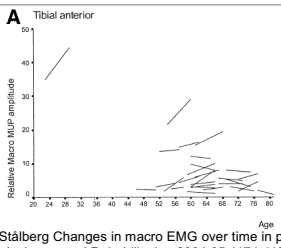
Macro EMG m.tibialis anterior



Sandberg and Stålberg Changes in macro EMG over time in patients with a history of polio. Arch pys med Rehabilitation 2004:85:1174-1182

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PPS is multifactorial

- Severe primary involvement of muscles
- Aging
- Arthrosis
- Depression
- Concurrent other diseases

- Percieved functional deficit

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Role of EMG in PPS

- Ascertain that the patient really had polio
  - Cerebral palsy, GBS
- Detect other concurrent disorders
  - CTS, Radiculopathies, Polyneuropathy
- Conventional EMG does not discriminate between stable and unstable patients with previous polio
  - Fibrillation potentials do not indicate PPS
  - Severe involvement may be suggestive
- Macro EMG or MU counting may be helpful
  - Research tool

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Normal findings with history of previous polio

- Primary diagnosis erroneous
  - CP
  - GBS
  - Meningitis
  - Other CNS disorders
  - Functional
- Paralytic polio
  - Motor neuron loss minimal

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Other viral causes of paralysis

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Other causes of polio-like paralysis

- West Nile virus
  - Flavivirus
  - Africa, North America, MiddleEast, South West Asia
- Entero virus 68
- GBS
- Live polio vaccine related paralysis
  - 2-4/one million vaccinated

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Hirayama's disease

Monomelic spinal muscular atrophy

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Monomelic spinal muscular atrophy

- Male : female 10:1
- 15-25 years
- C7-Th1 innervated muscles, rarely in the legs
- Often bilateral
- Progressive weakness over 1-4 years
- More common in Japan, occurs elsewhere
- Etiology unclear
  - Hirayama believes in mechanical factors in cervical spine (SIC!)
  - Genetic factors
    - Twins, families with two generations

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EMG findings

- Most common: C8-T1
- Partial involvement: C7
- Spared: C5-C6
- Rarely: Legs
- May be present in asymptomatic limbs
- Fibrillations in 45% to 70%, often fasciculations
- Chronic denervation
- Opposite arm or lower extremities: 30% to 100%
- No sensory abnormalities

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Tick borne encephalitis

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Ixodes ricinus

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Ixodes Ricinus (castor bean tick)

- Named by Linne 1758
- European hard bodied tick
- Transmits TBE and borreliosis
- 30% carry some pathogen
- Life-cycle 2-3 years
  - Adults feed on humans, deer, cattle, dogs, horses for 6-13 days before dropping off
  - A female lays thousands of eggs and dies
  - Out of eggs grow larvae that feed hedgehogs, rodents, rabbits, reptiles, bats etc for 3-6 days before dropping off and moulting
  - The resulting nymfs ascend on grass to find new hosts
  - Nymfs grow to be adults

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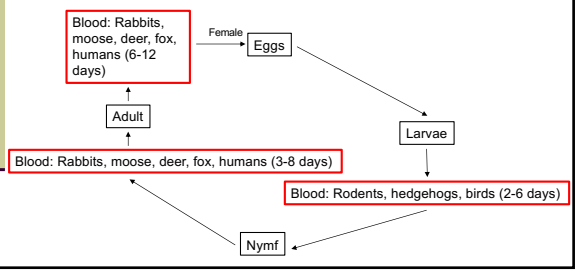
TBE cycle 2-6 years



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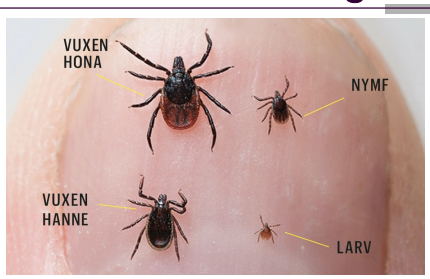
Ticks at different stages



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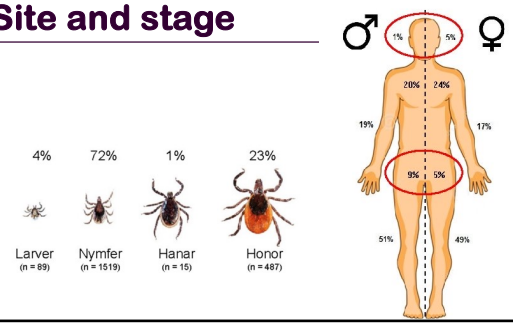
Site and stage



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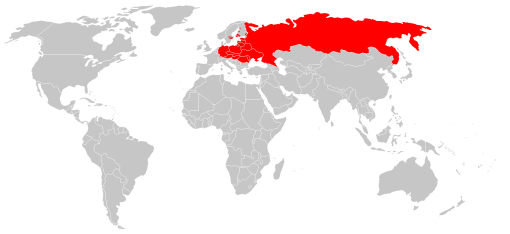
Spread of TBE



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Tick borne encephalitis (TBE)

- Flavirus (RNA), spread by ticks
- April-November
- Incubation 8 days (4-28 days)
- Encephalitis
  - Rarely severe, often mild residual cognitive symptoms
- Meningoencphalomyleitis
  - 5-10% of patients with TBE will have flaccid paralysis
  - Affection of alpha motor neurons
  - Predilection for cervical segments

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Tick borne encephalitis (TBE)

- Diagnosis
  - IgM/IgG on serum (1-2 weeks)
  - PCR on serum
  - PCR on CSF,
  - EEG
  - MRI
  - EMG if paralysis
- Treatment
  - No antiviral treatment available
  - Supportive
- Vaccination effective

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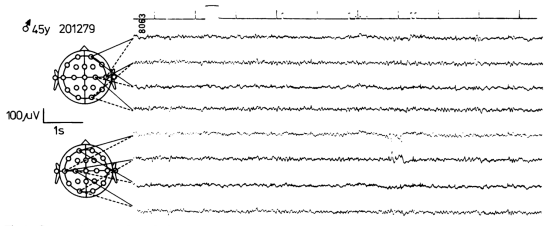
4 months after symptom onset



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Late onset spinal motor neuronopathy
LOSMoN

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RESEARCH ARTICLE

Late Onset Spinal Motor Neuronopathy Is Caused by Mutation in *CHCHD10*

Sini Penttilä, MSc,[1] Manu Jokela, MD,[2] Heidi Bouquin, BSc,[1] Anna Maija Saukkonen, MD,[3] Jari Toivanen, MD,[3] and Bjarne Udd, MD, PhD[1,4,5]

Objective: A study was undertaken to identify the responsible gene defect underlying late onset spinal motor neuronopathy (LOSMoN/SMAJ; Online Mendelian Inheritance in Man #615048), an autosomal dominant disease mapped to chromosome 22q11.2.
Methods: The previous genetic linkage approach by microsatellite haplotyping was continued in new families. A whole genome sequencing was performed to find all possibly pathogenic mutations in the linked area. The detected variations were verified by Sanger sequencing.
Results: Six new SMAJ families were identified based on the unique founder haplotype. A critical recombination in 1 family restricted the linked area to 727kb between markers SHGC-106816 and D22S345. In whole genome sequencing a previously unknown mutation c.197G>T p.G66V in *CHCHD10* was identified. The mutation was shown to segregate with the disease in 55 patients from 17 families.
Interpretation: Mutation c.197G>T p.G66V in *CHCHD10* is the cause of the lower motor neuron syndrome LOSMoN/SMAJ. During the preparation of this article other mutations were reported to cause frontotemporal dementia–amyotrophic lateral sclerosis syndrome, indicating that the *CHCHD10* gene is largely important for the motor and cognitive neuronal systems.

ANN NEUROL 2015;77:163–172

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LOSMoN

- Autosomal dominant, chromosome 22q11.2–q13.2
- 197G>T p.G66V in *CHCHD10* gene
- Onset 15-75, most in 40-50 years
- Slowly evolving muscle weakness
  - Legs>arms
  - Proximal > distal
- Painful cramps, fasciculations, areflexia
- Mild bulbar findings
- In Finland and Sweden prevalence 2/100 000
- Normal life expectancy
- CK elevated 2-8x times upper limit of normal

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LOSMoN – EMG

- EMG
  - Symmetric chronic neurogenic findings
  - Fasciculation
  - Legs > arms
  - Proximal < distal muscles
- Sensory neurography normal
- Motor neurography in early stages normal

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Distal hereditary motor neuropathies (DHMN)

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DHMN

- Distal, symmetric, mainly motor neuropathy
- Minor sensory involvement may be present
- Onset in first two decades, rarely in third
- Slow progression
- Sometimes bulbar or diaphragmatic involvement
- Dominant, recessive and x-linked forms

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Types of DHMN

Type	Inheritance	Phenotype
dHMD type I	Dominant	Juvenile onset, distal
dHMD type II	Dominant	Adult onset, distal
dHMD type III	Recessive	Slowly progressive
dHMD type IV	Recessive	Diaphragm affected
dHMD type V	Dominant	Upper limb predimnance
dHMD type VI	Recessive	SMA with respiratory distress
dHMD type VII	Dominant	Adult onset, vocal cord paralysis
X-linked dHMN	X-linked	Distal onset

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Genes

- 20% of patients have disoreder with genes identified
- 80% without known mutation
- Overlap with CMT2, HSP, ALS
- Rossor et al. The distal hereditary motor neuropathies. JNNP 2012: 83:6-14

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Hereditary spastic paraparesis HSP

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Hereditary spastic paraparesis

- Onset 10-30 years or < 6 years
- Prevalence 1/10000
- Family history
- Spasticity, mainly legs
- Mild weakness in distal part of legs
- Mild sensory symptoms
- **May also have lower motor neurone involvement**
- Mode of inheritance
  - Autosomal dominant, autosomal recessive and X-linked
- > 79 genes have been identified
- *SP4 most common - spastin gene*

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SPG4

- Chromosome 2p22.3
- Most frequent type 25-50% of all
- High penetrance (6% asymptomatic at age of 70)
- Affects mainly the lower limbs
- Variable age of onset, even within families
  - Typical 20-35 years
- Often neurogenic EMG abnormalities In leg muscles

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Benign fasciculations

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Benign fasciculation

- Only fasciculations without other abnormalities
- Common problem
- No epidemiological studies
- Often young subjects with no other symptoms
  - Medical students or health care personnel
- Duration of fasciculations variable
  - Sometimes lifelong
- Not a prelude to motor neuron disease
- Many ALS patients are not aware of their fasciculations

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J Neurol 2013:260:1743-1747

ORIGINAL COMMUNICATION

Fasciculation anxiety syndrome in clinicians

Neil G. Simon · Matthew C. Kiernan

- 20 doctors with fasciculation anxiety
  - 70% had fasciculation alone
  - 15% had cramp-fasciculation syndrome
  - One (5%) had ALS, he also had limb weakness!

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EMG in benign fasciculations

- Only symptom: fasciculation
  - Normal tendon reflexes
  - No muscle atrophy or weakness
- 6-8 muscles
- Demonstrate fasciculations
  - Simple FP
  - No double FPs
- No fibrillations
- MUPs normal
- Normal neurography

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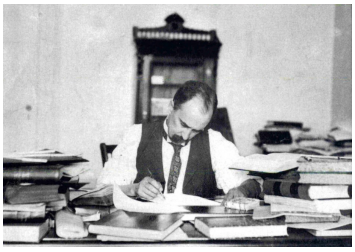
Oslerism of the day

"Soap, water and common sense are the best disinfectants."



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