Epidemiology and classification of neuromuscular diseases in Sub-Saharan Africa

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Definitions

- Neuromuscular diseases encompass cellular disorders of the motor-unit, wich include the lower-motor neurons in the spinal cord, peripheral nerve Schwann cells, neuromuscular junction, and skeletal muscle fibers

- Motor-Unit refers to one low motor neuron, its SCHWANN cells, and the muscle fibers it innervates. A neuromuscular disorder is one arising from abnormality of any part of the motor-unit

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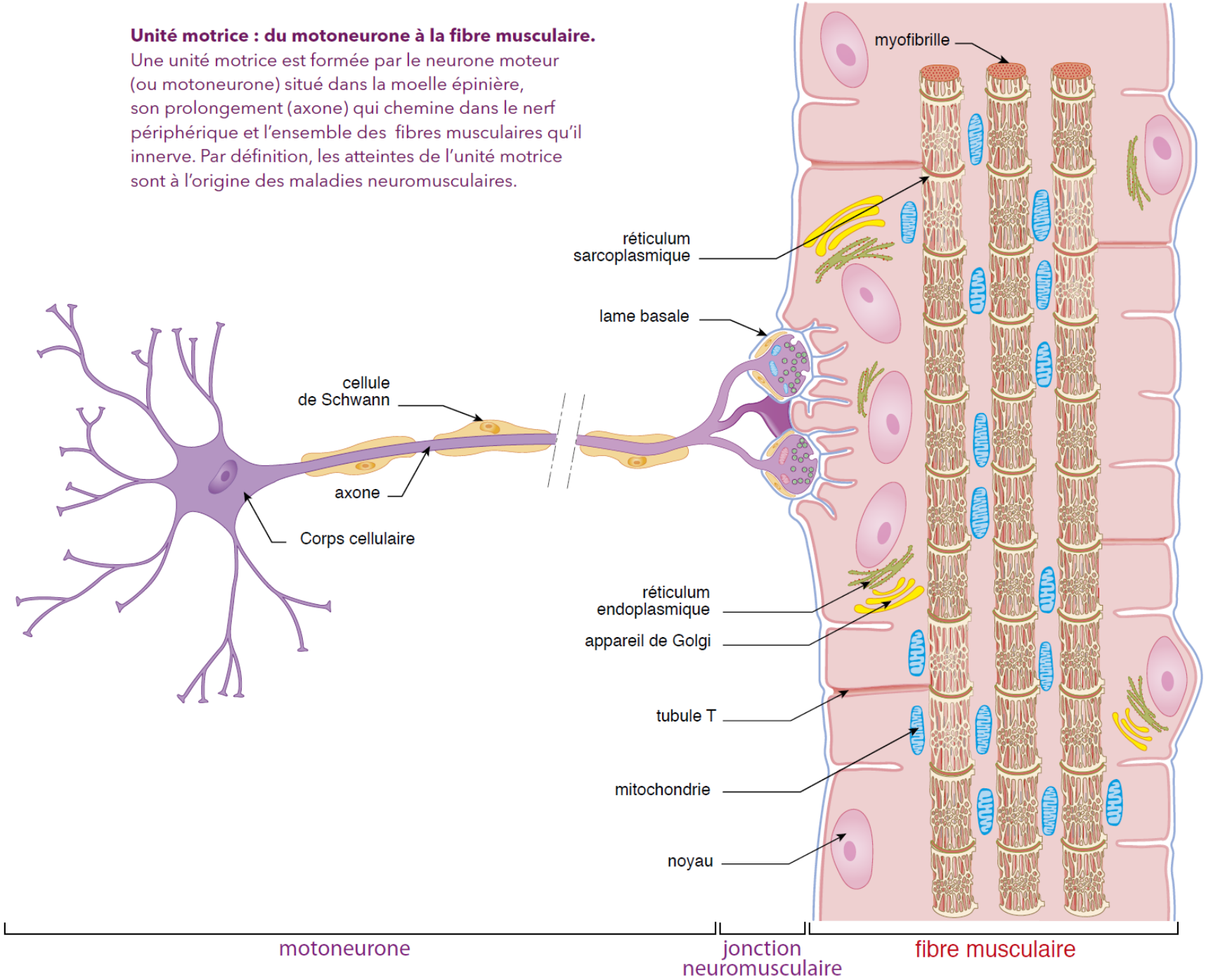
Unité motrice : du motoneurone à la fibre musculaire.
Une unité motrice est formée par le neurone moteur (ou motoneurone) situé dans la moelle épinière, son prolongement (axone) qui chemine dans le nerf périphérique et l'ensemble des fibres musculaires qu'il innerve. Par définition, les atteintes de l'unité motrice sont à l'origine des maladies neuromusculaires.



Outline

- Definitions
- Spectrum of NMD
  - Diseases of motor neuron (lower motor neuron)
  - Neuromuscular junction diseases
  - Muscular diseases
- Epidemiology of NMD in Sub-saharan Africa

Diseases of neuromuscular unit

Lesion level	Hereditary	Acquired
Spinal, Nerve cell body and axon SCHWANN cell and RANVIER nods	SMA, Familial ALS, Charcot Marie Tooth diseases and other hereditary motor and sensitive neuropathies (HMSN)	Sporadic ALS, Neuropathies of dysimmune, toxic, metabolic, nutritionnal, infectious, and other aetiologies
Neuromuscular junction	Congenital and familial myasthenia	Myasthenia Gravis, Lambert Eaton myasthenic syndromes, toxic (envenoming), botulism, peripheral nerve hyperexcitability syndromes
Muscle	Muscular dystrophies Congenital myopathies Channelopathies and myotonia Primary metabolic myopathies Mitochondrial myopathies	Inflammatory myopathies Infectious myopathies Endocrine myopathies Secondary metabolic myopathies Drug-induced and toxic myopathies

Spinal muscular atrophy

- It causes α motor neuron degeneration
- Proximal muscle weakness and paralysis
- downstream complications
  - Ambulation
  - Respiration
  - Nutrition
- There are many types of SMA
  - Type I (Werdnig Hofman, severe, early in infanthood)
  - Type II (Dubowitz, intermediate)
  - Type III (Kukelberg Welander, mild)
  - Type IV (adult onset, very mild)
  - X-linked SMA

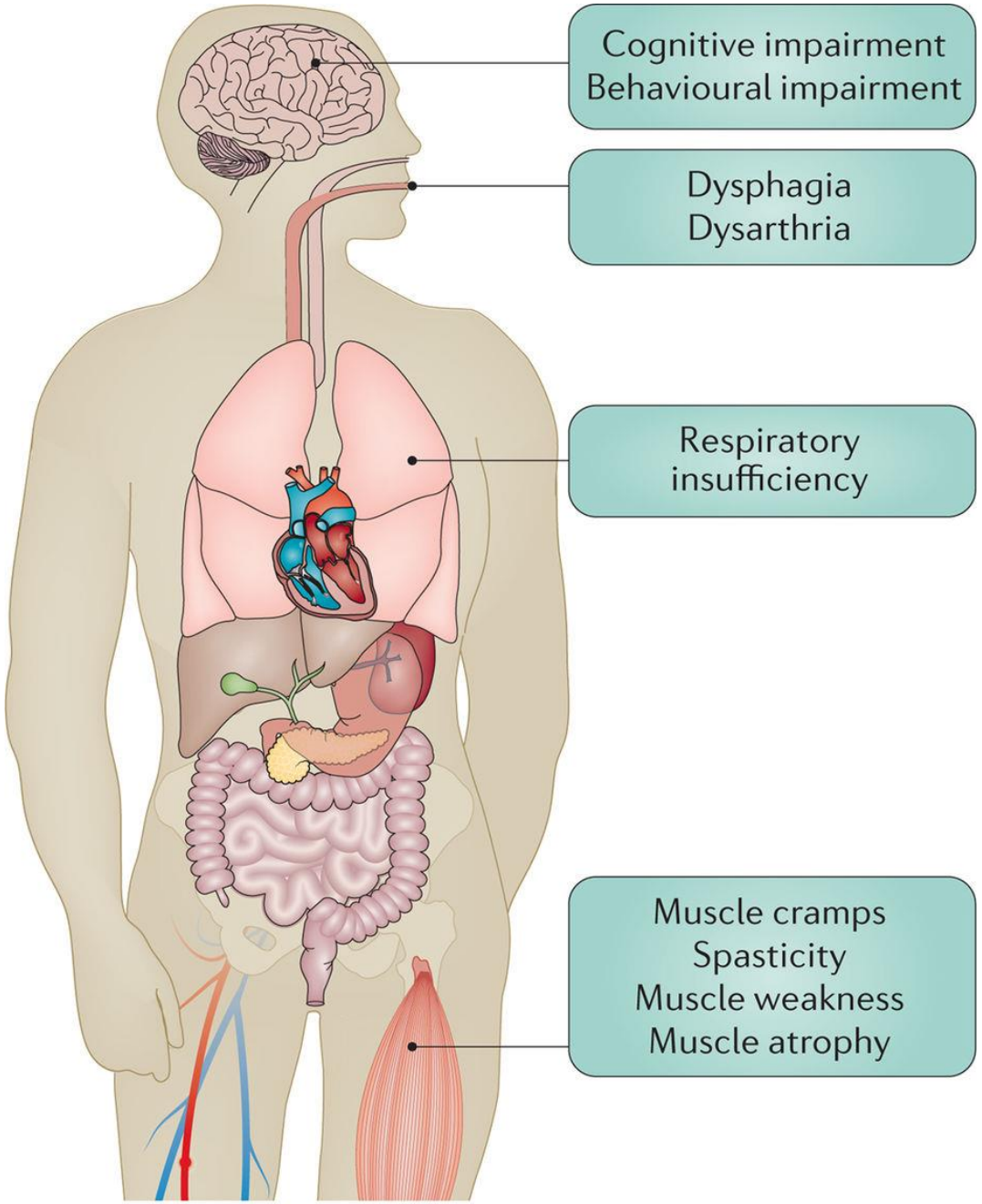
SMA is genetic disease

- Deletion or mutation of SMN 1 gene on chromosome 5 (5q13) lead to shortage of SMN1 protein
- Autosomal recessive (types I, II, III, and IV)
- Frequency: 1/10 000
- X-linked SMA is inherited in a X linked pattern, by UBA1 gene mutation on X chromosome (Xp11)

Amyotrophic Lateral Sclerosis

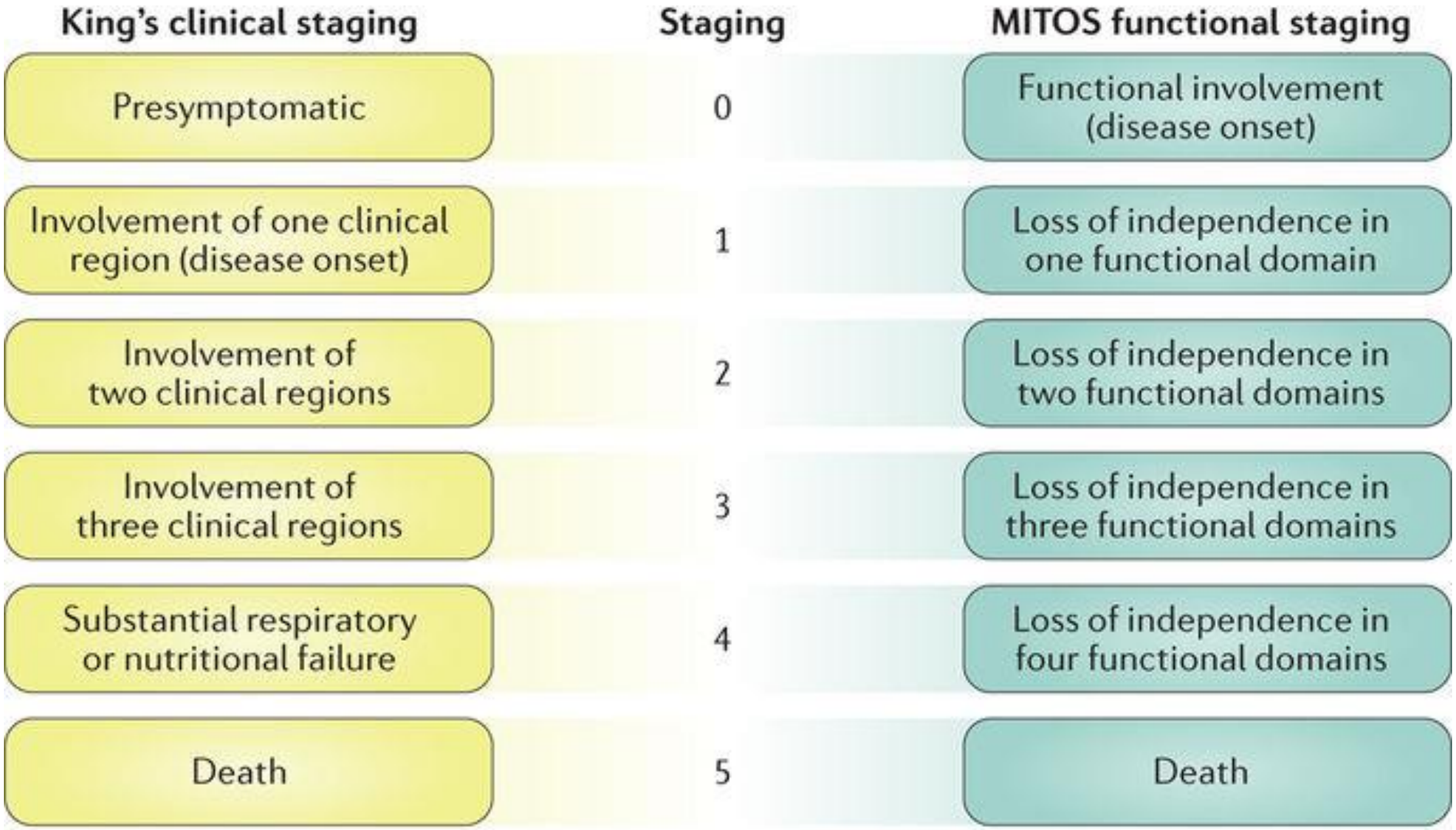
Two forms: familial ALS (10%) of all cases) and sporadic ALS (90%)

- Familial ALS aetiologies are various mutations:
  - SOD1 mutation on 21q22
  - C9orf72 mutation on 9p21
  - Other genes are TARDBP, FUS, ubiquilin2, profilin1..
- Sporadic ALS result from interactions beetwen genetic, environnemental, age-dependant risk factors



Nature Reviews | Disease Primers

Clinical manifestations of ALS



Staging system in ALS

Hereditary Motor and Sensory Neuropathy: Charcot Marie Tooth diseases

Current classification rely on neurophysiology and pattern of inheritance

- CMT1: autosomal dominant, **demyelinating** (nerve conduction velocity <38 m/s)
- CMT2: autosomal dominant, **axonal** (nerve conduction velocity > 45 m/s, low potential amplitude)
- CMT4: autosomal recessive
- CMTX: X-linked
- CMT3: Dejerine Sottas disease
- CMT is **intermediate** when nerve conduction velocity range from 25 m/s to 45 m/s in the forearm (CMTDI or CMTRI)

	CMT1, Autosomal, Dominant, demyelinating	CMT2, Autosomal, Dominant, axonal	CMT4, autosomal Recessive	CMTX X-linked
SCHWANN CELL	PMP22 MPZ EGR2 INF2 LITAF	MPZ DNM2	PRX FGD4 EGR2 MTMR2 SBF1 SBF2 SH3TC2 NDRG1 FIG4 HK1	GJB1
NEURON BODY and AXON	NFL2 GNB4	HSPB1 HSPB8 NEFL2 LRSAM1 TRIM2 DYNC1H1 TRPV4 LMNA MED25 AARS GARS MARS HINT1 RAB7A TFG MFN2 GDAP1 DHTKD1	GDAP1 KARS PLEKHG5	AIFM1 PDK3

Genes proteins causing Charcot Marie Tooth diseases

Classification and aetiologies of acquired neuropathies

Category	Aetiology	
Immune	• GBS and variants AIDP, AMAN, AMSAN, Miller-Fisher syndrome, sensory ataxic GBS, acute pandysautonomic neuropathy • Polyneuropathy with anti-MAG IgM • monoclonal gammopathy	• Vasculitis • Paraneoplasic syndromes • CIDP • Multifocal Mononeuropathy (MMN)
Infections	• Retroviruses: HIV, HTLV1 • Zika • CMV, VZV, EBV • Dengue • Enteroviruses (polio)	• *Mycobacterium leprae* • *Mycoplasma pneumonia* • *Campylobacter jejuni* • *Helicobacter pylori* • *Brucella melitensis, borrelia,…*
Toxic, nutritionnal and environmental	• Biological: vitamins deficiencies, heavy metals, envenoming, *manihot esculenta*, *lathyrus sativus*… • Chemicals: pesticids, organophosphate, PCB • Drugs: statins, nucleosides, aminosides, amiodarone, antineoplastics, antiretrovirals,	
Metabolic	• CKD, hypo/hyper thyroidism • Diabetes, porphyria,	

Neuromuscular junction disorders

NMJ Disorder	Synaptic location	Autoantibody or protein involved	Age at onset
Autoimmune myasthenia Gravis AChR MG MuSK MG LRP4 MG	Post-synaptic	Nicotinic Ach Receptor Muscle specific receptor tyrosin kinase Lipoprotein receptor-related protein 4	Young adults
Lambert Eaton myasthenic syndrome	Pre-synaptic	P/Q type voltage-gated calcium channel	40-60 years
Congenital myasthenic syndromes	Pre-synaptic, synaptic, cleft, post-synaptic	Various mutated proteins	Predominantly in childhood
Acquired peripheral nerve hyperexcitability syndromes (acquired neuromyotonia)	Pre-synaptic	Voltage-gated potassium channel	30-40 years
Botulism	Presynaptic	BoNT and SNARE proteins	All ages

Classification of myopathies

Hereditary

- Muscular dystrophies
- Congenital myopathies
- Channelopathies and myotonia
- Primary metabolic myopathies
- Mitochondrial myopathies

Acquired

- Inflammatory myopathies
- Infectious myopathies
- Endocrine myopathies
- Secondary metabolic myopathies
- Drug-induced and toxic myopathies

Genetic muscular disorders major subtypes

LGMD	CONGENITAL MD	PRIMARY METABOLIC MD	CHANNELOPATHIES MYOTONIA	MITOCHONDRIAL MD
Dystrophinopathies • DMD • BMD Autosomic dominant MD LGMD1 A-through H Autosomic recessive MD LGMD2 A through Z	Without major brain malformation • Merosin absent • CMD • CMD with rigid spine • Ulrich myopathy With major brain malformation • Fukuyama CMD • Muscle-eye-brain disease • Walker Marburg syndrome	Glycogen storage • Pompe disease • Cori disease • Mac Arde disease • Tarui disease Lipid storage • Carnitin deficiency • Neutral lipid storage disease with myopathy • Carnitin palmitoyl transferase II deficiency	Periodic paralysis • Gamstorp disease SCN4A gene (17q23) • Wesphal disease CACNA1S (1q32) Congenital myopathies • Becker disease CLCN1 gene (7q34) • Thomsen disease CLCN1 gene (7q34) • Schwartz-Jampel myotonia HSPG gene (1 • Von Eulenburg paramyotonia SCN4A gene (17q23)	Sporadic myopathy and fatigue syndromes MELAS MERRF Kerns Sayre

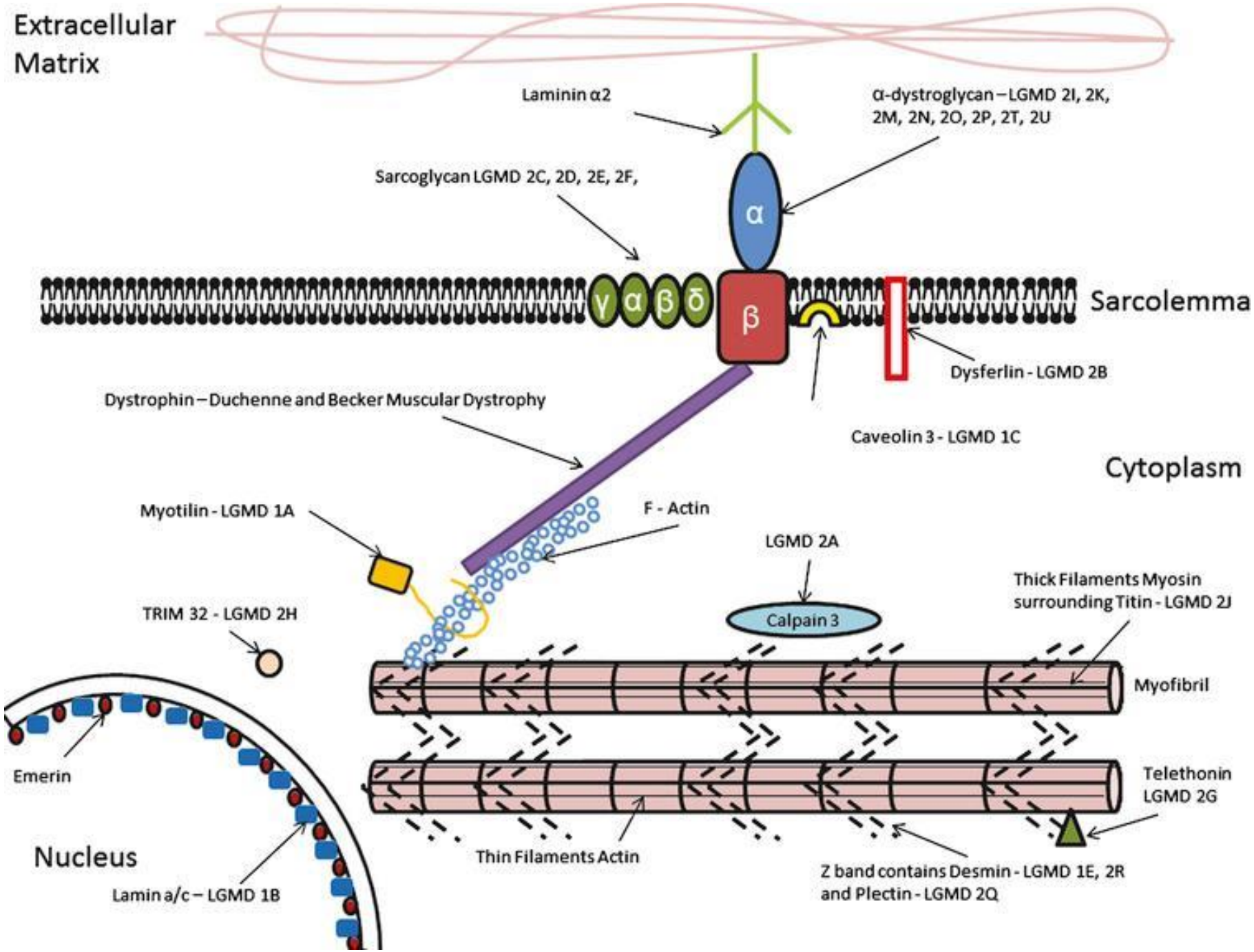
Limb Girdle Muscular Dystrophy spectrum

LGMD1

LGMD1A	**Myotilin**	**5q31**
LGMD1B	**Lamin A/C**	**1q21**
LGMD1C	**Caveolin-3**	**3p25**
LGMD1D	**DNAJB6**	**7q36**
LGMD1E	**Desmin**	**2q35**
LGMD1F	**TNPO3**	**7q32**
LGMD1G	**HNRPDL**	**4q21**
LGMD1H	**??**	**3p23**

LGMD2

LGMD2A	***Calpain-3***	**15q15**
LGMD2B	***Dysferlin***	**2p13**
LGMD2C	***γ-Sarcoglycan***	**13q12**
LGMD2D	***α-Sarcoglycan***	**17q21**
LGMD2E	***β-Sarcoglycan***	**4q12**
LGMD2F	***δ-Sarcoglycan***	**5q33**
LGMD2G	**T*elethonin***	**17q12**
LGMD2H	***TRIM32***	**9q33**
LGMD2I	***FKRP***	**19q13**
LGMD2J	***Titin***	**2q24**
LGMD2K	***POMT1***	**9q34**
LGMD2L	***ANO5***	**11p14**
LGMD2M	***Fukutin***	**9q31**
LGMD2N	***POMT2***	**14q24**
LGMD2O	***POMGnT1***	**1p32**
LGMD2P	***DAG1***	**3p21**
LGMD2Q	***Plectin***	**8q24**
LGMD2R	***Desmin***	**2q35**
LGMD2S	***TRAPPC11***	**4q35**
LGMD2T	***GMPPB***	**3p21**
LGMD2U	***ISPD***	**7p21**
LGMD2V	***GAA***	**17q25**
LGMD2W	***LIMS2***	**2q14**
LGMD2X	***POPDC1***	**6q21**
LGMD2Y	***TOR1AIP1***	**1q25**
LGMD2Z	***POGLUT1***	**3q13**


Extracellular Matrix
Laminin α2
α-dystroglycan – LGMD 2I, 2K, 2M, 2N, 2O, 2P, 2T, 2U
Sarcoglycan LGMD 2C, 2D, 2E, 2F,
α
γ α β δ
β
Sarcolemma
Dysferlin - LGMD 2B
Dystrophin – Duchenne and Becker Muscular Dystrophy
Caveolin 3 - LGMD 1C
Cytoplasm
Myotilin - LGMD 1A
F - Actin
LGMD 2A
Thick Filaments Myosin surrounding Titin - LGMD 2J
TRIM 32 - LGMD 2H
Calpain 3
Myofibril
Telethonin LGMD 2G
Emerin
Nucleus
Lamin a/c – LGMD 1B
Thin Filaments Actin
Z band contains Desmin - LGMD 1E, 2R and Plectin - LGMD 2Q

Acquired muscular disorders

Inflammatory	Infectious	Endocrine	Toxic and Drug induced	Secondary metabolic myopathies
• Polymyositis • Dermatomyositis • Inclusion-body myositis • Cancer associated myositis • Myositis associated with autoimmune disease • Juvenile benign myositis	Viral • Influenza • Dengue • HIV, HTLV1 Bacterial • Leptospirosis • Lyme • Pyomyositis • Tuberculosis • Legionaire • Typhus Parasitic • Trichinosis • Toxoplasmosis	Thyroid • Hypothyroidism • Hyperthyroidism Parathyroid disease • Hypoparathyroidism • Hyperparathyroidism Corticostéroids • Steroid myopathy • Acromegaly • Corticoid binding protein deficiency	D penicillamin AZT Corticoids Colchicin Statin Alcohool	Diabetes mellitus Malignant hyperthermia

BRAIN

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ON THE CLASSIFICATION, NATURAL HISTORY AND TREATMENT OF THE MYOPATHIES

BY

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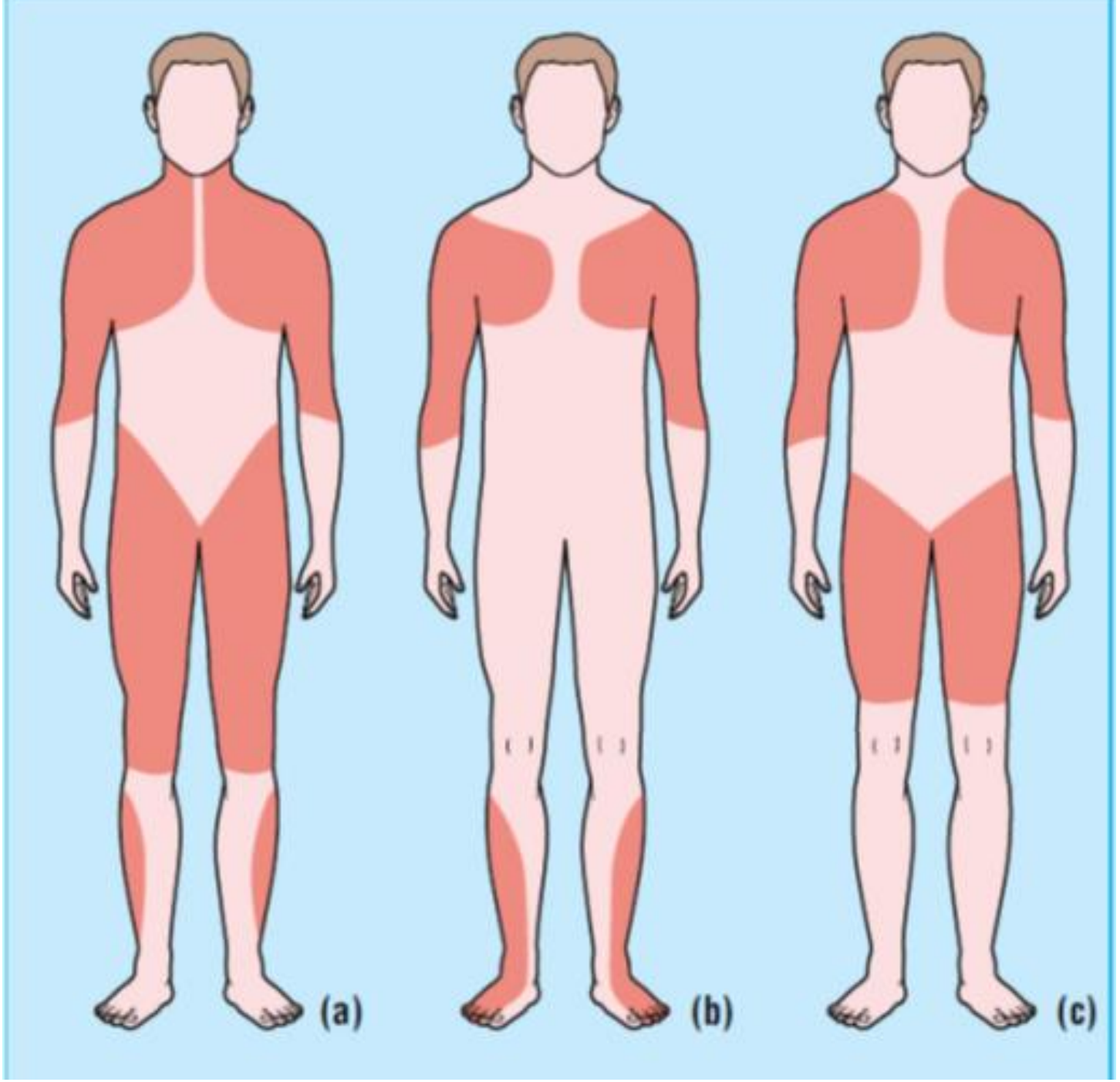
INTRODUCTION

IN the early part of the nineteenth century numerous reports appeared in the medical literature describing cases in which progressive atrophy of the voluntary muscles occurred. Aran in 1850 gave a detailed clinical

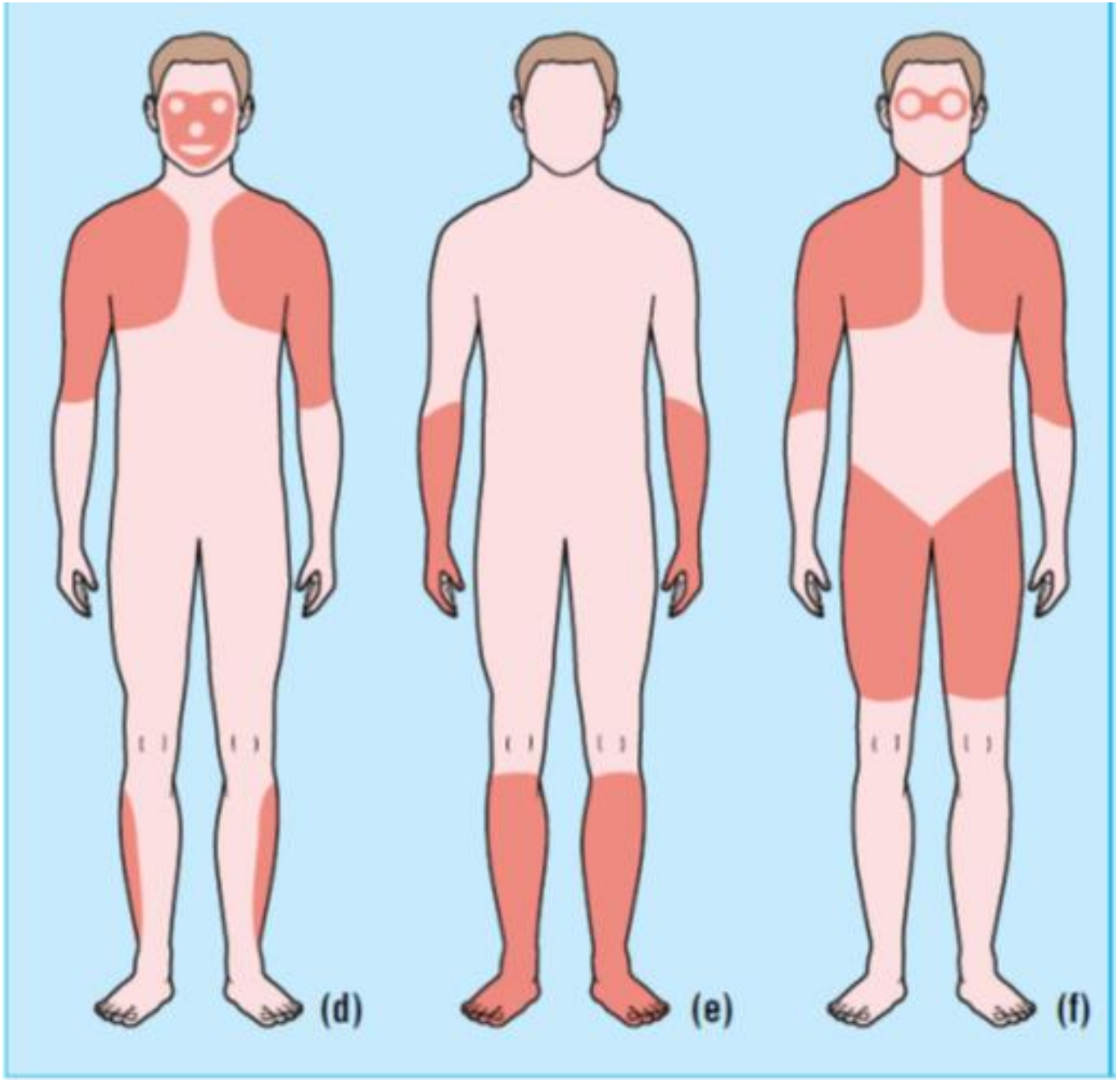
Classification of WALTON and NATTRASS (1954)

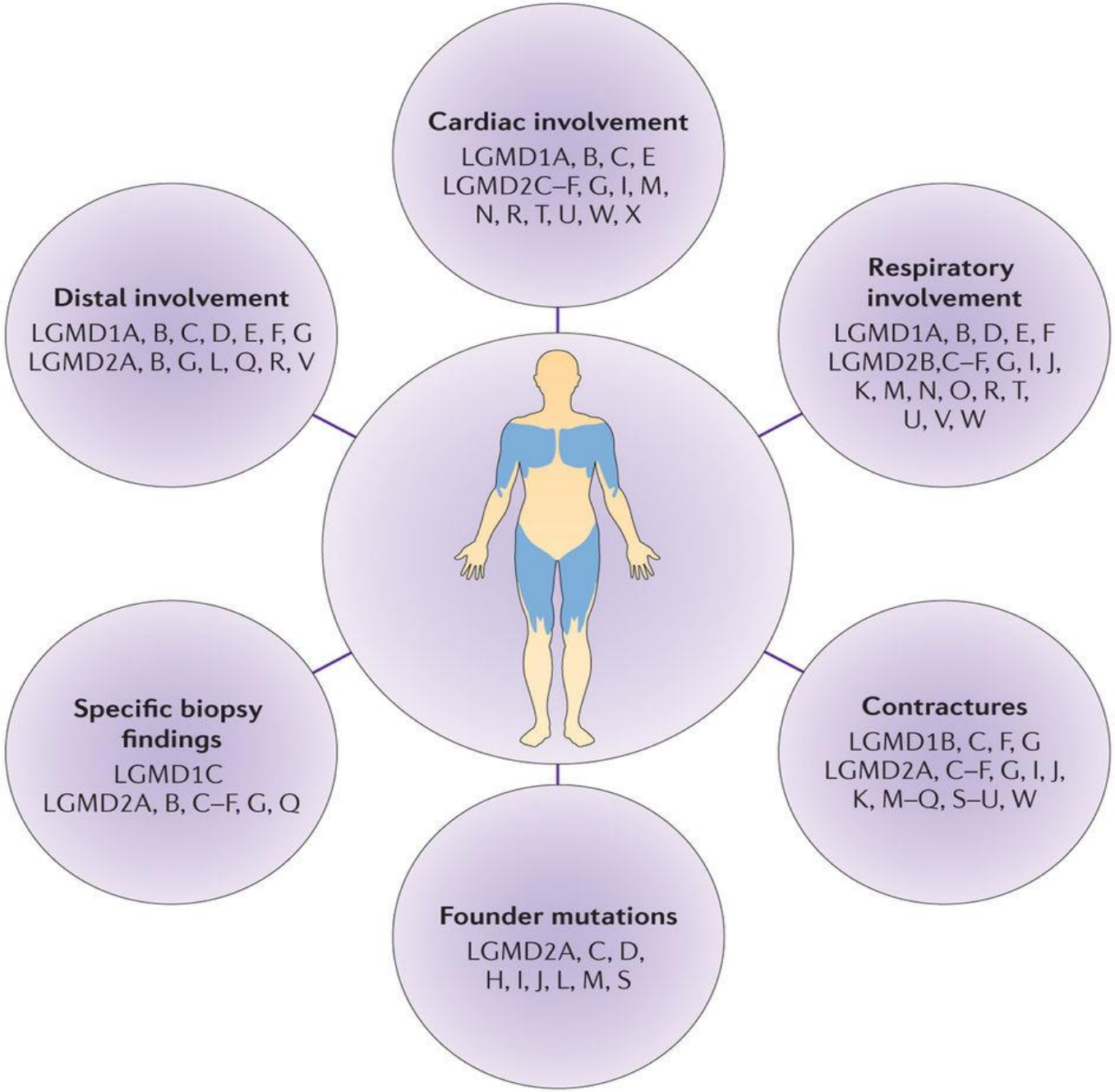
a) Duchenne-type and Becker-type
b) emery-Dreyfuss type
c) limb girdle muscular dystrophy



Classification of WALTON and NATTRASS (1954)

d) facioscapulohumeral
e) distal
f) oculo-pharyngeal





Clinical aspects of LGMD

Epidemiology of NMD in Sub Saharan Africa

Prevalence of muscular dystrophies: a systematic literature review

Neuroepidemiology 2014;43:259–268

NMD in SSA

- There are studies from South Africa and northern Africa (Egypt, Tunisia, Libya, Algeria and Morocco) *la myopathie maghrébine*

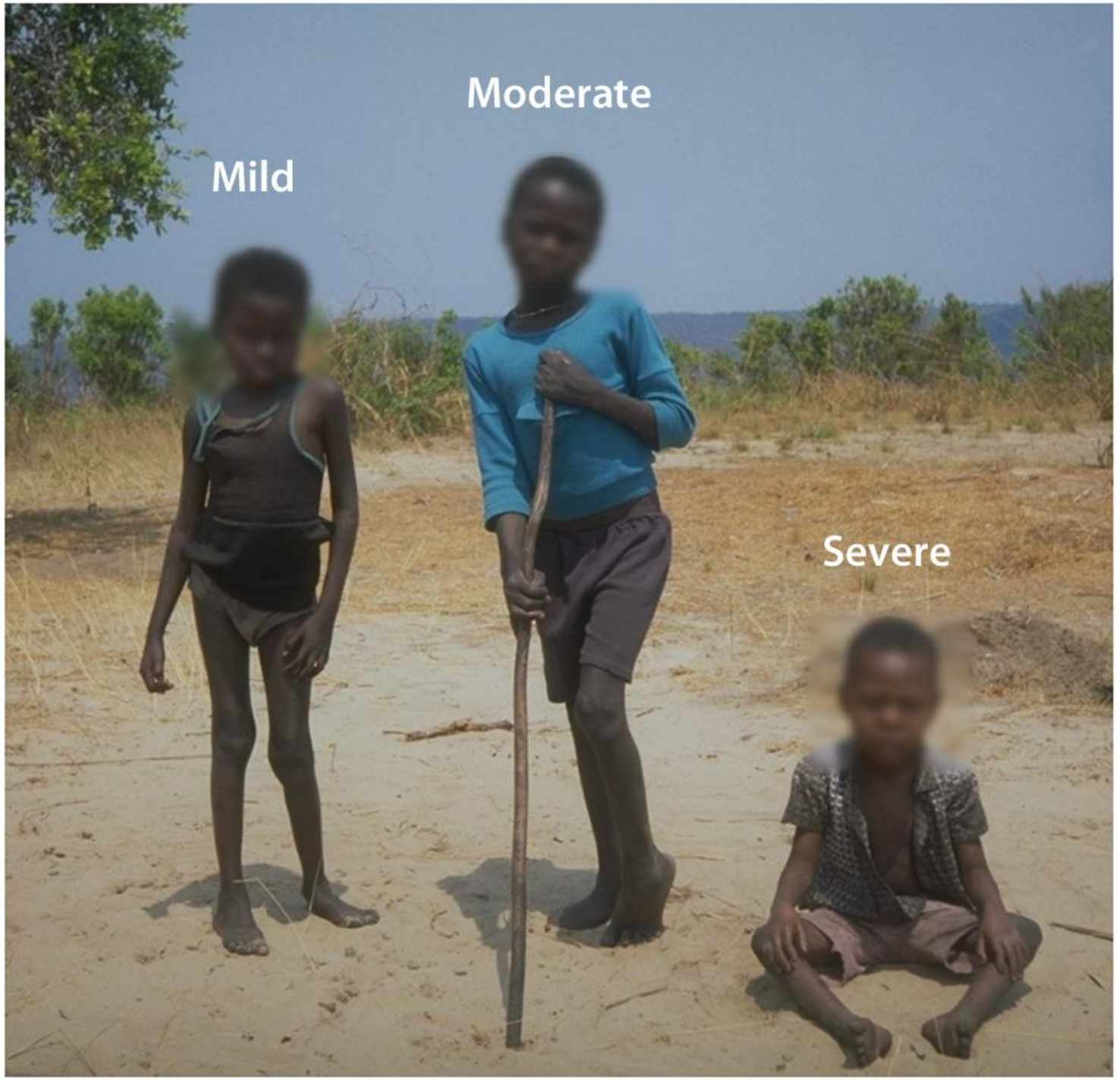
- Studies on tropical spastic paraparesia (TSP/HAM) in Sub Saharan Africa by Dumas et *Al*, have shown the role of HIV and HTLV-1
  - 15-20% of cases of PST in SSA have a viral aetiology
  - The rest are various nutritionnal, toxic or unknown aetiologies

- Scarce studies in sub-Saharan Africa, mainly hospital datas on ALS, NMJ diseases, and peripheral neuropathies (GBS)

2 diseases of epidemiological importance:

- Konzo
- Lathyrism

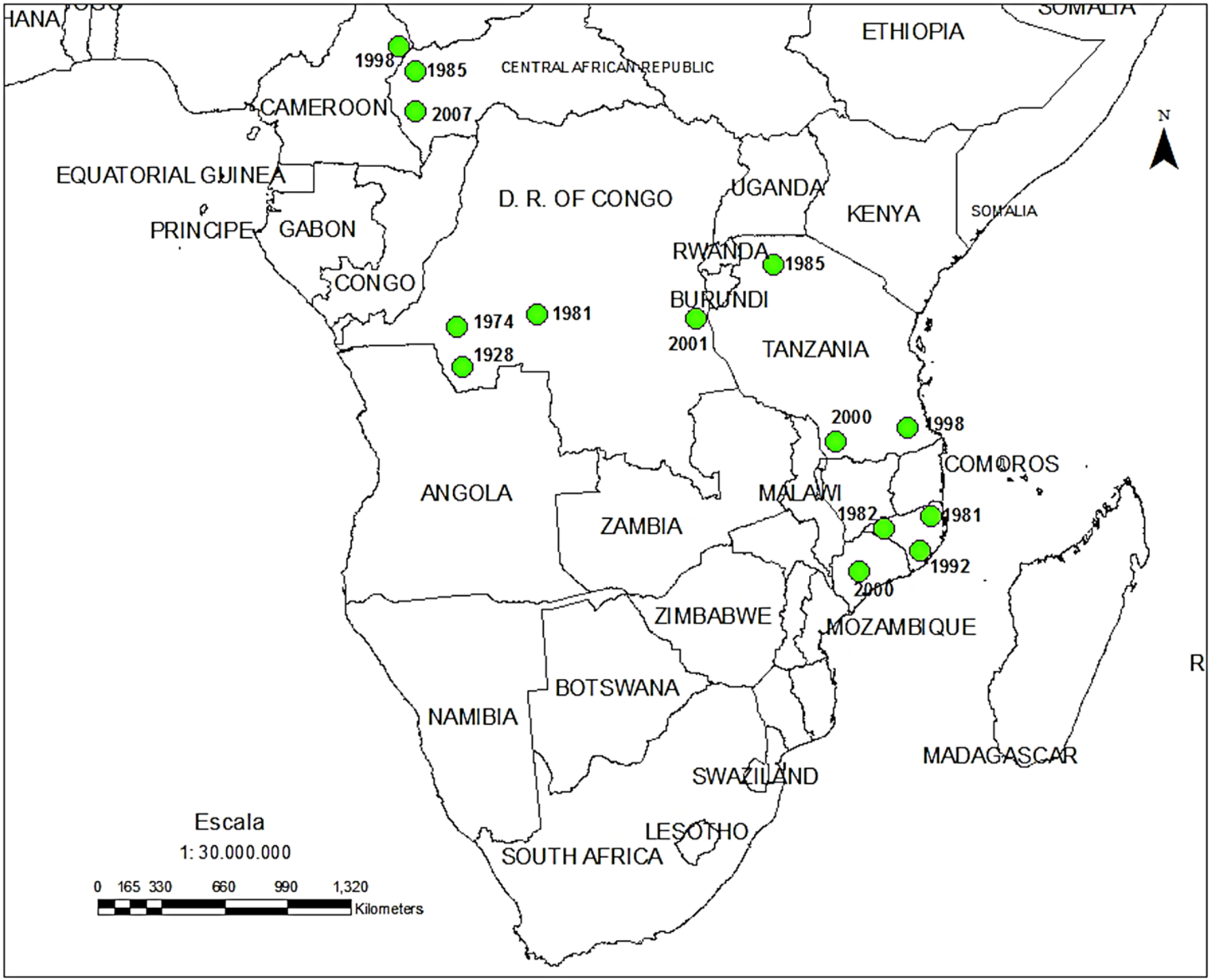
1 clinical entity: Tropical neuromyelopathy



Clinical presentations of KONZO

Image Credit: Thorkild Tylleskar

Manihot esculenta

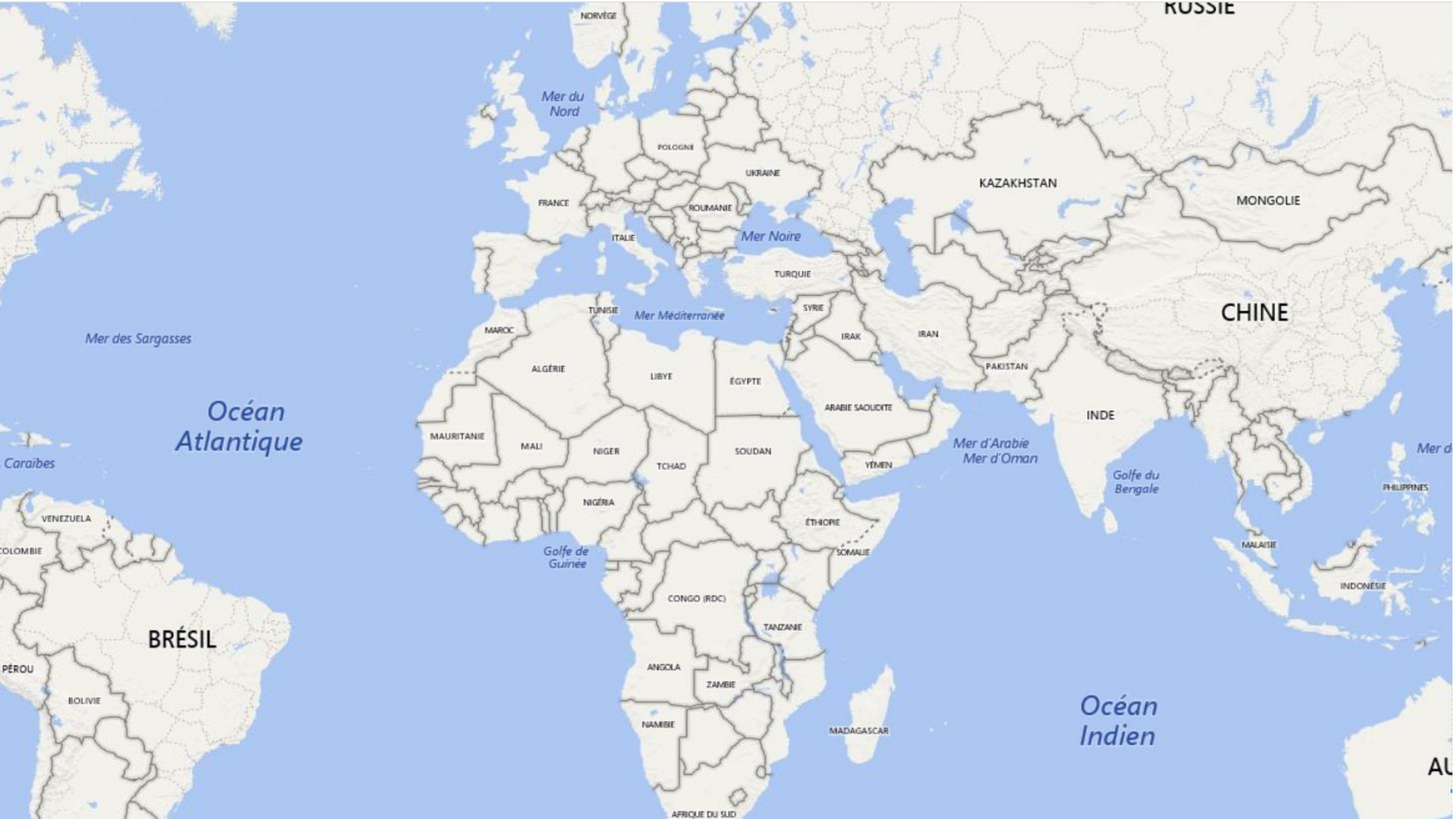


Geographic area of Konzo

Lathyrus Sativus: a lifesaver in times of famine but is toxic if consumed as a major part of the diet over an extended period of time.

Origin and geospatial distribution of *Lathyrus sativus*

Tropical neuromyelopathy



Environmental, nutritionnal (toxic), infectious factors evoqued.

Tropical Ataxic Neuropathy

Our study of diseases of the nervous system in the tropics is now in the stage which the neurology of temperate climates reached about 50 years ago—namely, recognition, description, and analysis of disorders and their correlation with the underlying pathological lesions.[1] Though recent work has suggested that certain obscure tropical neurological syndromes such as kuru,[2] which has been observed in New Guinea, and possibly the Parkinsonism-dementia complex occurring in the

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- *http://neuromuscular.wustl.edu/*
- *www.musclegenetable.fr/*
- *www.fitima.org/*


Thank You