Polyneuropathies and myopathies in SSA children: diagnostics, neurogenetics and therapeutic management

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Topics

- Not just genetics….

- What is relevant / prevalent in LMICs?
- How does this relate to care?
- What should standard care be?
- What are future priorities?

What is relevant / prevalent in LMICs?

Neuromuscular diseases in LMIC - Africa

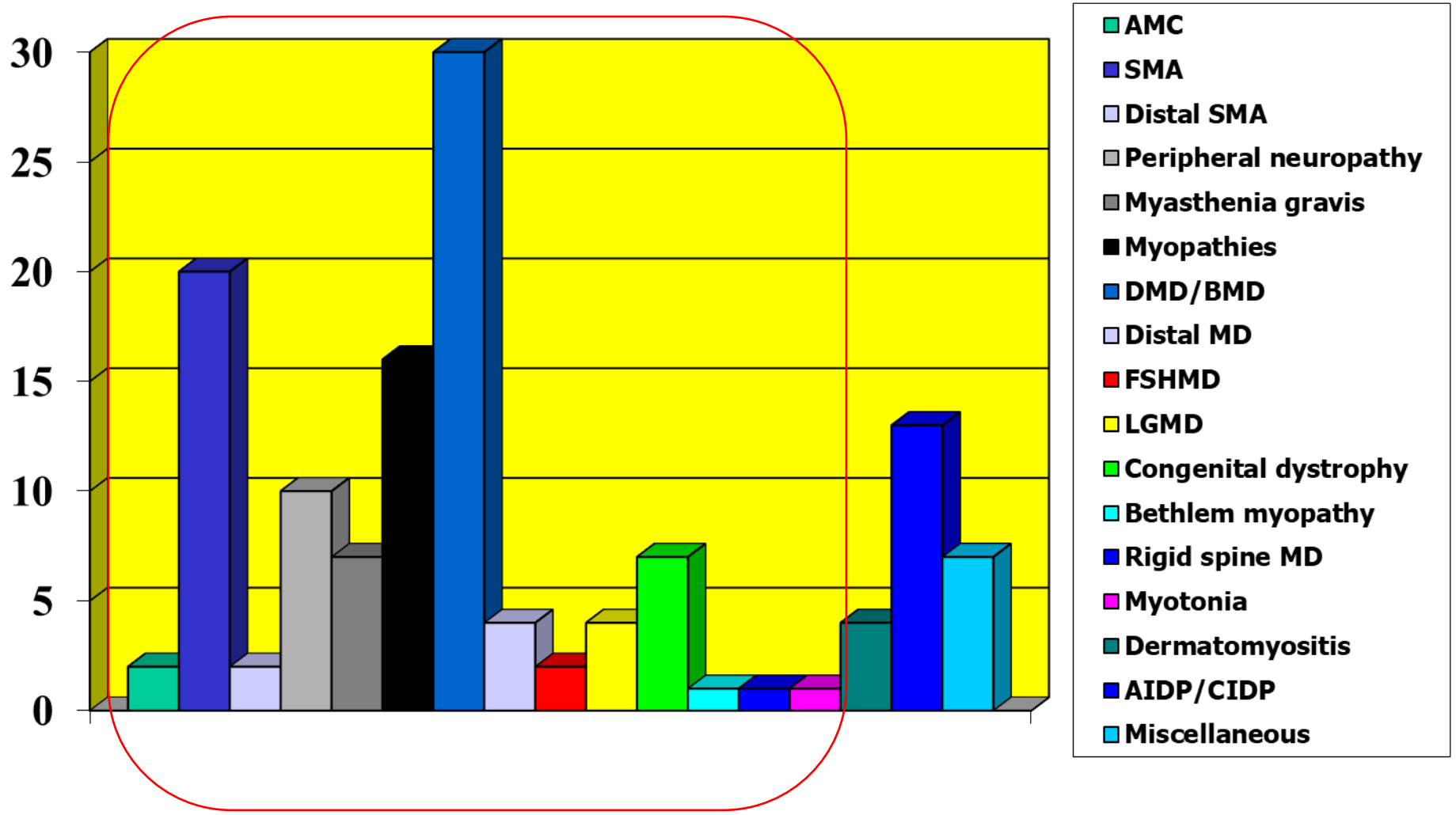
Using search terms “*neuromuscular disease*” “*children*” “*Africa*”

Main results:-

- Infections
  - Polio
  - Enteroviruses
- Secondary complications
  - HIV
  - Erroneous injection sites
- Nutritional conundrums
  - Konzo / cassava

Very little on genetic disorders…….

Neuromuscular clinic stats



where are the genetic disorders?

Realities and Challenges

- In most RPC the prevalence of NMD (communicable / non-communicable / genetic) is not known
  - The true burden is not defined
  - This challenges motivation for adequate services

- Related to
  - Limited clinical skills
    - many patients are mislabelled with cerebral palsy
  - Lack of access to diagnostic tools
    - from CSF to CK to muscle biopsy to molecular genetics
  - Limited access to trained rehabilitation therapists and orthotic centres

INFECTIONS

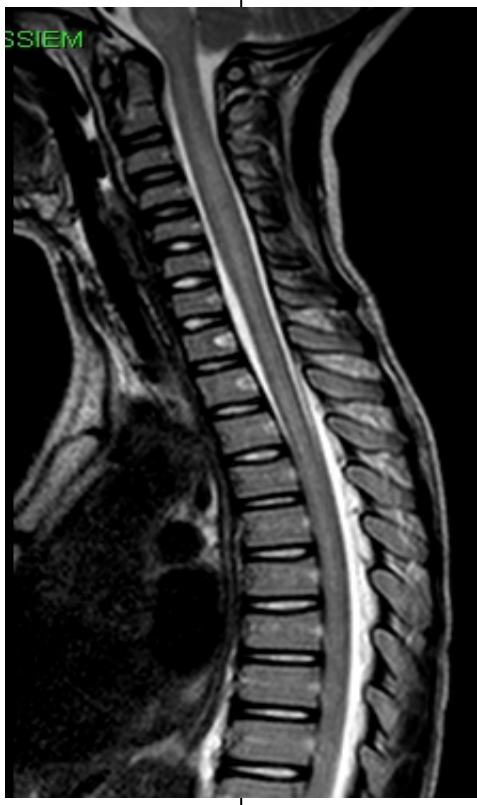
Poliomyelitis

Spectrum of Disease – Entire Neuraxis

Clinical

- Asymptomatic (90 – 95%)
- Abortive poliomyelitis (4 -8%)
- Non-paralytic polio (1 – 5%)
- **Paralytic (spinal; bulbar; bulbospinal) <2%**

- Encephalitis
- Cerebellitis
- Striatal necrosis (IBSN)
- Brainstem encephalitis
- Myelitis (ATM)
- Radiculoneuritis
- (Myositis)



Polio Eradication:
World Health Assembly–2008-2012

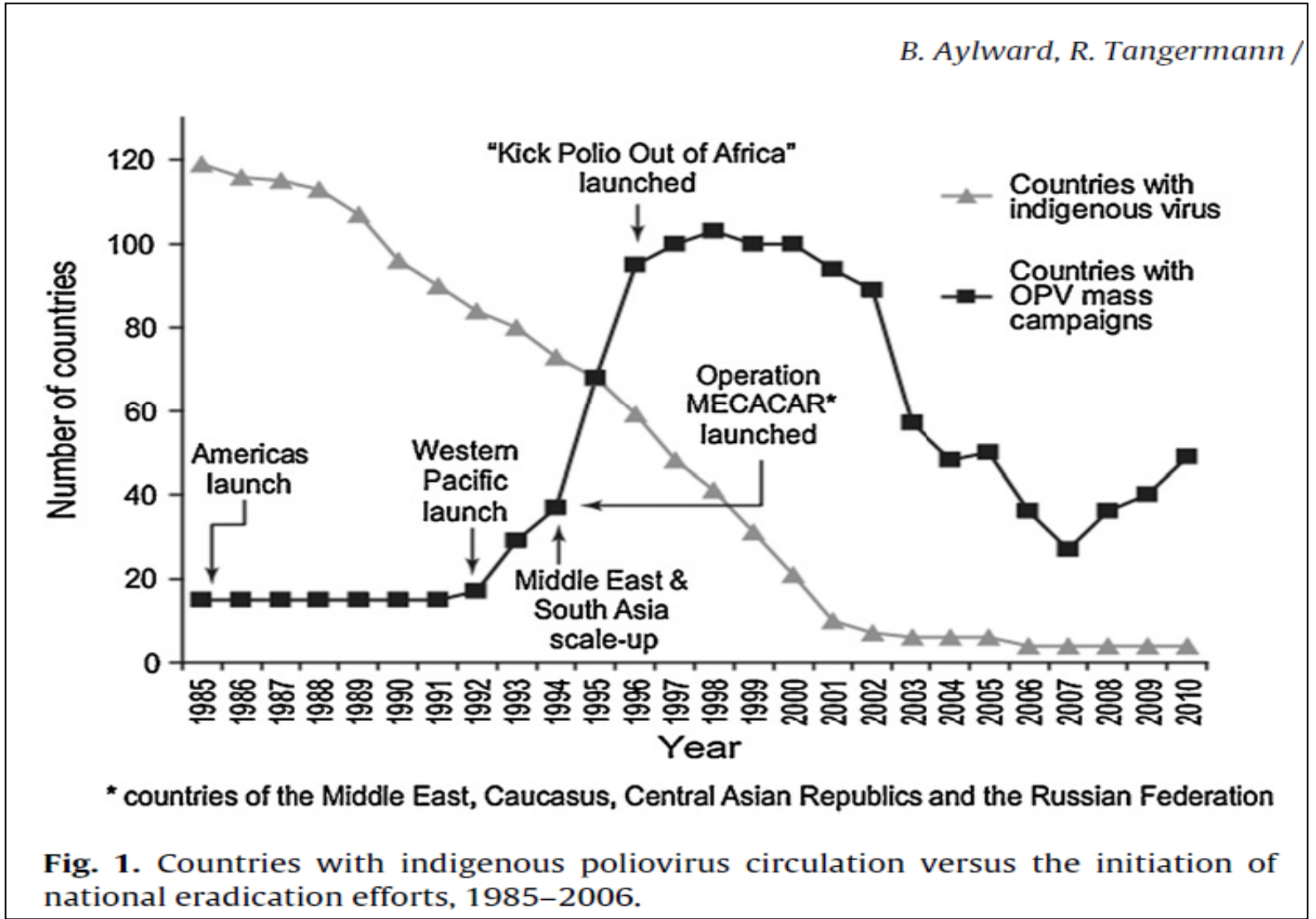
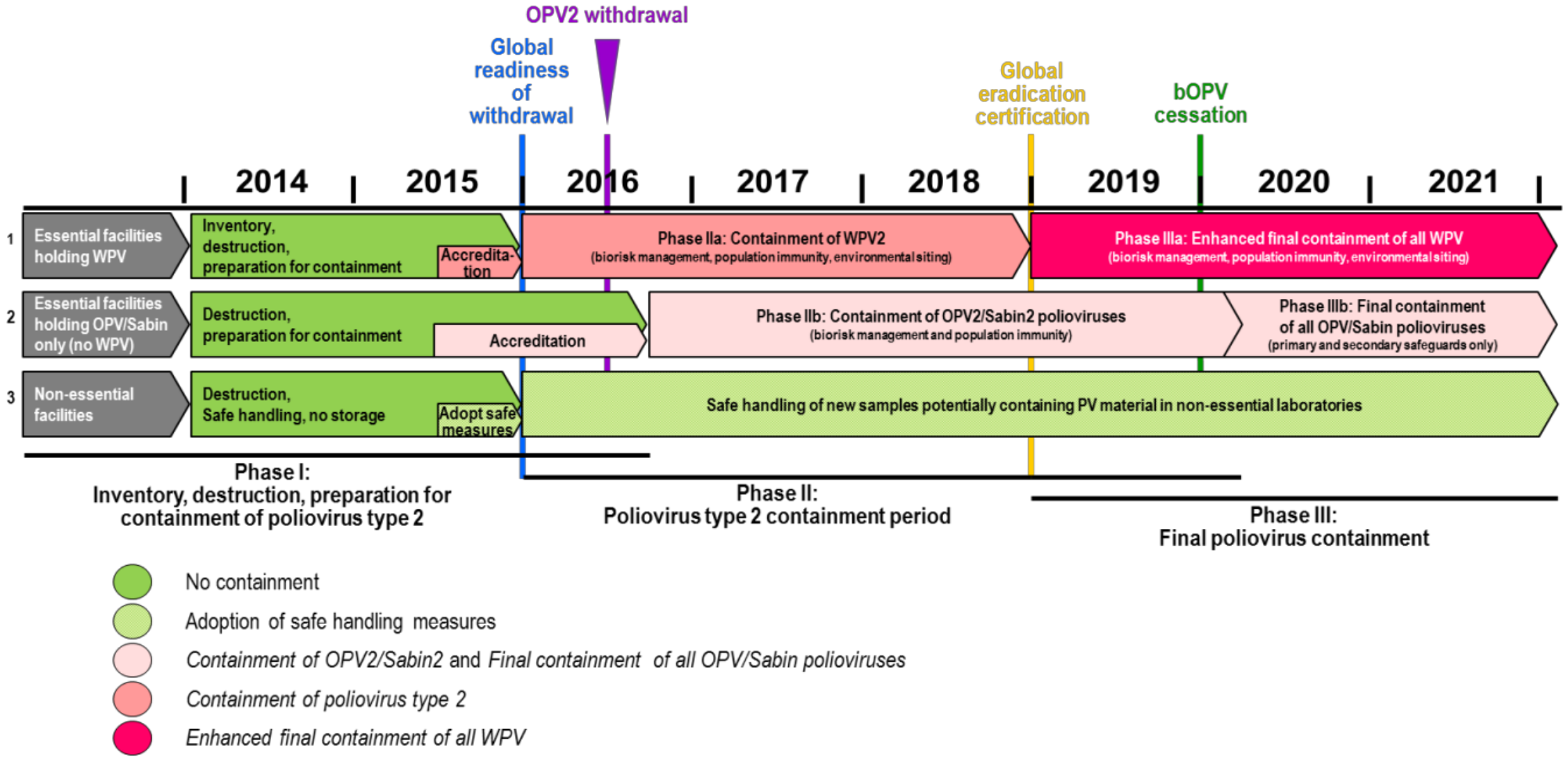


Fig. 1. Countries with indigenous poliovirus circulation versus the initiation of national eradication efforts, 1985–2006.

History

- **WHA voted in 1988** for Global Polio Eradication Programme
- **Then**:
  - 350 000 paralytic cases
    - in 185 countries
- **In 2013**:
  - 3 countries
  - Nigeria, Pakistan, Afghanistan

Milestones of Polio Eradication Process



Enteroviruses

Non-polio Enteroviruses

- Enterovirus D68
- Enterovirus A71

Enterovirus A71 Genogroups C and E in Children with Acute Flaccid Paralysis, West Africa

Maria D. Fernandez-Garcia, Ousmane Kebe, Aichatou D. Fall, Hamet Dia, Ousmane M. Diop, Francis Delpeyroux, Kader Ndiaye

Author affiliations: Institut Pasteur, Dakar, Senegal (M.D. Fernandez-Garcia, O. Kebe, A.D. Fall, H. Dia, K. Ndiaye); World Health Organization, Geneva, Switzerland (O.M. Diop); Institut Pasteur, Paris, France (F. Delpeyroux); Institut National de Santé et de La Recherche Médicale, Paris (F. Delpeyroux)

DOI: http://dx.doi.org/10.3201/eid2204.151588

Review

Global emergence of enterovirus D68: a systematic review

Charlotte Carina Holm-Hansen, Sofie Elisabeth Midgley, Thea Kølsen Fischer

Since its discovery in California in 1962, reports of enterovirus D68 have been infrequent. Before 2014, infections were confirmed in only 699 people worldwide. In August, 2014, two paediatric hospitals in the USA reported increases in the number of patients with severe respiratory illness, with an over-representation in children with asthma. Shortly after, the authorities recognised a nationwide outbreak, which then spread to Canada, Europe, and Asia. In 2014, more than 2000 cases of enterovirus D68 were reported in 20 countries. Concurrently, clusters of children with acute flaccid

Lancet Infect Dis 2016; 16: e64–e75

Published Online February 23, 2016 http://dx.doi.org/10.1016/S1473-3099(15)00543-5

Recent upscale in cases enterovirus D68 worldwide

Journal of Clinical Virology 71 (2015) 1–9

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

European surveillance for enterovirus D68 during the emerging North-American outbreak in 2014

Randy Poelman[a,*], Isabelle Schuffenecker[b], Coretta Van Leer-Buter[a], Laurence Josset[b,c], Hubert G.M. Niesters[a], Bruno Lina[b,c], on behalf of the ESCV-ECDC EV-D68 study group[1]

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[b] *National Enterovirus Reference Centre, Laboratoire de Virologie, Centre de Biologie Est des Hospices Civils de Lyon, Bron, France*

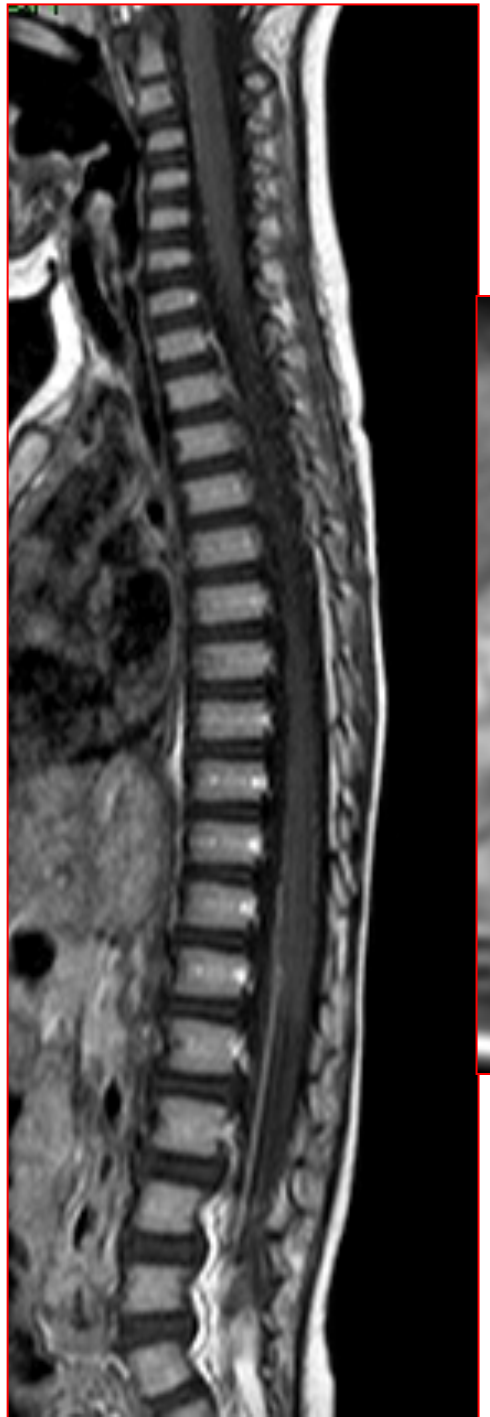
[c] *Virpath Lab, EA4610, Faculté de Médecine Lyon Est, Université Claude Bernard Lyon1, Université de Lyon, Lyon, France*

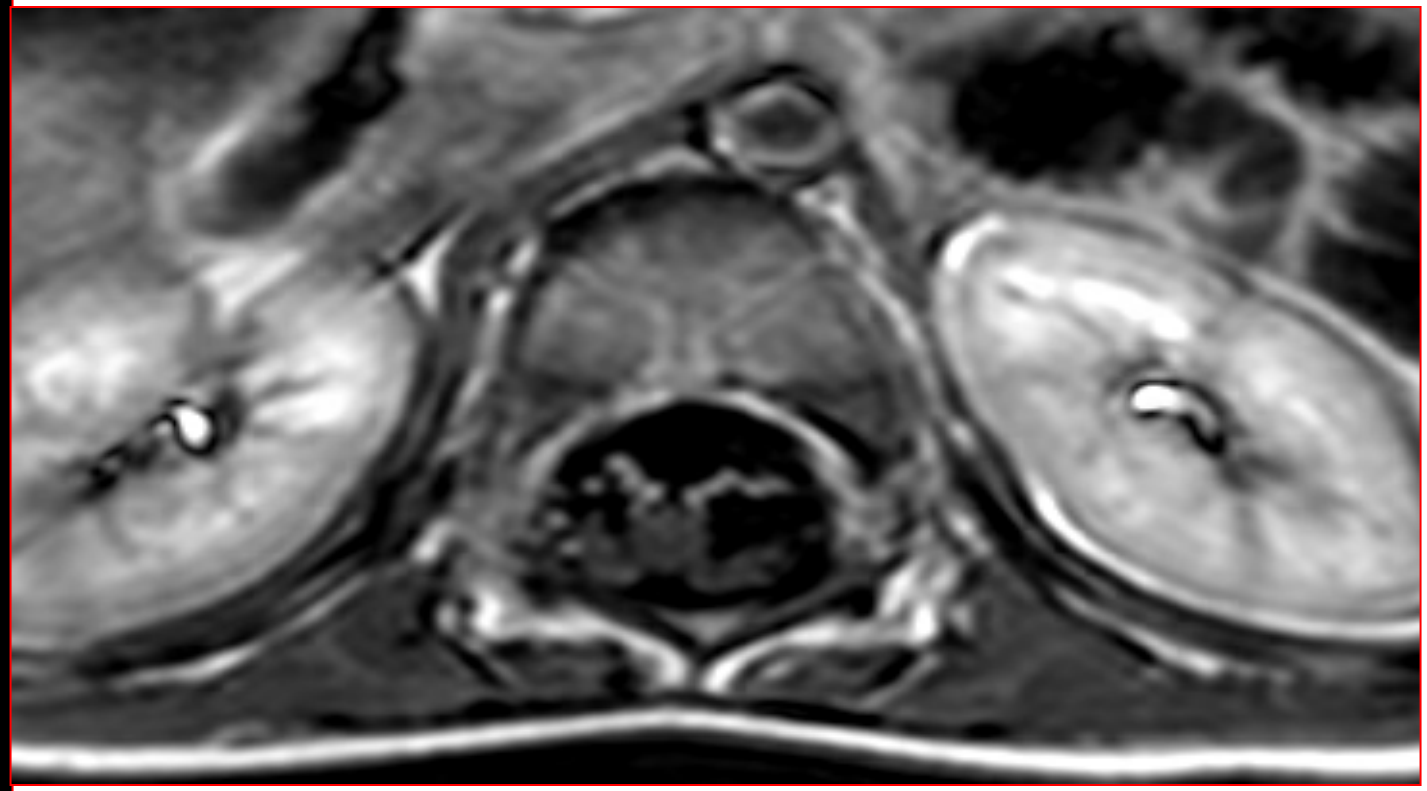
Red Cross War Memorial Children's Hospital, Cape Town, South Africa

- Acute flaccid paralysis (esp. Asymmetric)
  - Excluding patients with AIDP
- N=14 (April 2012 – September 2015)
- Age range: 1 – 12 years (median 4 years)
- Prodrom (n=12; respiratory/gastroenter.)
- Bulbar-respiratory: n=6
- **Enterovirus positive**:

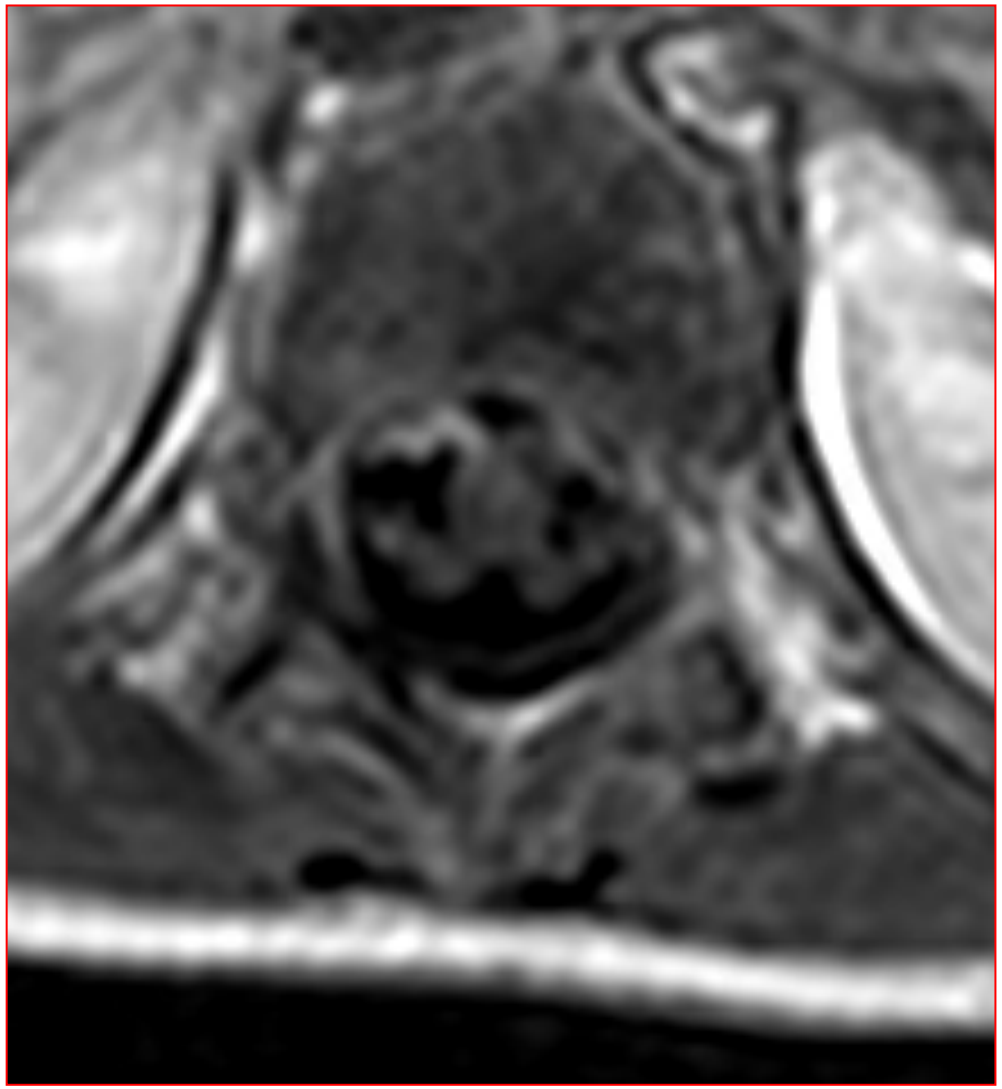
  - (**n=7; 6 stool – NCID lab / 1 NPA**)

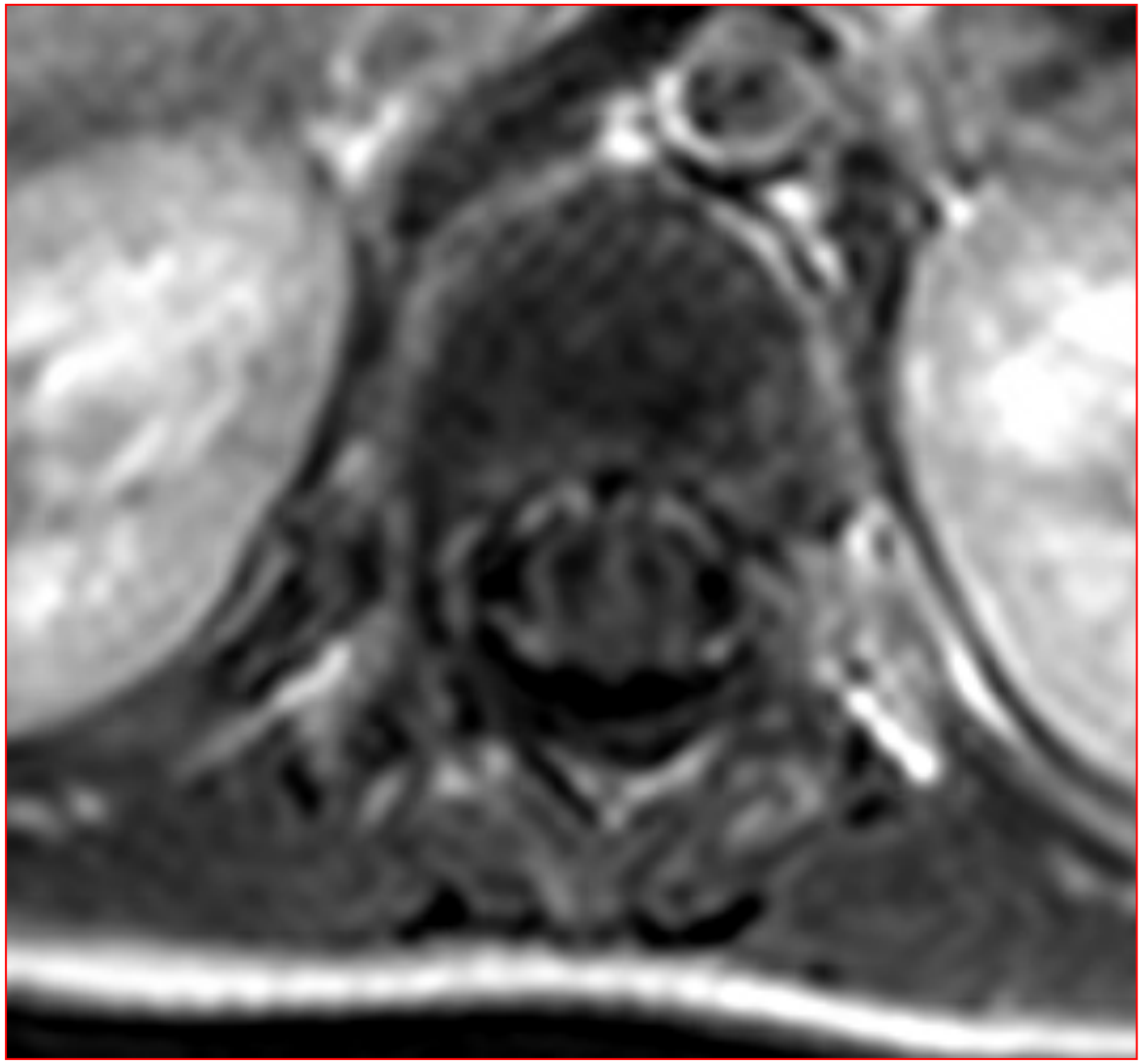
Radiculitis



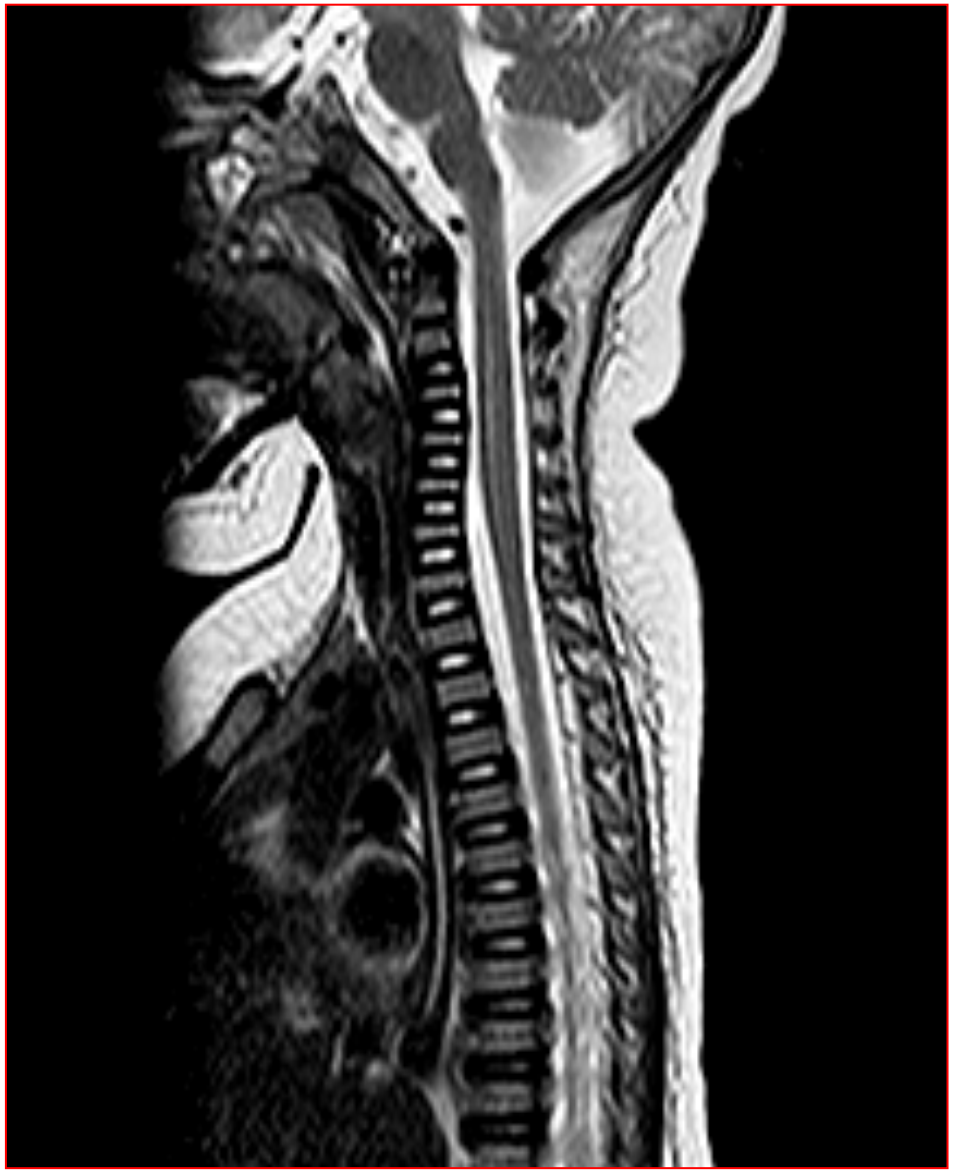


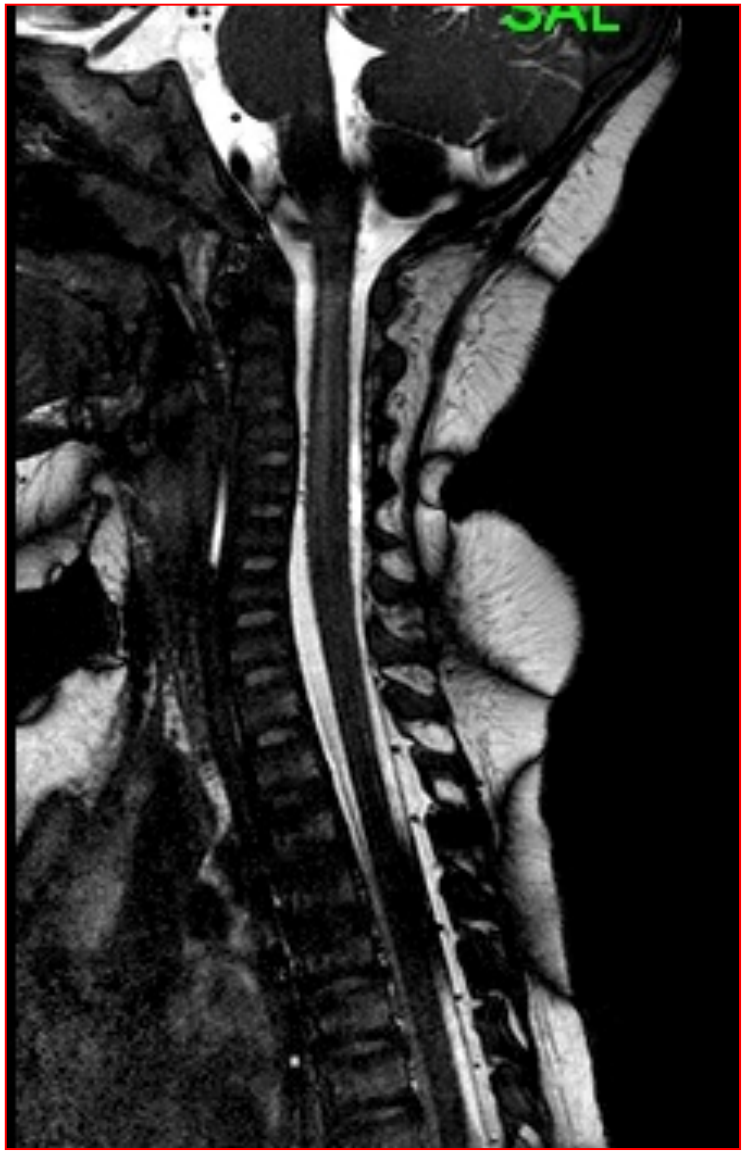
Myeloradiculitis - Asymmetric



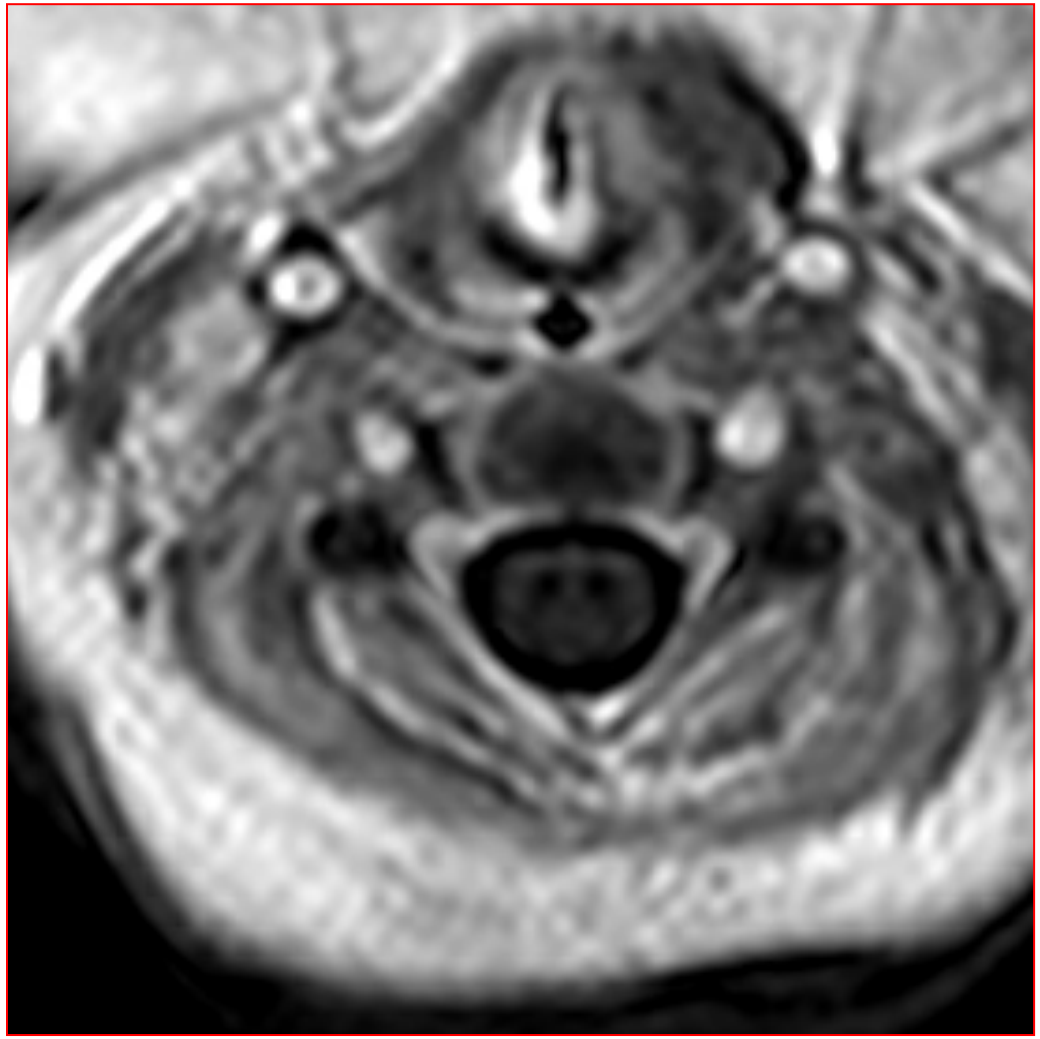


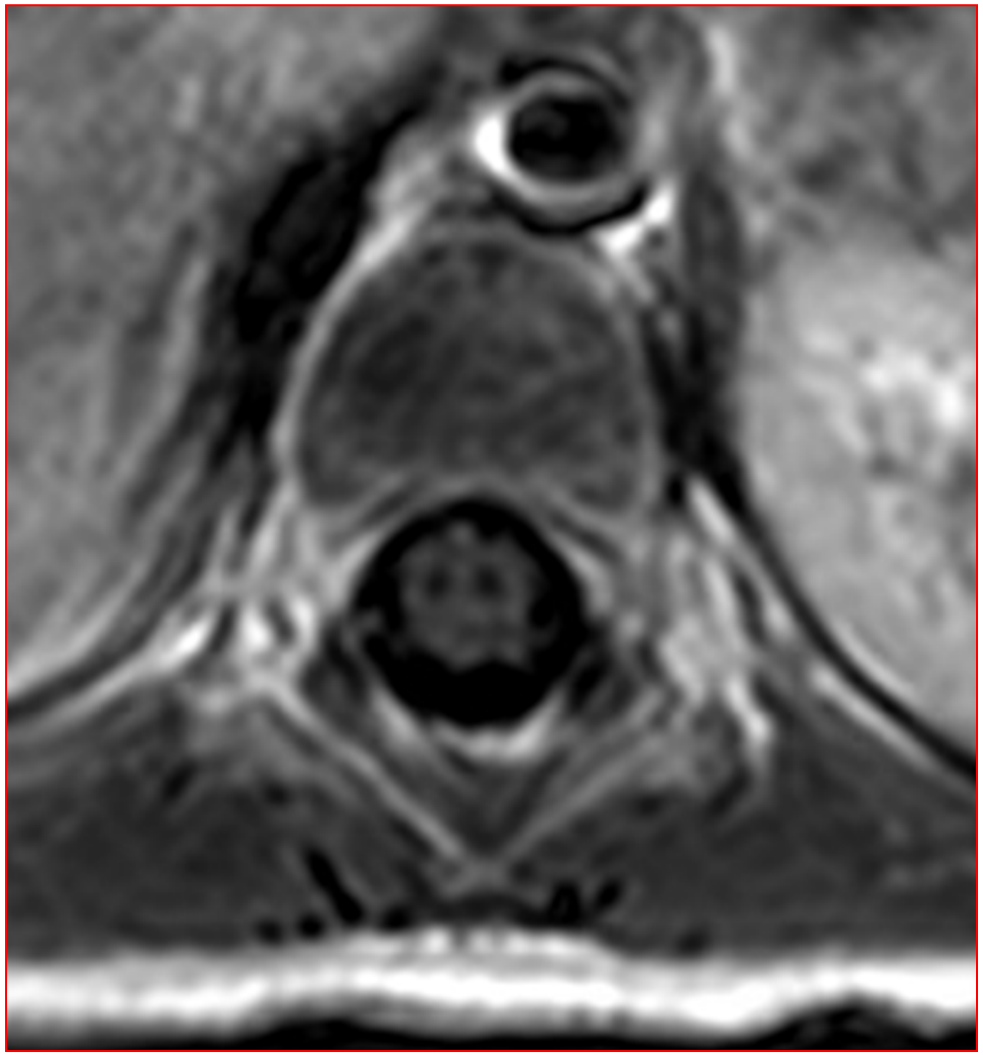
Myelitis – anterior grey matter



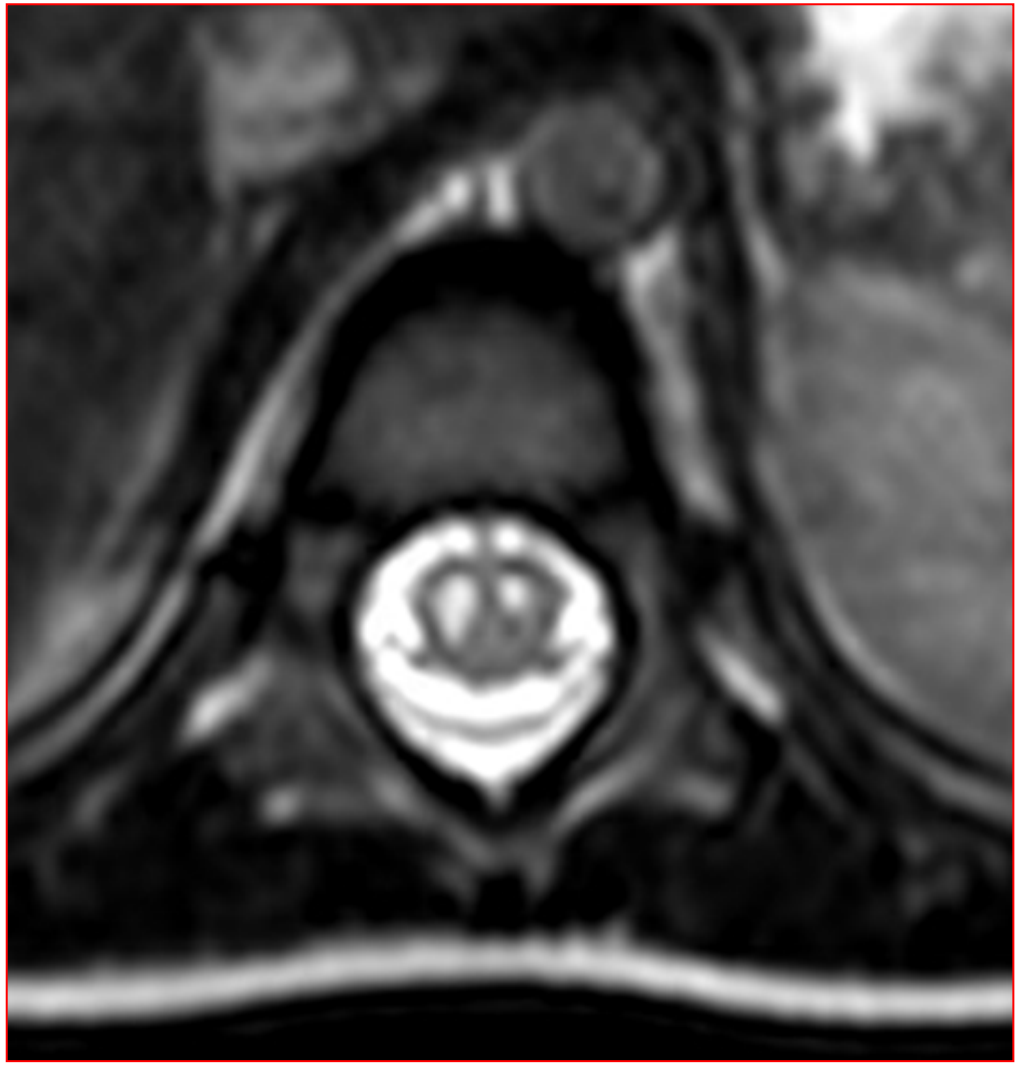


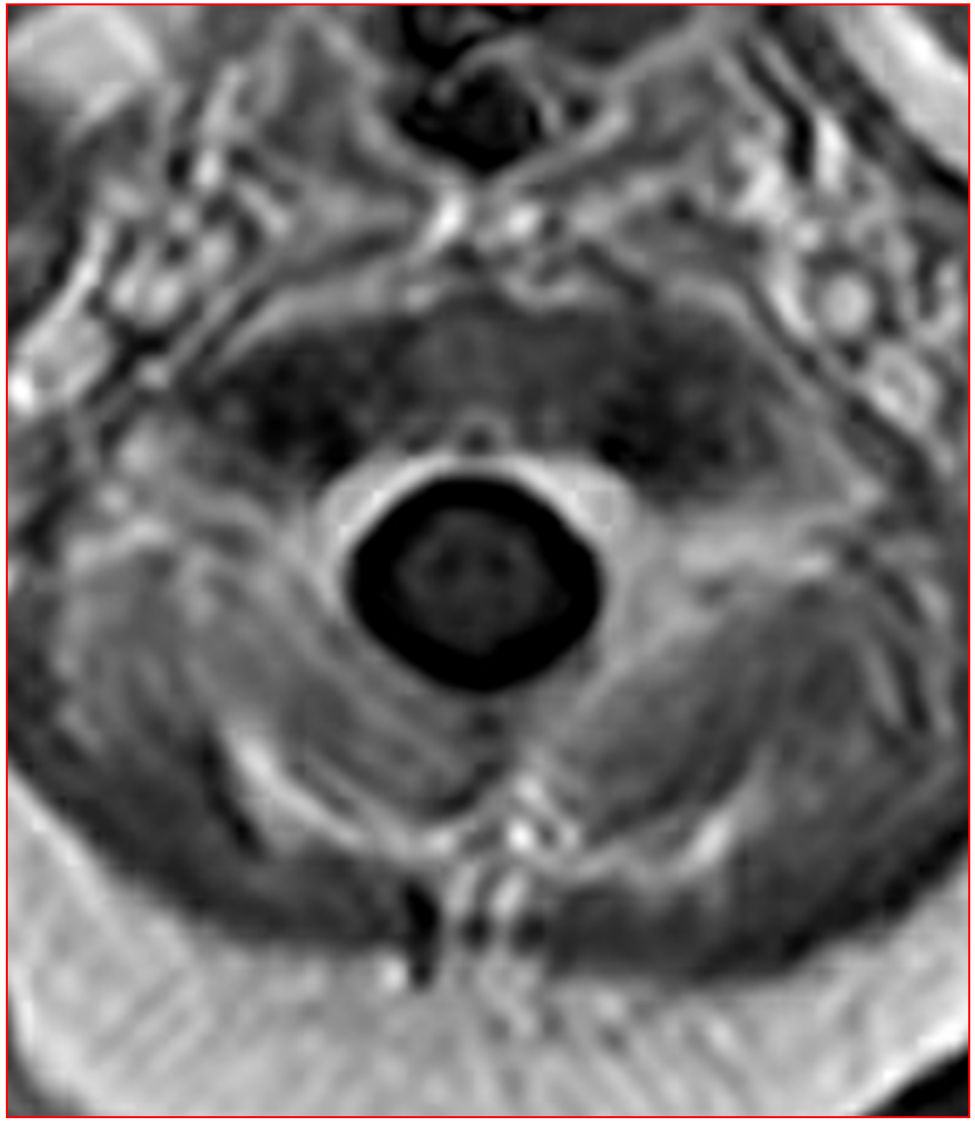
Myelitis – Anterior Horn Cells





Asymmetrical





Outcomes of the Red Cross series

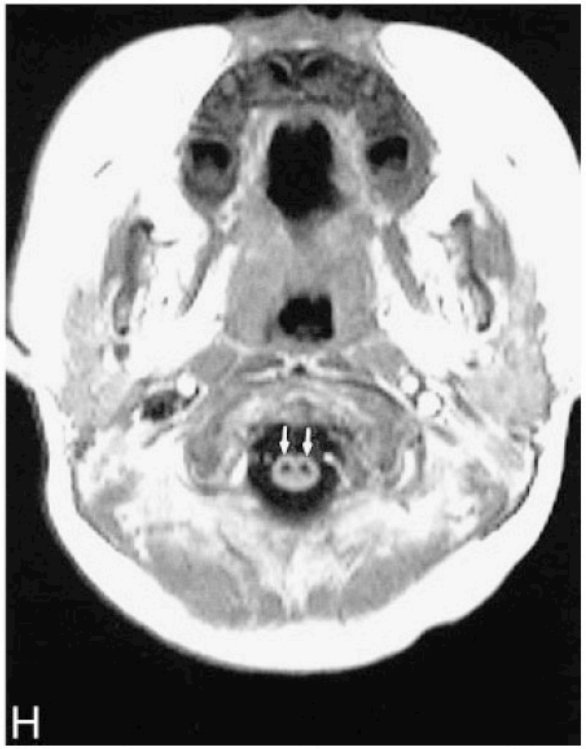
- Survival n=14
- Artificial ventilation n=6

- Residual neurology at discharge n=14
  - asymmetric weakness n=14
  - diaphragm weakness n=1 (home ventilation)
  - bulbar weakness n=1
- Ambulation at discharge n=9

Neuroimaging of patients with non-polio enteroviral infections can mimic poliomyelitis

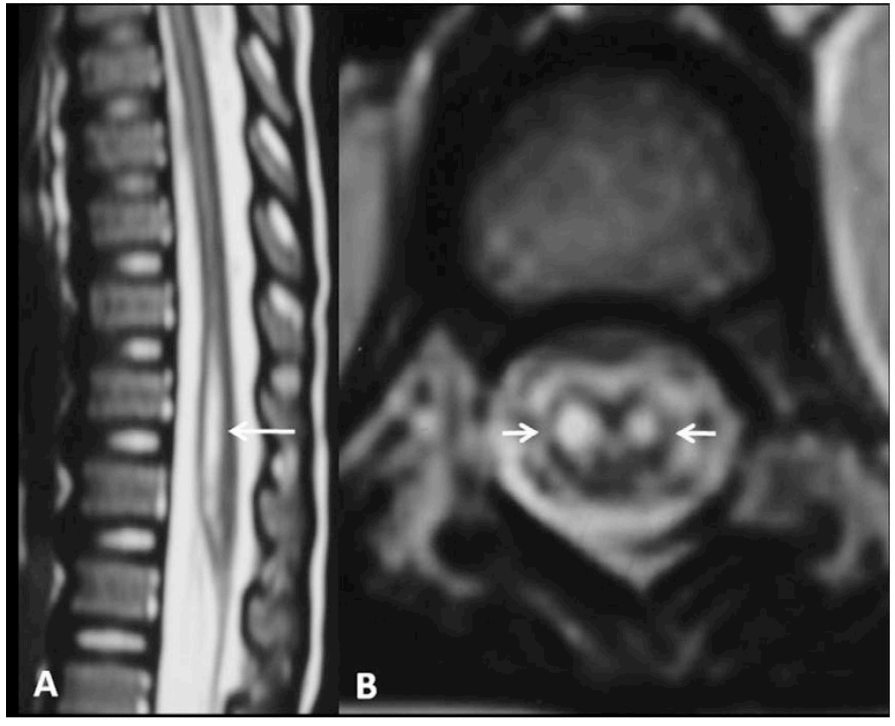
Non-polio enteroviruses

Jang *et al* Neuroradiology 2012 /Shen *et al* AmJNeurorad 1999



Polio

Choudhary *et al* JCN 2010



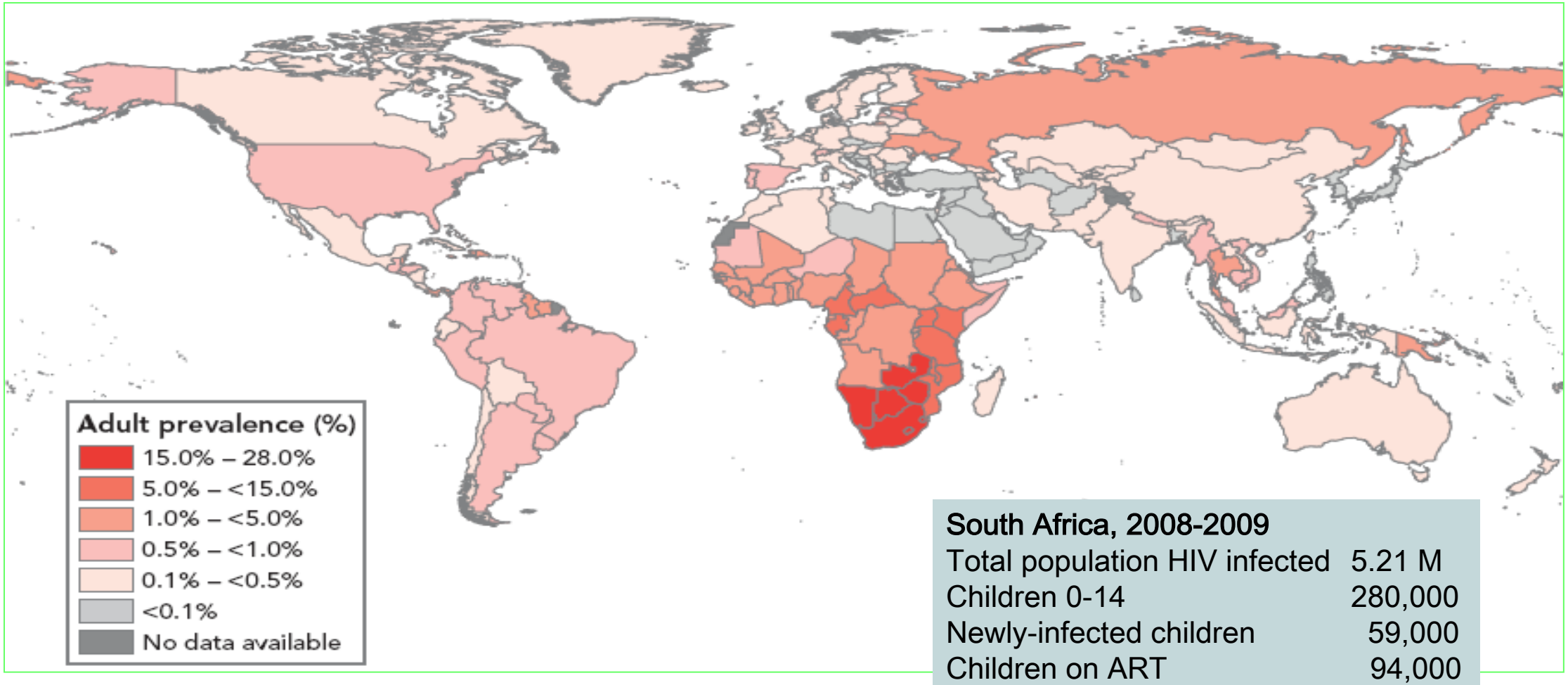
Overall

- Poliomyelitis is soon becoming extinct……
- But **other enteroviruses** continue to affect children and to cause serious morbidity.
- Modern neuroimaging role in aiding diagnosis.
  - Major challenge for access to imaging in LMICs
- Must keep reporting all cases of Acute Flaccid Paralysis

Secondary neuromuscular diseases

A global view of HIV infection

33.4 million people [31.1–35.8 million] living with HIV, 2008
Including 2.1 million children [1.2-2.9 million]



South Africa, 2008-2009	
Total population HIV infected	5.21 M
Children 0-14	280,000
Newly-infected children	59,000
Children on ART	94,000
Estimated ART coverage	61%

UNAIDS, http://www.who.int/lib/publications/global_report/2009/pdf/full_report.pdf
UNICEF, http://www.uniteforchildren.org/files/CA_FSR_LoRes_PDF_EN_USLetter_11062009.pdf
Statistics South Africa, http://www.statssa.gov.za/publications/P0302/P03022009.pdf

HIV

Multiple causes

- Underestimated in children
- Signs may be masked by poor nutritional state
- Paraesthesias and pain most common complaint, then weakness
- Myopathy (rarer in children)
- Vacuolar myelopathy (very rare in children)

- Neuropathy
  - Direct – mutation of Schwann cell nucleus function
  - Opportunistic infection eg cytomegalovirus
  - **Adverse effects of antiretroviral therapy eg stavudine (d4t)**
    - Convenience sample 78/600 – **6%** affected *(Govender et al JCN 2011)*

Guillain-Barré syndrome

- Common and often severe
  - Typically motor axonal type
  - Diaphragm often involved
- **Prolonged hospital stay – tracheostomy / ventilation**

– not viable option elsewhere

- Red Cross experience
  - Prolonged stay
  - 8 children per year
  - Median 4.5 years
  - 31% PICU
    - 28% tracheostomy
  - Mycoplasma, enterovirus commonest identified pathogens

Injection sites

- Acquired foot drop…
- Injections account for 1/5 of all traumatic nerve injuries in LMICs

- Malawian study
- N=50 children with acquired foot drop
- 90% gluteal IM injection of quinine

Namate et al Trop Doc 2012

Shah et al BMJcase reports 2016

Jung Kim and Hyun Park J Int Med Res 2014

Nutritional

Konzo / cassava – Epidemic spastic paraparesis

- Minimal protein intake
- Cassava roots consumption
- Cyanide toxicity

- Prevalent in Nigeria, Tanzania, Sierra Leone, Mozambique, Central African Republic, and Democratic Republic of the Congo.

- 4-12 years and young women.

- Symmetrical spastic parapaesis disease
- **Marked sensory polyneuropathy and ataxia**.

- Overlap with features of dry beriberi.
- The condition may be result of thiamine deficiency from over consumption of cassava roots.

Adamolekun B. Metab.Brain Dis. 2011 Mar;26(1):79-85.
Tshala-Katumbay et al Ann N Y Acad Sci 2016

Genetic conditions

Most commonly seen in SA

- Duchenne muscular dystrophy
- Other MDs (rigid spine, LGMD etc)
- Spinal muscular atrophy
- Congenital myopathies
  - **Centronuclear myopathy**
- CMT

Congenital Myopathies
- Many different types (2008)

• Central core myopathy	n=1
• **Centronuclear/myotubular myop**	**n=14**
• Minicore myopathy	n=1
• Nemaline myopathy	n=2
• Congenital myopathy	n=4
• Congenital dystrophy	n=7

Ryanodine 1 mutations – **9/11** confirmed

Marker	Mb
D19S224	2.46
D19S896	1.51
D19S570	1.26
D19S220	0.56
18xAC	0.27
D19S897	0.23
RYR1	0.00
RYR1_IVS89	0.00
D19S422	0.11
D19S881	0.29
D19S47	1.26
D19S200	1.64

Patient 1

363	378
202	218
212	216
330	338
176	165
302	302
282	282
370	358
229	233
242	246
382	386

Patient 2

383	389
200	196
210	205
329	321
176	165
303	302
267	282
358	358
225	233
236	244
384	391

Patient 3

387	391
196	218
210	212
323	330
166	166
302	309
280	282
358	358
229	233
244	244
376	388

Patient 4

369	369
196	196
205	214
329	332
170	172
302	303
284	282
366	358
231	233
232	242
374	382

Patient 5

363	383
218	200
216	210
338	321
176	165
303	302
267	282
358	358
225	233
244	244
384	388

Patient 6

383	376
200	200
210	210
329	321
176	170
303	304
267	282
358	358
225	238
236	246
384	386

Patient 7

378	380
196	196
210	210
330	317
176	170
302	302
282	278
360	370
229	229
242	244
386	391

Patient 8

356	369
196	241
205	209
329	334
170	172
320	303
280	282
370	358
233	233
232	240
382	382

Patient 9

369	394
196	196
205	212
327	329
165	180
302	303
276	282
375	358
223	233
230	240
388	397

Courtesy of Heinz Jungbluth

Outcome aspects for our patients
Wilmshurst et al Ann Neurol 2010

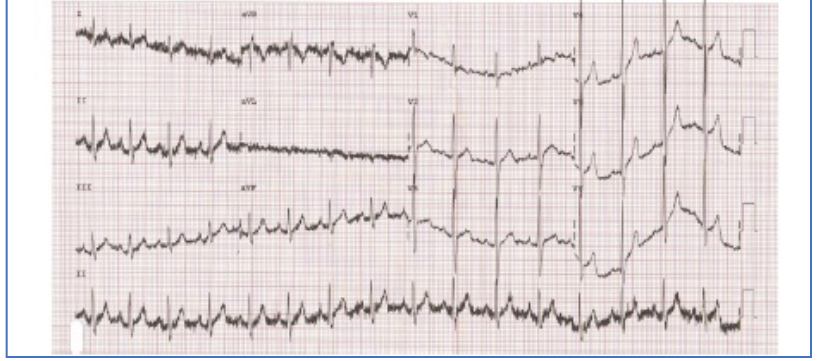
- Centronuclear myopathy is the most prevalent congenital myopathy in Western Cape
- Similar findings across South Africa (personal communication with centres in Gauteng, Kwa-Zulu Natal and Free State)

- Infants profoundly weak
- Show steady improvement, half will gain ambulation
- Early supportive care imperative to maximise their long-term potential
  - Respiratory care
  - Nutrition
  - Ancillary input
  - Caution with anaesthetics – risk malignant hyperthermia

Spinal muscular atrophy

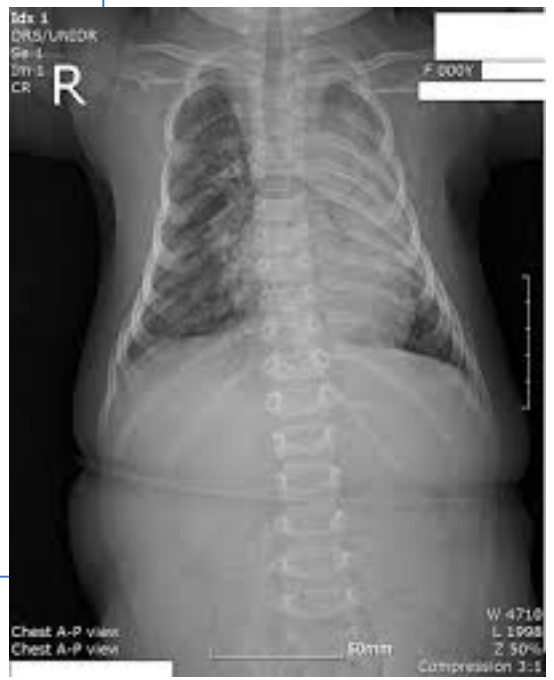
- Programmed cell death of the AHC
- Types 1, 2 and 3
- Genetic diagnosis available and prenatal counselling
- NO cure

Classic phenotype



- many centres are reliant on clinical and basic investigations to confirm the "diagnosis"

- Proximal weakness
- Bell shaped chest *(classic X-ray)*
- Tongue fibrillations *(fibs on ECG)*
- Distal tremor
- Normal facial expression / eye movements
- Normal intelligence



Approach - depends on type

- Type 1 (non-sitters < 1 yr) - supportive, not for ventilation
- Type 2 (sitters – 1-3 yrs) - Lots of physio, monitor the back, appropriate schooling …. Clever children - plan for the future …..
- Type 3 (walkers ± 2-5 yrs) - diagnosis helps a lot – counselling
- Offer salbutamol to type 2 and 3.

J Child Neurol. 2007 Aug;22(8):1027-49. Consensus statement for standard of care in spinal muscular atrophy. Wang CH, et al; Participants of the International Conference on SMA Standard of Care

Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Finkel RS, *et al* Lancet. 2016

- Nusinersen alters splicing of SMN2 pre-mRNA and increases functional survival motor neuron (SMN)
- Open-label, phase 2, **multiple intrathecal doses** of nusinersen in patients with infantile-onset SMA
  - 20 participants
- **INTERPRETATION:**
- Acceptable safety and tolerability, pharmacology consistent with its intended mechanism of action, and **encouraging clinical efficacy.**
- **ETHICS OF THE COST AND ACCESS IMPLICATIONS……**

SMARD - Spinal muscular atrophy with respiratory distress

- Cognitively intact infant
- Diaphragmatic paralysis (3-6 mths)
- Distal weakness
  - Foot and wrist drop
  - Areflexia
- Features typical of SMARD 1 mutation (Spinal muscular atrophy with respiratory distress) / (SIANR - severe infantile axonal neuropathy with respiratory failure)
- *IGHMBP2* mutation

Grohmann et al. Nature Genetics 2001; 29: 75-77

Wilmshurst et al.,Muscle Nerve 2001

Further complications

- Premature adrenarche / ?precious puberty
- Episodes of autonomic dysfunction (pallor / flushes, abdominal bloating / dumping syndrome)
- Complete oral aversion – fully PEG fed.

Messages / Clues

- SMARD1 - most likely under-recognised NMD

- May have a juvenile form – spectrum of disease
- Longitudinal data evident – some plateauing.
- More complex phenotype with additional systemic involvement.

- Ethics of intervention – considering Mx of SMA 1

Bush A 2006 Intens Care Med

Long-term outlook for SMARD1 Eckart *et al* Pediatrics Jan 2012

- Found rapid decline clinical score until 2 years of age
- Plateau in residual capabilities / or even improvement
- Markedly heterogeneous clinical outcome.
- Scores 3 mths of age positive linear correlation with outcome at 1 year and 4 years of age.
- Survivors – 2/3 in kindergarten or school.

Riboflavin transporter deficiency

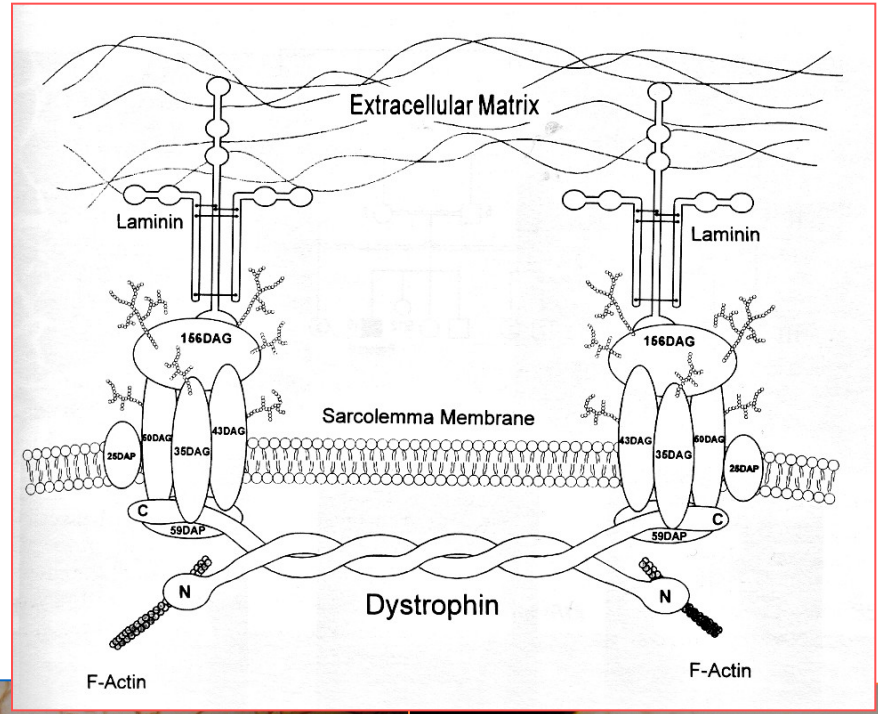
Brown-Vialetto-van Laere syndrome

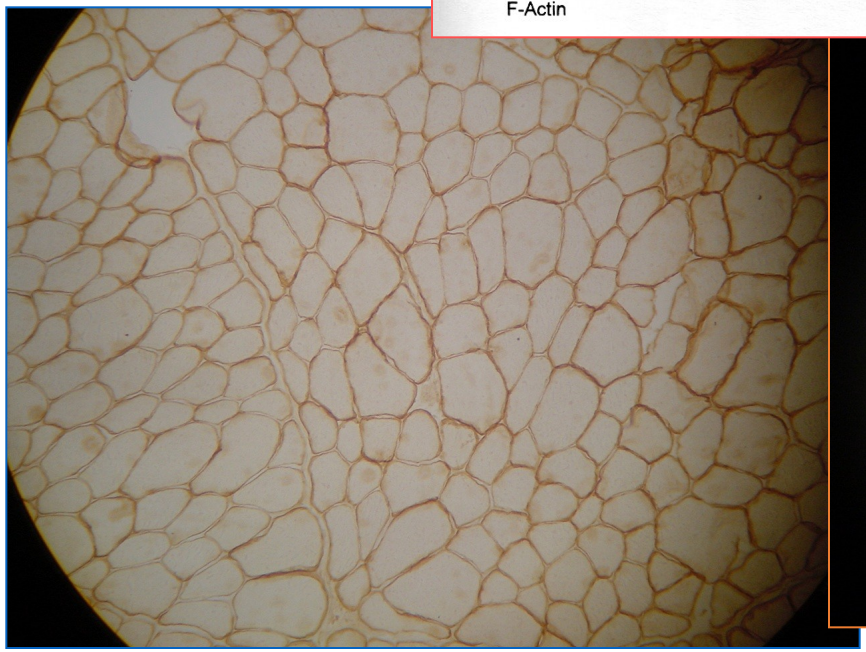
- Rare clinical condition
  - auditory neuropathy
  - bulbar palsy
  - stridor
  - muscle weakness – axonal neuropathy
  - respiratory compromise - diaphragmatic & vocal cord paralysis
- Autosomal recessive condition
  - causative mutations in the riboflavin transport genes(*SLC52A2* and *SLC52A3*)
- Responds to high dose riboflavin (50-80mg/kg/day)

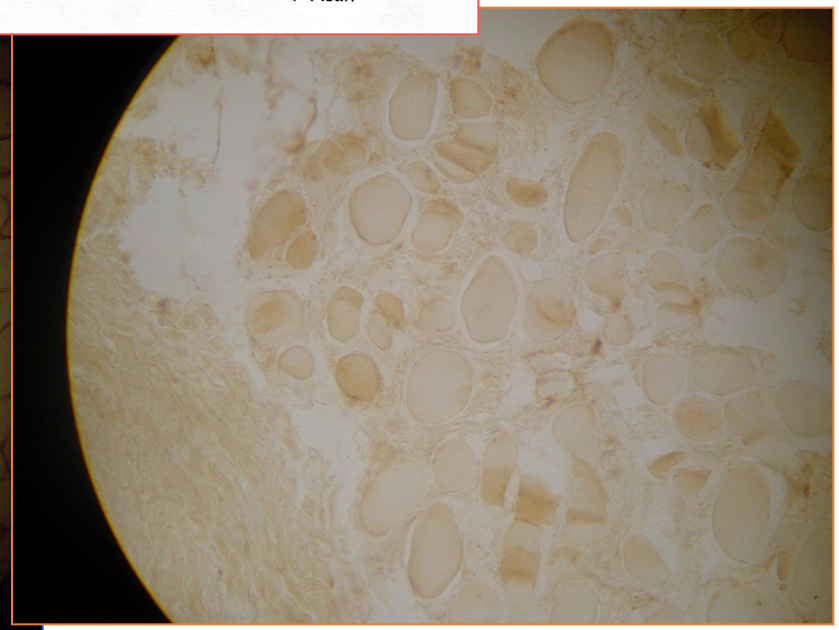
Bosch et al. Orphanet J Rare Dis 7:1, 2012

Duchenne Muscular Dystrophy / BMD

- X-linked condition
- 1 in 3600-6000 live male births
- Presents between 2 - 4 years
- Language delay
- Calf hypertrophy
- Waddling gait
- CK >10 000u/l
- NO CURE …..
- Diagnosis in ~60% molecular genetics
- Treatment symptomatic - physiotherapy, back, T-As, cardiac


Extracellular Matrix
Laminin
Laminin
156DAG
156DAG
Sarcolemma Membrane
50DAG
43DAG
25DAP
35DAG
43DAG
50DAG
35DAG
25DAP
C
C
59DAP
59DAP
N
N
Dystrophin
F-Actin
F-Actin





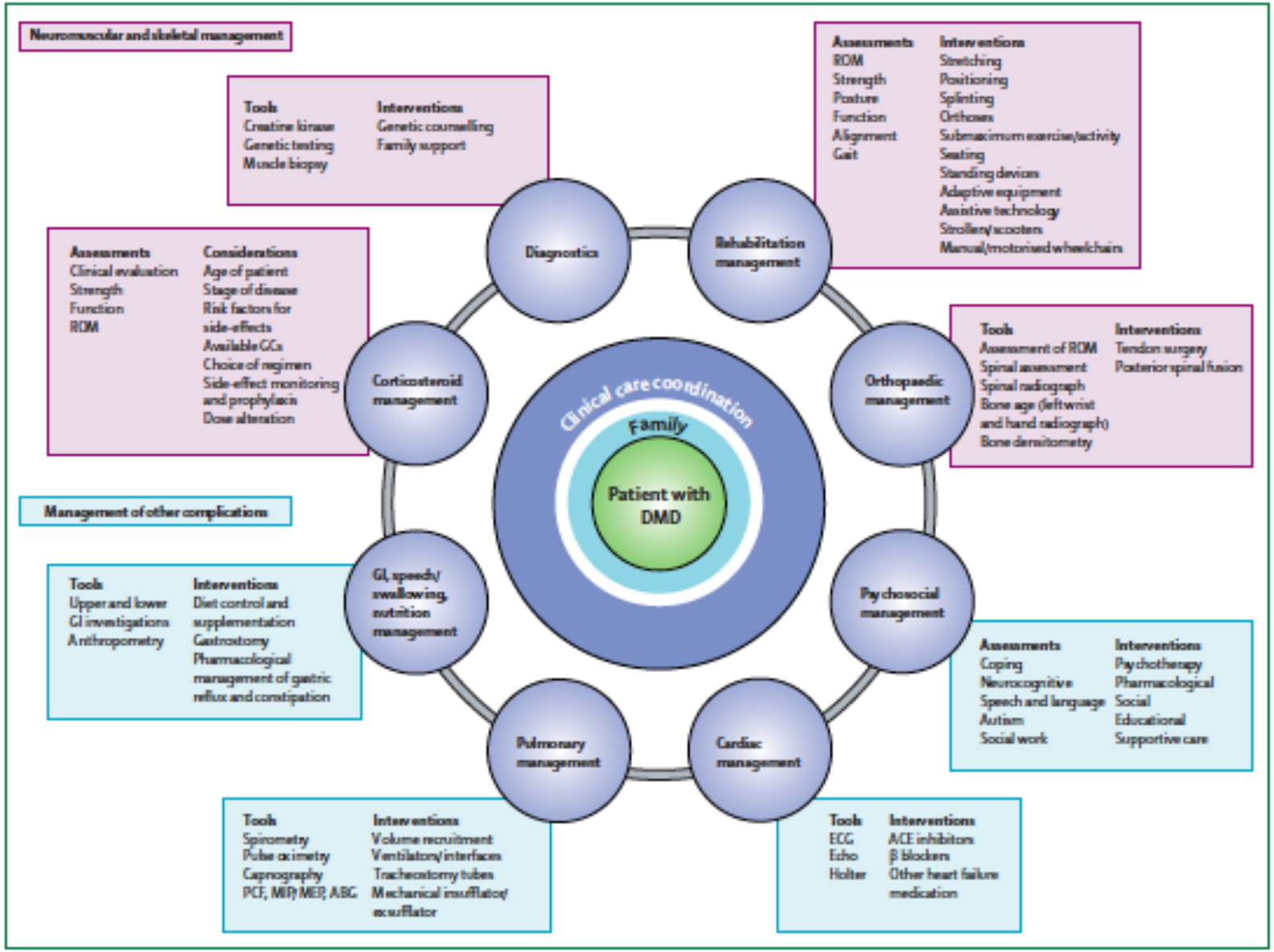


Figure 1: Interdisciplinary management of DMD

Coordination of clinical care is a crucial component of the management of DMD. This care is best provided in a multidisciplinary care setting in which the individual and family can access expertise for the required multisystem management of DMD in a collaborative effort. A coordinated clinical care role can be provided by a wide range of health-care professionals depending on local services, including (but not limited to) neurologists or paediatric neurologists, rehabilitation specialists, neurogeneticists, paediatricians, and primary-care physicians. It is crucial that the person responsible for the coordination of clinical care is aware of the available assessments, tools, and interventions to proactively manage all potential issues involving DMD. ABG=arterial blood gas. ACE=angiotensin-converting enzyme. DMD=Duchenne muscular dystrophy. Echo=echocardiogram. ECG=electrocardiogram. GC=glucocorticoids. GI=gastrointestinal. MEP=maximum expiratory pressure. MIP=maximum inspiratory pressure. PCF=peak cough flow. ROM=range of motion.

Role for corticosteroids

- Start: clinically affected (~4-5 yrs)
- Vaccinate: varicella, pneumovax and influenza
  - Prednisone 0.75mg/kg/day
  - Deflazacort 0.9mg/kg/day
- NOT a cure BUT gain 2-3 years of ambulation
- Reduces risk of scoliosis and stabilises pulmonary function
- Review pts every 3 months
- Time to stop, either
  - when loose ambulation
  - continue for “cardiac benefits”

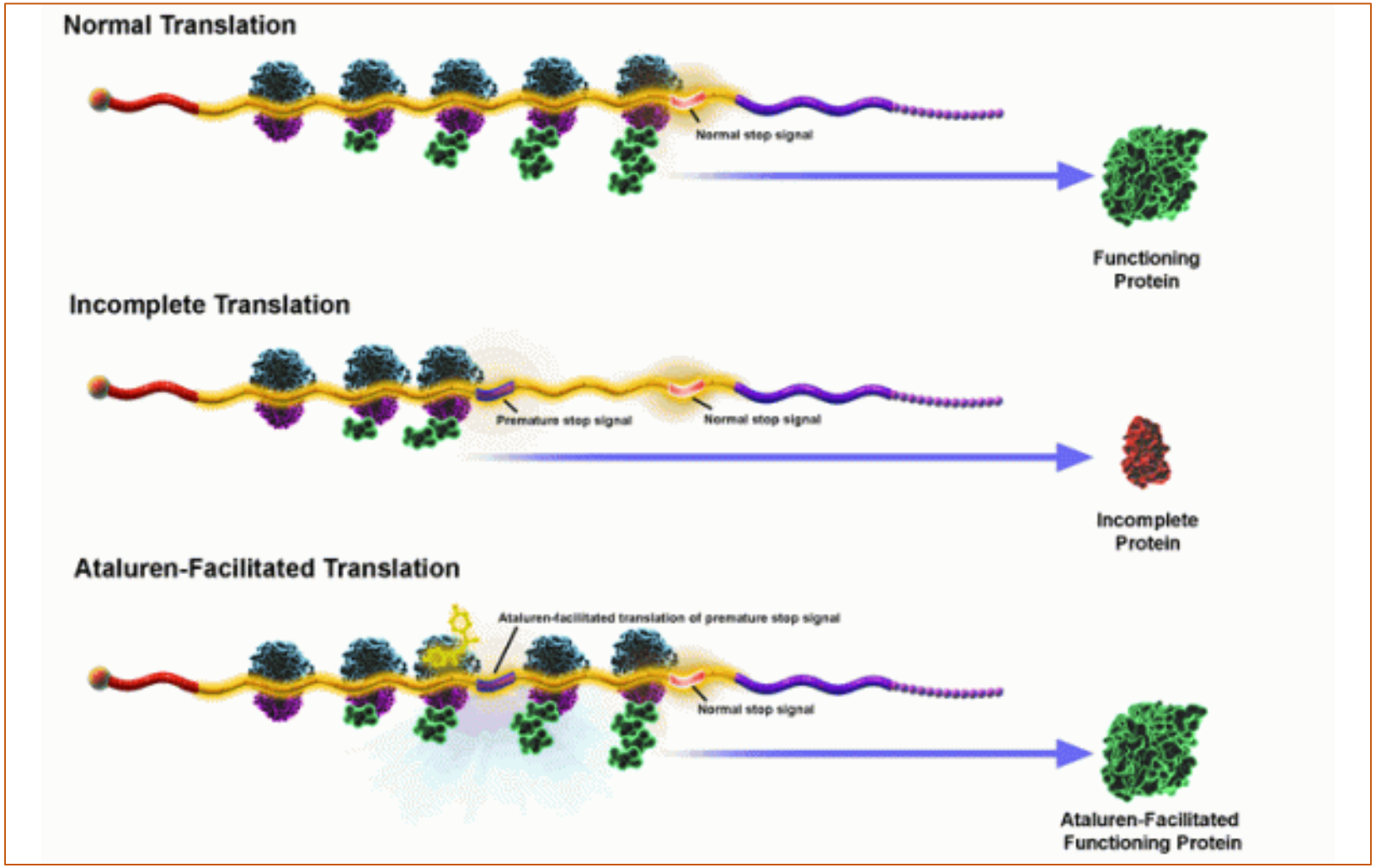
Markham et al Neuromuscular Disord 2008;

Dubowitz Lancet Neurol 2010

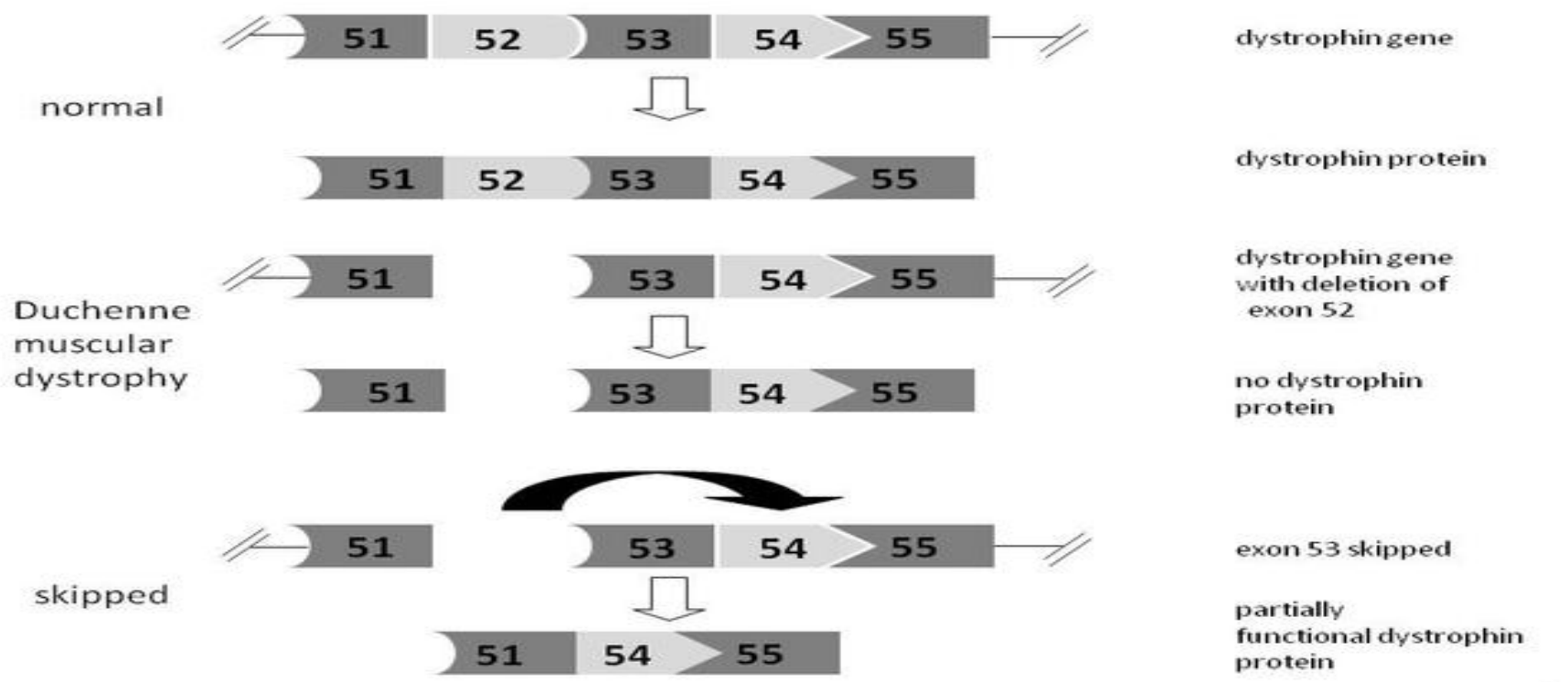
Pharmacogenetics and DMD

Premature stop-codon. (~6%)

Intervention to permit “read-through”



Exon-skipping (~6%)



The reality ….with

- Multidisciplinary centralised care
- Scoliosis avoidance
- Prolonged ambulation (steroids, vitamin D, intensive stretches)
- Cardiac review (prophylaxis – ACE inhibitors)
- Screening for nocturnal hypoventilation – nocturnal BIPAP
- Survival beyond 30 years

Aims of care for NMD pts in LMICs

Diagnosis

•NMD conditions which are important / relevant?

- Genetic counseling e.g. SMA
- Targeted therapies e.g. Duchenne MD

Overall management

•Optimal motor capacity

•Avoidance of complications e.g. scoliosis, respiratory track infections, oromotor, nutritional challenges

•Planning optimal educational placement, orthotic devices

•i.e. “standard” not “state of the art / experimental”

Challenges for Africa

Diagnoses

- Lack of training / experience
  - Dedicated neuromuscular centres lacking in Africa
- Access to investigations
  - From CSF to histology / immunohistochemistry to genetics
- Interpretation of results
  - NCS
- Training
  - Need for focused and structured training to enable early recognition / intervention
  - Skills for optimal interventions – home / community care

Management

- Therapists
  - Lacking over all Africa
  - Burden of disease dominates and pulls them away from NMD
- Equipment
  - Lack of access to wheelchair, orthotics etc
- Tracheostomy support
  - Most interventions / home ventilation programs are only effective if the parent / caregiver is trained
- Drugs
  - Need for reliable access and monitoring e.g. DMD

Genetics

- Diagnostics
  - Limited to a few centres in Africa – expensive
  - DMD, SMA and CMT1A
- Unique African expression
  - *RYR1* mutations
  - Debate around SMA
  - CMT
- Counseling
  - Need to sensitive and culturally insightful counselors
- Therapeutics – ethics…..
  - E.g. exon skipping, translarna, nusinerisen….

Summary

- Burden of NMD in Africa is skewed towards acquired and communicable causes
- Layering effect complicates issue of recognition further
- Genetic NMD disorders are likely to be as prevalent as in HICs
  - Maybe slight variation in expression for some ancestries

Challenges faced

- Prevention
- Recognition / diagnosis
- Early ancillary intervention
- Counseling
- Ethics of screening and role of pharmacogenetic interventions..