SMA as a Whole Body Disease:

Evidence from Patients

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Spinal muscular atrophy (SMA) is…

A generic term

SMA is a genetic disorder, characterized by degeneration and loss of motor neurons in the anterior horns of the spinal cord and brain stem, leading to symmetrical muscular atrophy and weakness

Chromosome 5q SMA

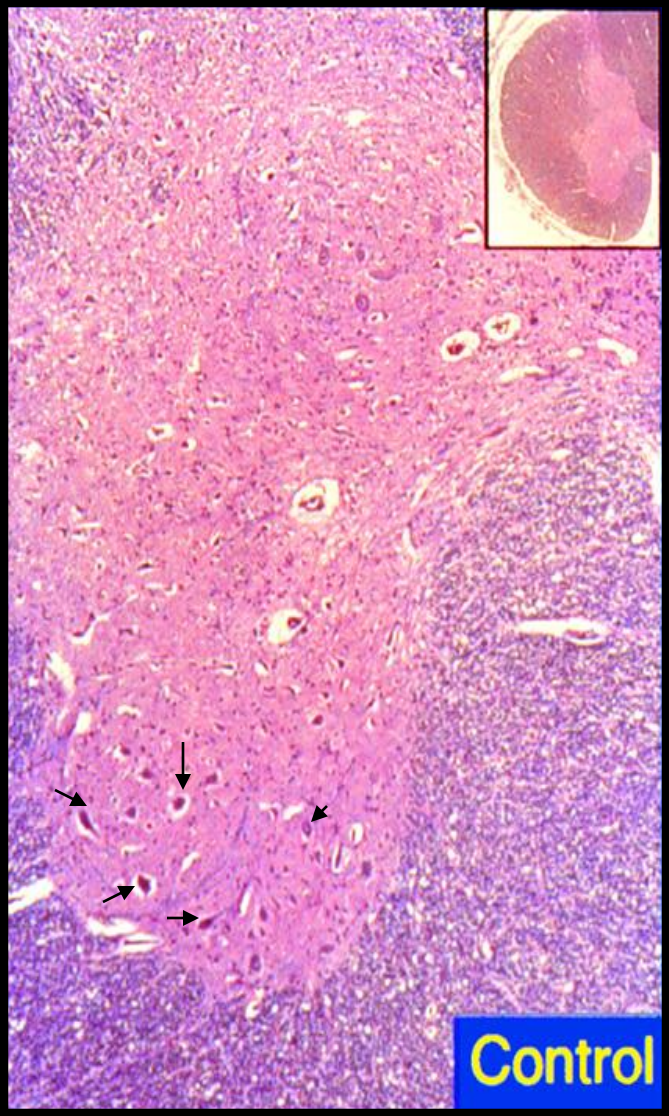
5q Proximal SMA is…

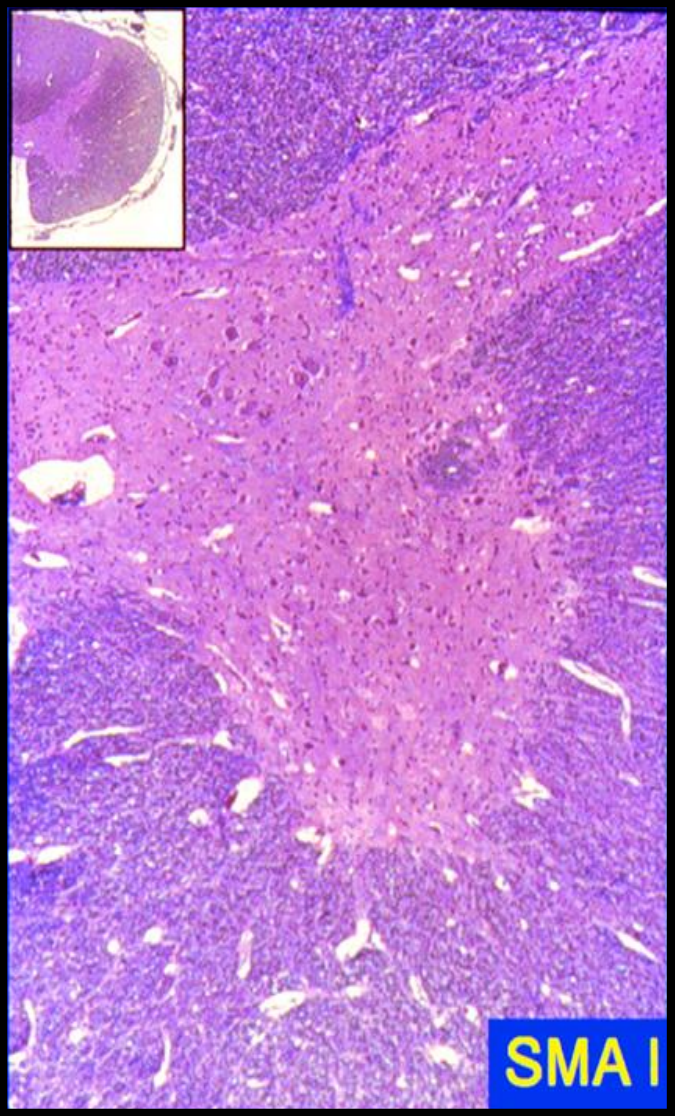
- **An autosomal recessive disorder caused by loss or mutation of the *SMN1* gene and retention of the *SMN2* gene**
- ***SMN1* and *SMN2* genes encode the "survival (of) motor neuron (SMN)" protein**
- **SMA is caused by decreased levels rather than complete loss of the SMN protein, leading to selective dysfunction of motor neurons in the spinal cord**

SMA is a disease of α-motor neurons

- Probably an oversimplification
- Multiple studies indicate that SMN protein deficiency compromises the function of other tissues

Loss of Anterior Horn Cells in SMA



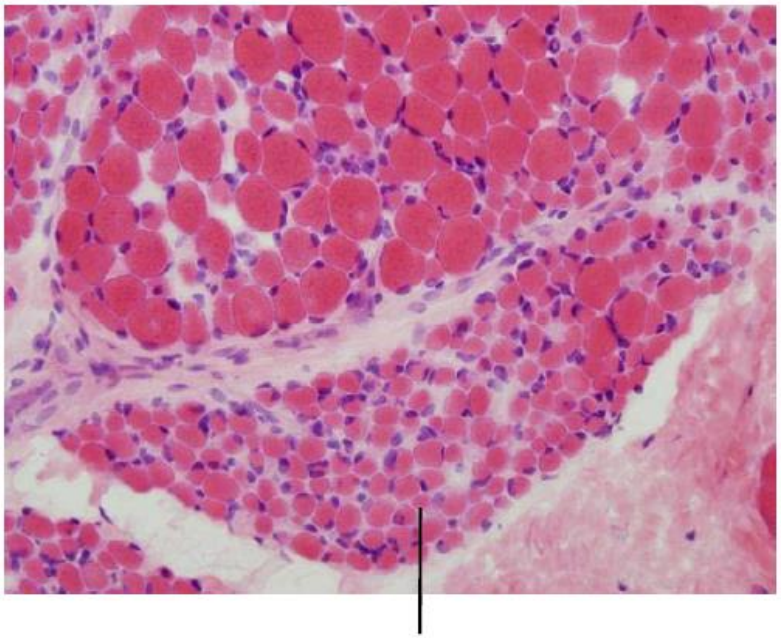


Other cell types / tissues / organs

- Skeletal muscle/ Neuromuscular junction
- Heart
- Vasculature / Autonomous nervous system
- Liver
- Kidney
- Pancreas
- Gastro-intestinal
- Bone / Connective tissue
- Lungs
- Variety of other neuronal populations

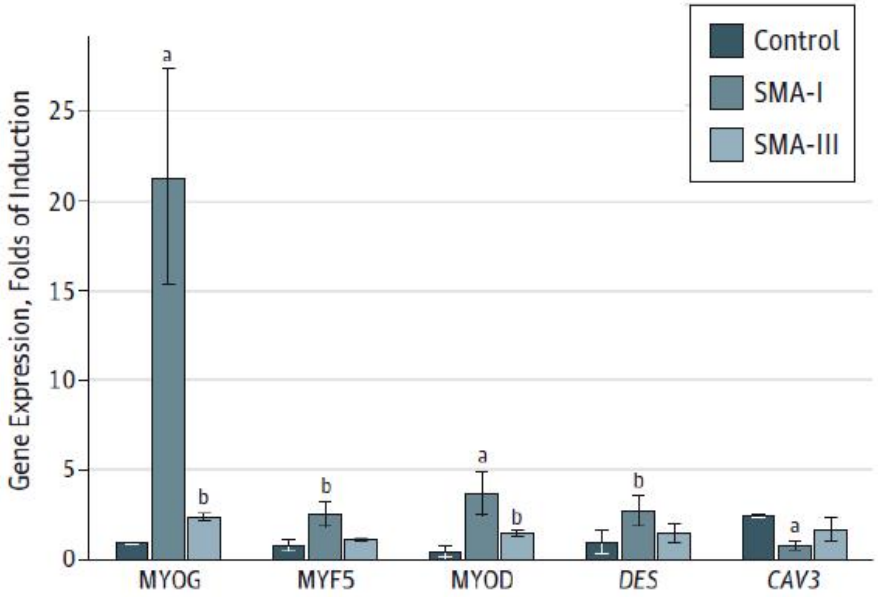
TYPE I SMA MUSCLE: MANY SMALL MYOFIBERS FEATURES OF DELAYED MATURATION

Type I SMA



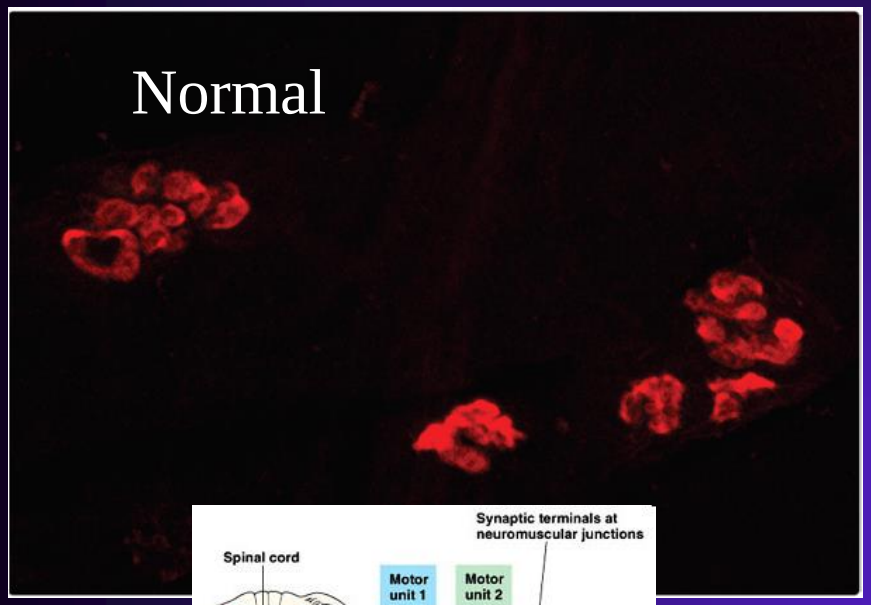
Round and small myofibers believed to be developmentally immature

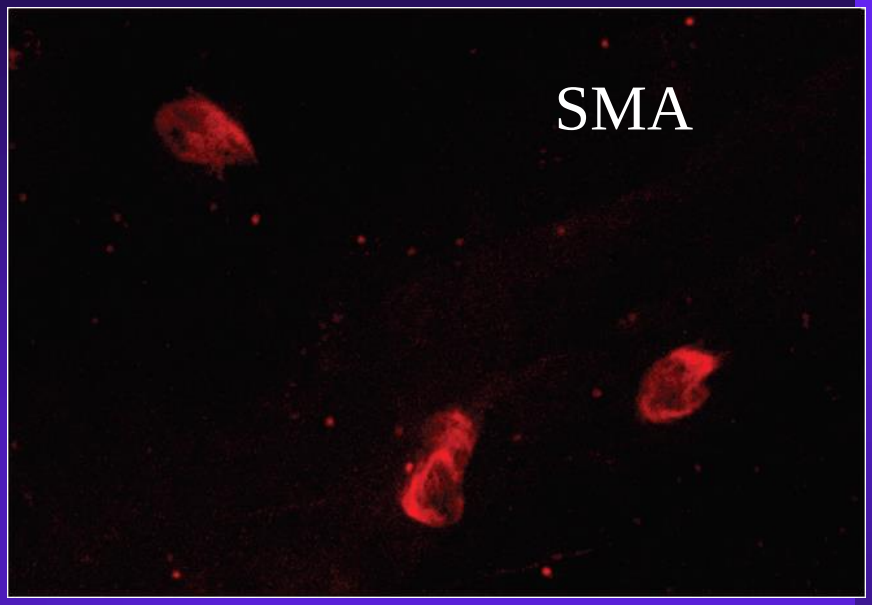
Takei et al., Medscape

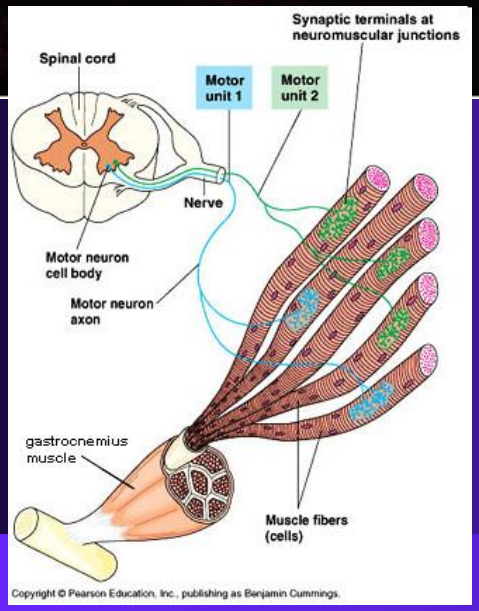


Ripolone et al., 2015

Neuromuscular Junction in SMA







- Abnormal morphology
- Abnormal EPhysiology
- Fatigue
- Synaptopathy?

Heart

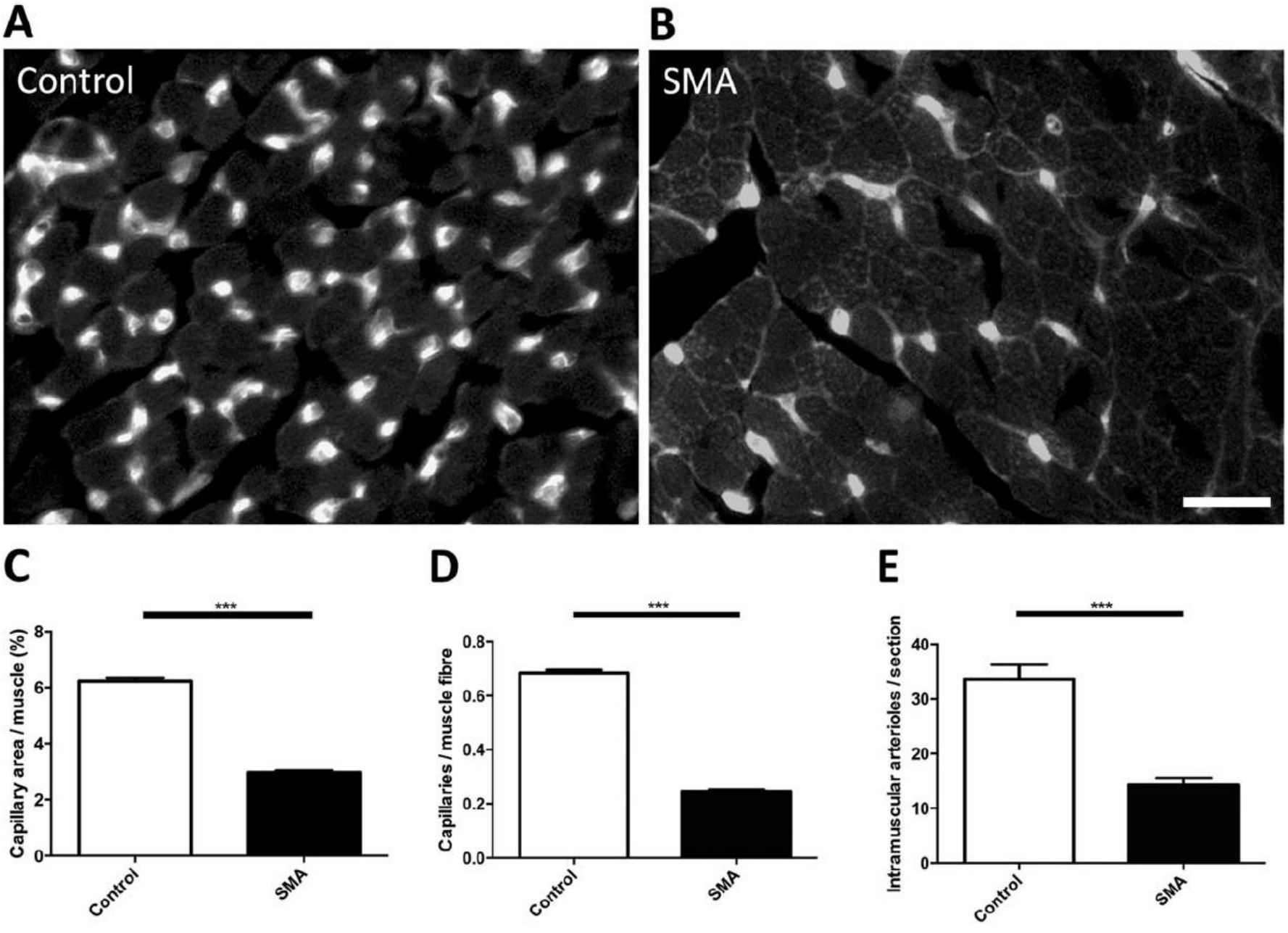
- No “apparent” cardiac abnormalities in most patients
- Cardiac defects in severe Type I patients
- SMA Type II : function, rhythm stable
- SMA Type III : none of reported patients had genetically confirmed SMA

Heart

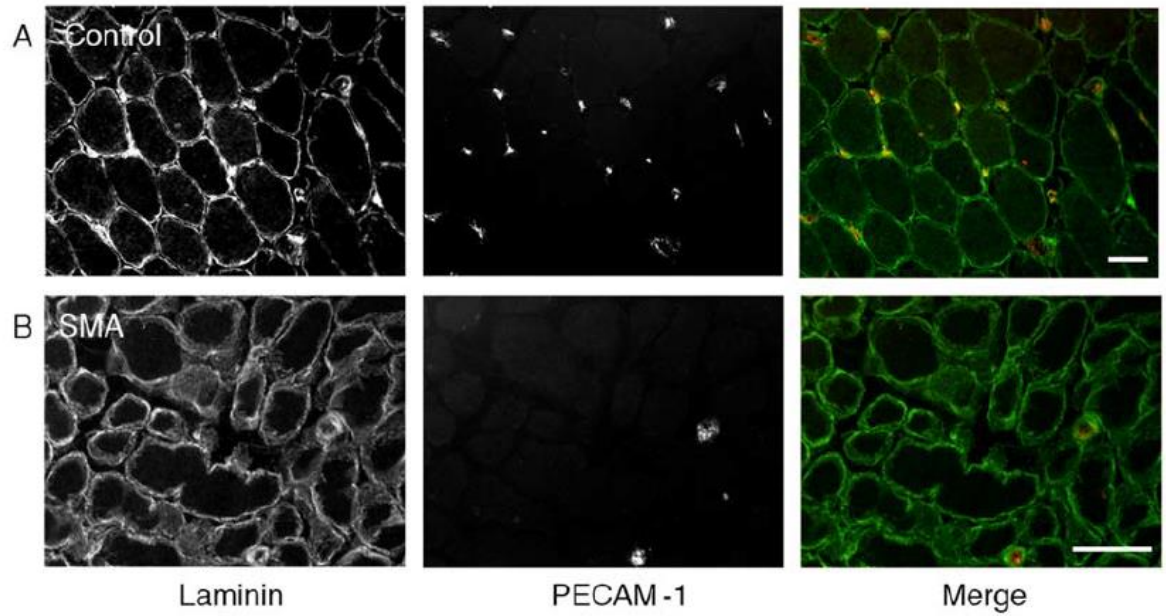
- Cardiac defects in SMA Type I with one copy of SMN2 (Type 0, or 1a)
- Numerous reports in SMA Type I
  - Atrial septal defects
  - AV septal defects
  - Aortic valvular stenosis, coarctation
  - Hypoplastic aortic arch
  - Hypoplastic left heart syndrome
- Association not coincidental
- 3 / 4 Type 0 patients (75%) — expected incidence < 1 / 50 million

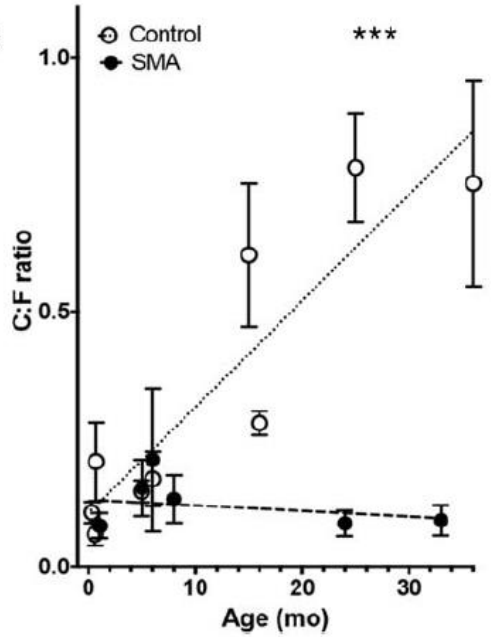
Vasculature / Autonomic nervous system

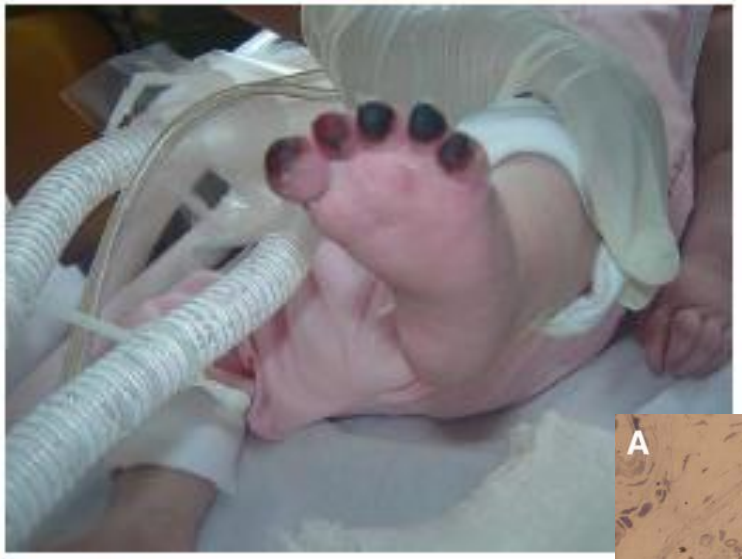
- Symptomatic bradycardia (15 / 63 Type I, Bach, 2007)
- Fluctuations in blood pressure
- Distal finger necrosis (Type I patients)
- Reduced capillary density in muscles of SMA mice and Type I and II patients
- Microvascular abnormalities in Type II, III patients
  - Microvascular injury
  - Impaired repair


A
Control
B
SMA
C
***
Capillary area / muscle (%)
8
6
4
2
0
Control
SMA
D
***
Capillaries / muscle fibre
0.8
0.6
0.4
0.2
0.0
Control
SMA
E
***
Intramuscular arterioles / section
40
30
20
10
0
Control
SMA

Vasculature in SMA







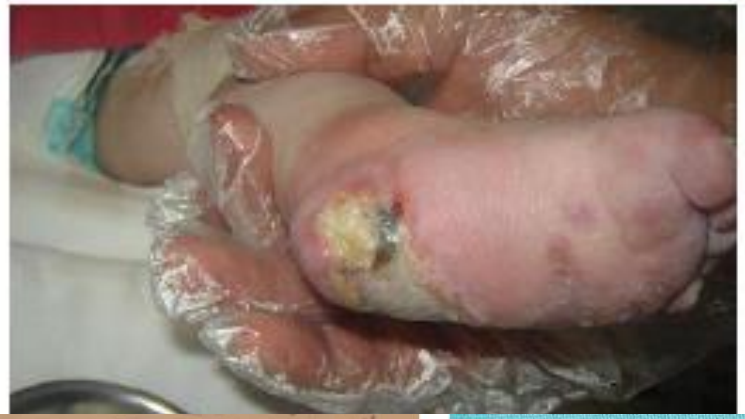
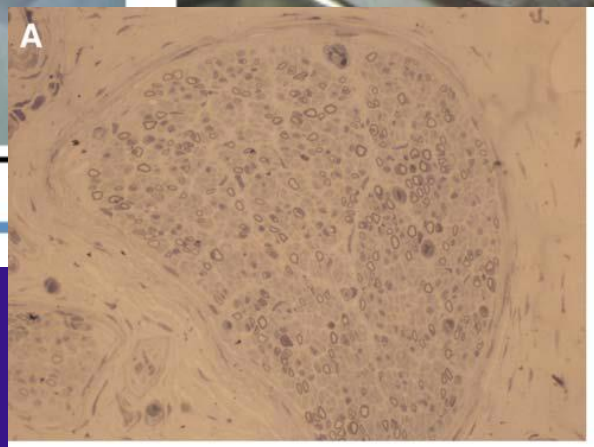
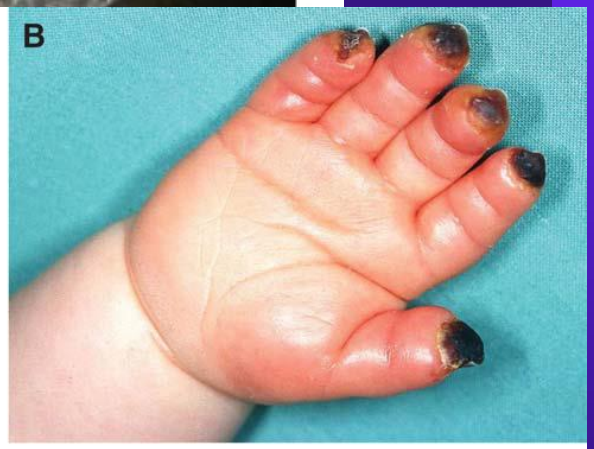
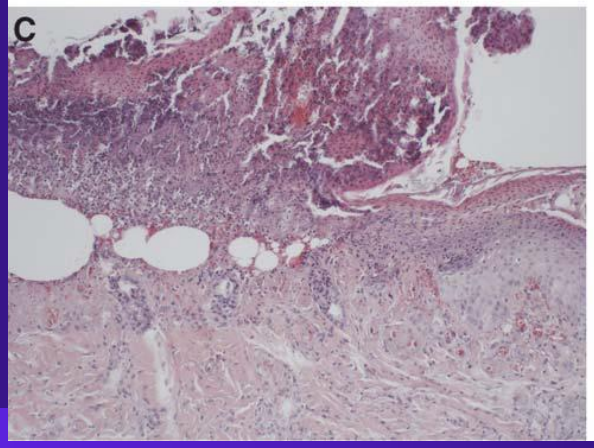
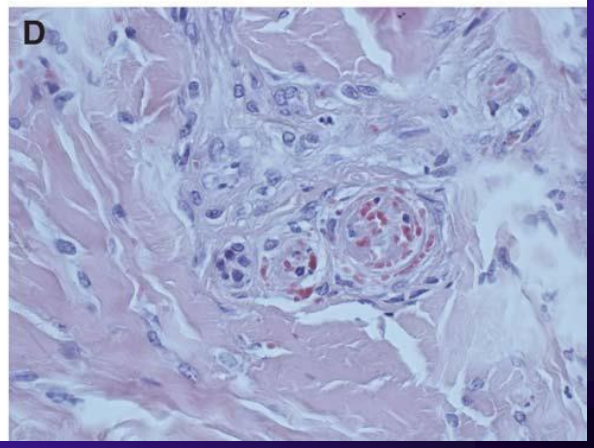


Figure 1. Digital necrosis.









Liver

- Fatty vacuolization of liver (severe SMA)
- Dicarboxylic aciduria
- Increased levels of esterified carnitine
- Increased C12:C14 ratio (all SMA patients) compared to healthy controls and non-SMA denervating conditions
- Level of ketones normal, not reduced in urine

Kidney

- Proteinuria in 20% of Type I patients (nusinersen trial data)

Spleen / Lymphatic system

SMA Type I

- Morphological changes in spleen
- Reduced size
- Lack of lymphocytes
- Increased levels of megakaryocytes

Bone

- Decreased bone mineral density
- Increased incidence of fractures
- Greater rates of vertebral fractures

Connective tissue

- Joint pain
- Joint hypermobility / hyperextensibility
- Abdominal wall hernias
- Poor wound healing

Pancreas

- Three cases of acute pancreatitis (Bach, 2007)
- Abnormalities of islet cells (↑ alpha, ↓ beta)
- Abnormal glucose levels
  - Hyperinsulinemia, resistance to insulin
  - Hypoglycemia
  - Hyperglycemia (39% of Type I patients — nusinersen data)

Gastro-intestinal

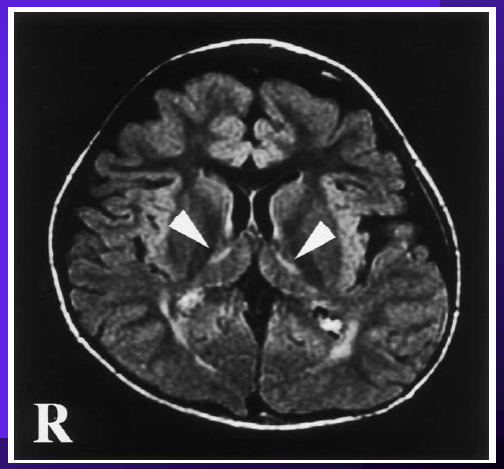
- No gross necrosis of GI tract
- Poor motility, acute ileus, pseudo-obstruction
- Progressive intolerance to bolus feedings
- Failure to absorb nutrients

Lungs

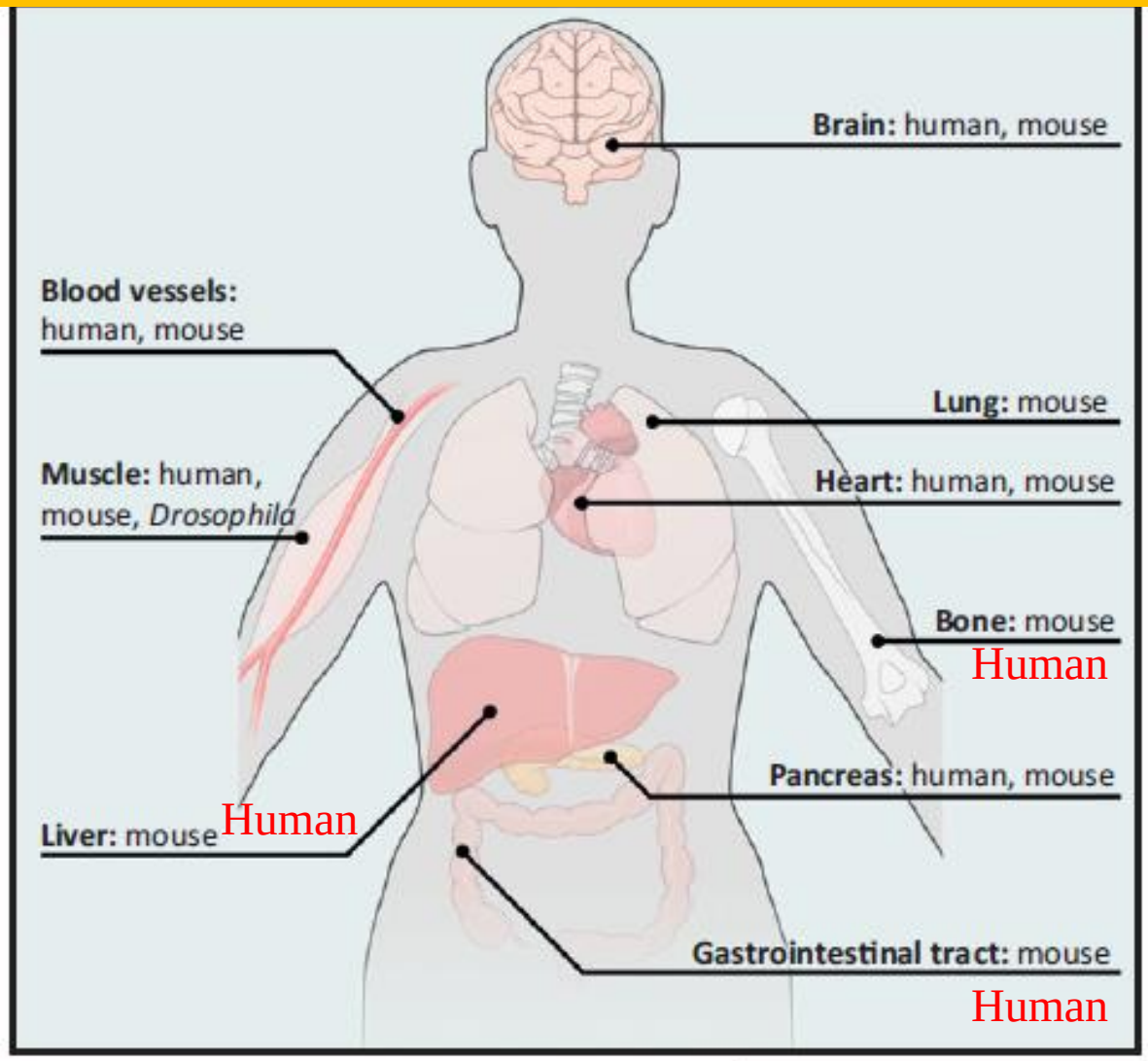
- Pulmonary complications are very common in SMA
- Limited information on structural lung damage in SMA autopsies

Brain/sensory system

- Cognitive function is well preserved in chronic SMA. Not enough data for Type I patients.
- Pathological changes in the brain, particularly the thalamus, are common at the severe end of the SMA spectrum
- Disrupted sensory pathways



SMA is a multi-organ/whole body disease

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Thank you