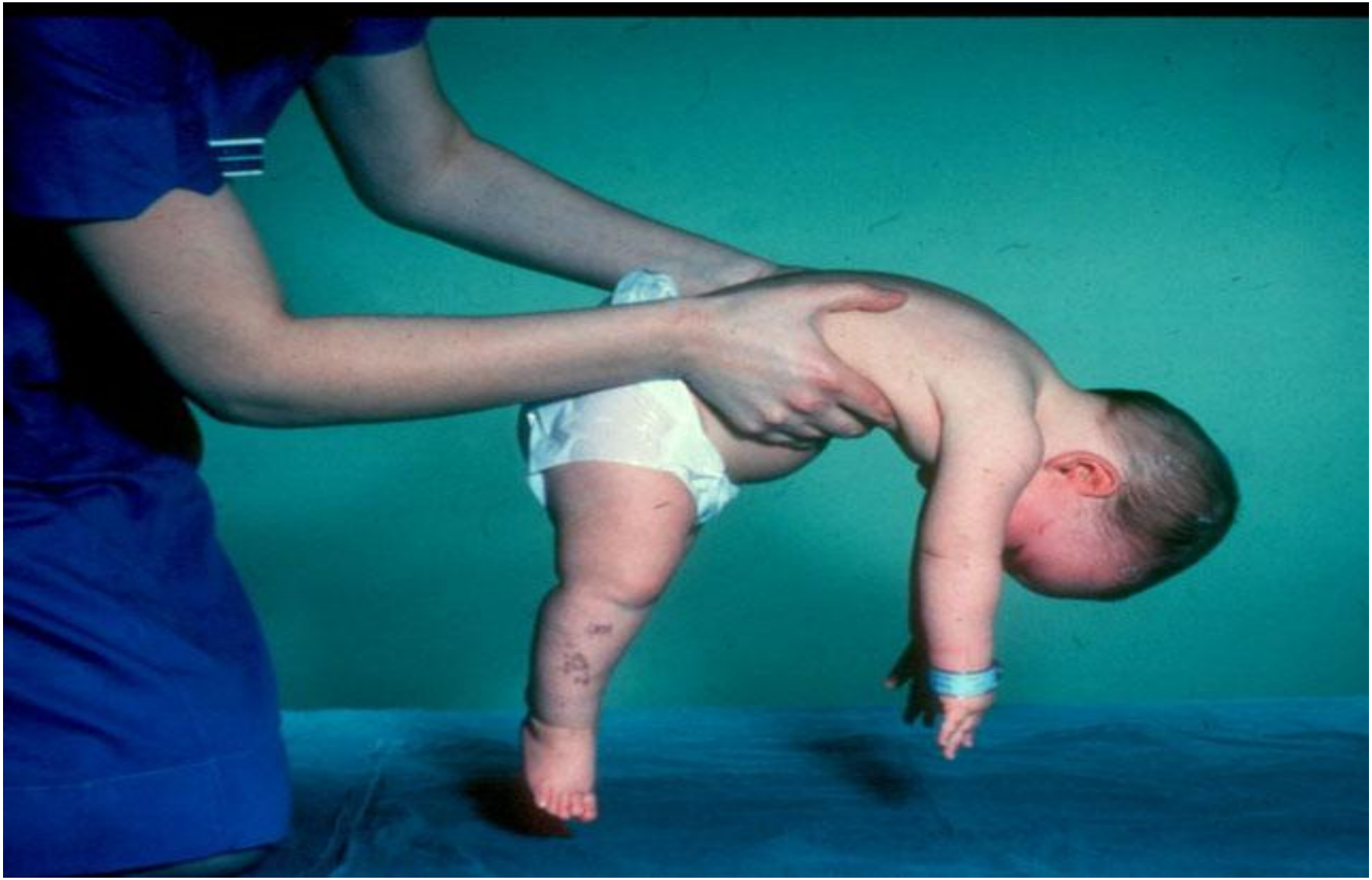
LIMP BABIES - WHAT MAY THAT MEAN ?




ARE WE LOOKING WHERE WE SHOULD ?

FLOPPY = LIMP = FLACCID = WEAK

Poor head control when pulled
C-posture sitting, or in ventral susp.
Frog-leg lying
Dropping arms

Casey

WON'T YOU SEE THIS CHILD WITH PRESUMED MUSCULAR DYSTROPHY ?

Table 92-1 **Classification of the Muscular Dystrophies**

Disease	Gene Locus	Gene Product	Mode of Inherita
LIMB-GIRDLE MUSCULAR DYSTROPHY CAUSED BY SARCOLEMMA OR CYTOSOLIC PROTEIN DEFECTS			
Duchenne/Becker muscular dystrophy	Xp21	Dystrophin	XR
LGMD1A	5q22	Myotilin	AD
LGMD1B	1q11–q21	Lamin A/C	AD
LGMD1C	3p25	Caveolin-3	AD
LGMD1D	6q23	Not identified	AD
LGMD1E	7q	Not identified	AD
LGMD1F	2q	Not identified	AD
LGMD1G	4Q21	Not identified	AD
LGMD1H	3p23	Not identified	AD
LGMD2A	15q15	Calpain-3	AR
LGMD2B/Myoshi's myopathy	2p13	Dysferlin	AR
LGMD2C	13q12	γ-Sarcoglycan	AR
LGMD2D	17q112	α-Sarcoglycan	AR
LGMD2E	4q12	β-Sarcoglycan	AR
LGMD2F	5q23	δ-Sarcoglycan	AR
LGMD2G	17q11	TCAP	AR
LGMD2H	9q31	TRIM32	AR
LGMD2I	13q13	FKRP	AR
LGMD2J/Tibial muscular dystrophy	2q31	Titin	AR/AD
LGMD2K	9q34	POMT1	AR
LGMD2L	11p4	ANO5	AR
LGMD2M	9q31	Fukutin	AR
LGMD2N	14q24	POMT2	AR
CONGENITAL MUSCULAR DYSTROPHIES SECONDARY TO GLYCOSYLATION DISORDERS			
Fukuyama's muscular dystrophy	9q31–q33	Fukutin	AR
Muscle-eye-brain disease	1p3	POMGnT1 glycosyltransferase	AR
Walker–Warburg syndrome	9q34	POMT1	AR
MDC 1A	6q22	Laminin-2 (merosin)	AR
MDC 1B	1q42	Not identified	AR
MDC 1C	19q13	FKRP	AR
MDC 1D	22q12	LARGE	AR
OTHER CONGENITAL MUSCULAR DYSTROPHIES			
CMD with early rigid spine	1p36	Selenoprotein 1	AR
CMD with *ITGA7* mutations	12q	Integrin α7	AR
Ullrich's syndrome/Bethlem's myopathy	21q22.3 (A1, A2) 2q37(A3)	Collagen 6 A1, A2, and A3	AD
MUSCULAR DYSTROPHIES SECONDARY TO NUCLEAR ENVELOPE DEFECTS ("NUCLEAR ENVELOPATHIES")			
Emery–Dreifuss muscular dystrophy (EDMDX)	Xq28	Emerin	XR
Emery–Dreifuss muscular dystrophy (EDMD1)	1q11–q23	Lamin A/C	AD/sporadic
MUSCULAR DYSTROPHIES SECONDARY TO RNA METABOLISM DEFECT			
Myotonic dystrophy 1 (DM1)	19q13	DM	AD
Myotonic dystrophy 2 (DM2)	3q21	ZFN9	AD
MUSCULAR DYSTROPHIES OF UNKNOWN MECHANISM			
Facioscapulohumeral muscular dystrophy	4q35	? Toxic gain of function DUX4	AD
Oculopharyngeal muscular dystrophy	14q11.2–q13	PABp2	AD

REFERRAL NOTE :

He is 20 months old , has a healthy baby sister of 7 weeks , no family history.

I saw him at 16 months because of late walking , but showed good “pull to stand” . He sat at about 6 months .

Had good reflexes and power grading of 5/5 in arms and legs .

Now at 20 months there is a clear loss of strength in proximal muscles and absent knee reflexes , does a Gower-like action to get to stand . He needs to hold on to furniture. There is atrophy of the foot muscles .

There are tongue fasciculations . No pseudo-hypertrophy is noticed .

His Brain MRI and the spinal MRI is normal .

More clinical facts

He was “fine” up to age 18 months . The father loved “wrestling” with him .

No he does not want to walk unless we hold his hands . He never did really walk.

Can only stand up if helped up . At 12 months he could stand up by himself.

Crawls about everywhere .

Hand use is not great – messes much when he feeds himself - a weakness feature

Speech is age-appropriate (2-word-phrases) . Swallowing/chewing good.

Muscle strength poor all over , no pattern (perhaps the lower-limb girdle mm.), but sparing face and sparing extra-ocular Mm . No scapular winging.

Strength of his cry is weak (respiratory muscles)

No hypertrophy , no polyminimyoclonus , no fasciculations , no macroglossia .

DTR virtually absent , get a flicker at the ankles !

Sensory functions fine . Sphincter functions fine . No visceromegaly .

Heart :

clinically normal

Cardiology report :

was awaited (later arrived :" Dr L you're misguided! ")

Muscle enzymes :

CK 2274 U/L (normal <228)

EMG

THE MEDIAN AND PERONEAL NERVES HAVE NORMAL AMPLITUDES , LATENCIES AND CONDUCTION VELOCITIES

THE ANTERIOR TIBIALIS AND VASTUS LATERALIS SHOW

- **INCREASED INSERTIONAL ACTIVITY WITH FIBRILLATIONS**
- **POSITIVE SHARP WAVES**
- **COMPLEX REPETITIVE DISCHARGES AND MINIMAL FASCICULATIONS**
- **THE MUAPs ARE POLYPHASIC WITH LOW AMPLITUDES AND SHORT DURATION**

THERE WERE NO HIGH AMPLITUDE , LONG DURATION , NEUROGENIC MUAPs

IT SUPPORTS THE DIAGNOSIS OF A MYOPATHIC , POSSIBLE SMA ILLNESS

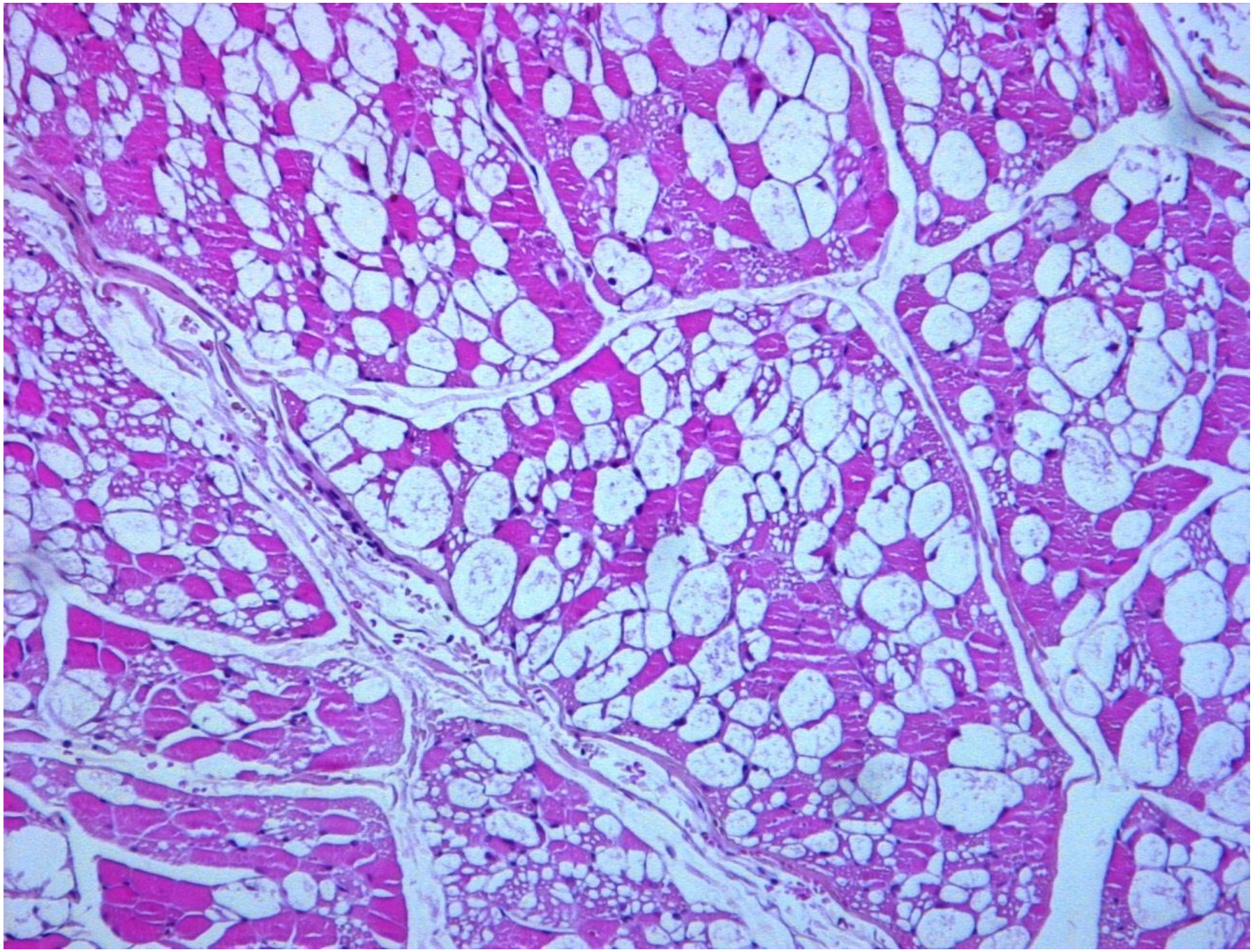
DNA TESTING COULD NOT CONFIRM A SMA

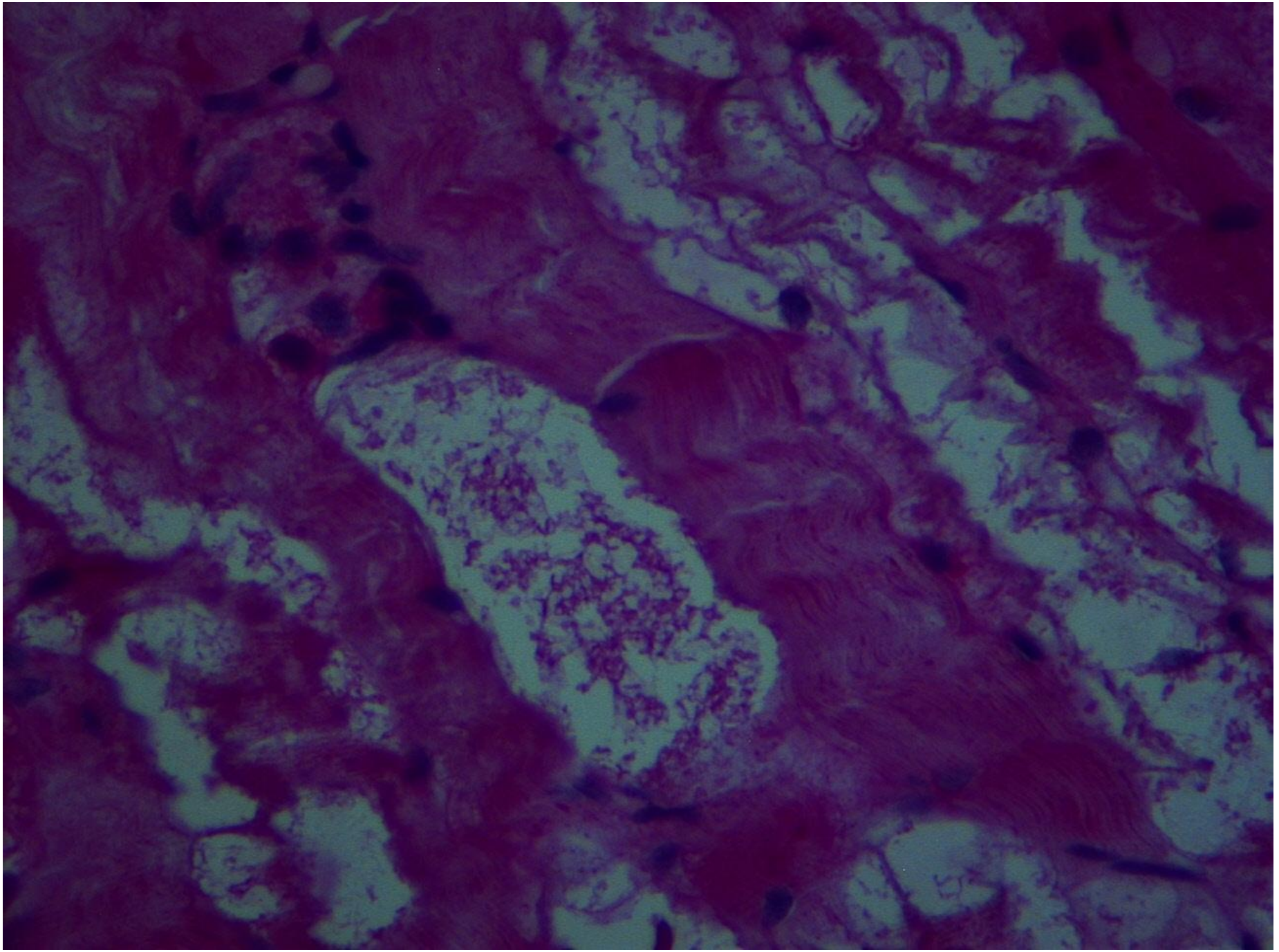
NO HOMOZYGOSITY FOR THE LOSS OF EXON 7 OF THE SMN1 GENE

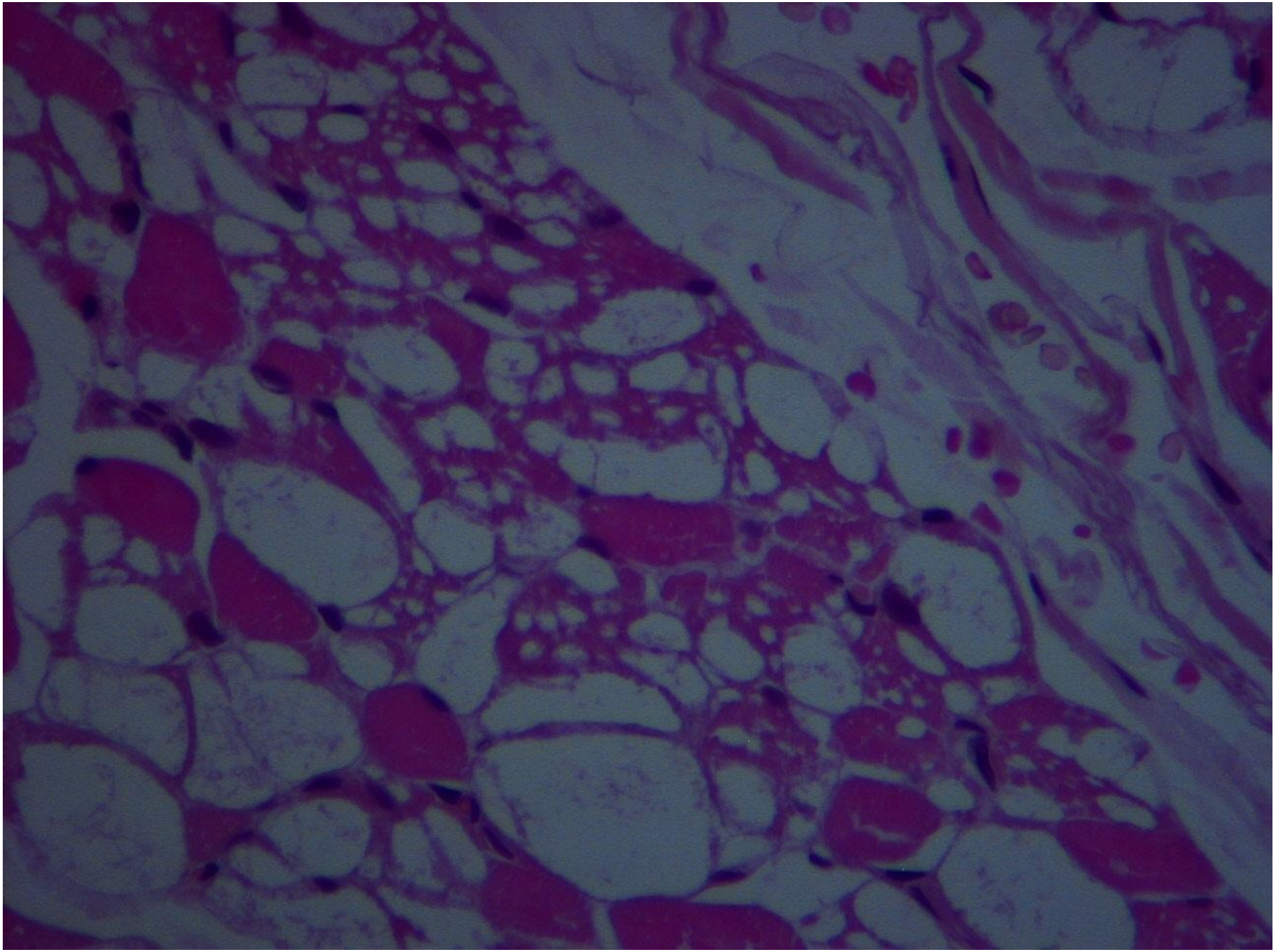
Needed to do , as Werdnig-Hoffmann disease is one of two dismal progressive neuro-muscular diseases that are uniformly fatal by 12 months .

BIOPSY FINDINGS

Marked vacuolation of skeletal muscle fibres
with granular deposits in the lumina , staining PAS positive .
This material is digested on PAS-diastase stain .





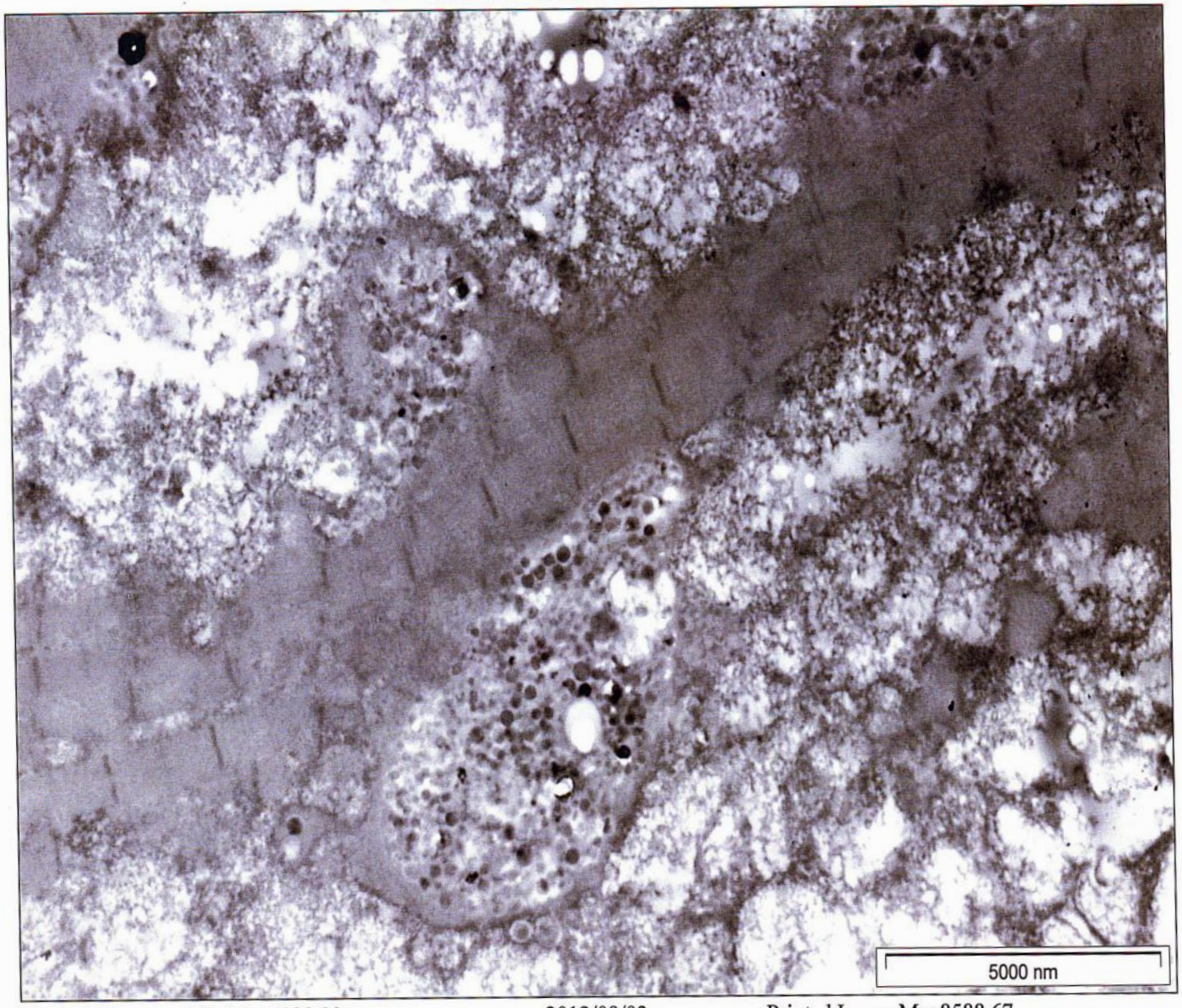


E / M

Focally there is replacement of the cytoskeletal architecture by large aggregates of membrane-bound and non-membrane-bound glycogen , replacing skeletal muscle fibres and entire groups of skeletal muscle fibres in areas. In these areas there is myofibrillar loss and around these areas , there is some disorganization of the banding pattern.

Lipid does not appear increased in amount and ultra-structural abnormalities of mitochondria are not observed .

TJA28839-12b EDWAN GRIFFIEON



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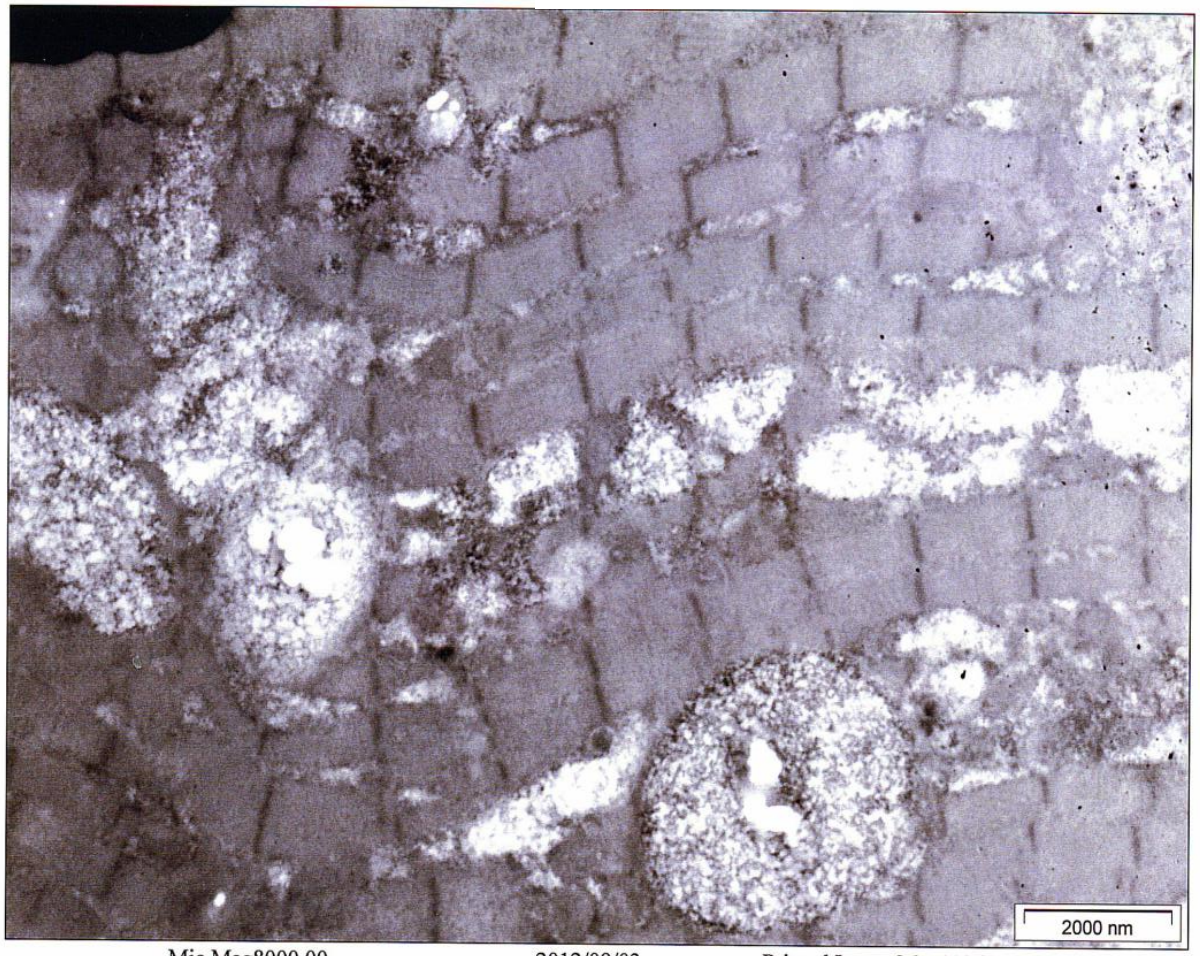

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Requested : ., **POMPES DISEASE**

REFERRED OUT WORK

Test	Result		Reference
> **POMPES DISEASE**	**2.21**	**L**	10.80 - 16.48

Although the patient appears to have a significant deificiency of alpha-glucosidase, his levels are slightly higher than is normally seen in most Pompes patients. This, along with the fact that the blood received from this patient yielded a low number of leucocytes, suggests that it would be prudent to re-test this patient again on a fresh sample of ACD blood in order to confirm / clarify this result and rule out any possibility that the sample had been compromised in transit.

Normal	*10.80 - 16.48 nmol/hr/mg protein*
Affected	*Mean level not calculated, but levels are generally between zero and +/- 10% of normal.*

No reliable data is available for heterozygote levels.

This test was not performed at Lancet Laboratories.
Data entry verified by Lancet Laboratory.
For consultation by pathologist, contact Johannesburg (011) 358-0800
Pretoria (012) 483-0100
Durban (031) 308-6500

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Tel.: +49-40-7410 55026
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metabolic laboratory, UKE, Department of Pediatrics and Institute (N23)
Martinistr. 52, 20246 Hamburg, Germany

Unitas
Dr. M.M. Lippert
Clifton Ave.

Littleton Centurion
South Africa

Griffioen, Ewan

Born:	29.09.2010 (M)
Lab.number:	29549574
Sample taken:	19.09.2012,
Received:	27.09.2012, 16:05
Reporting date:	02.10.2012, 14:35
External requestnumber:	

Final report

Submitter code: s7920

Dear colleague,

the analysis of the sample which has been sent to our laboratory yielded the following results:

Parameter	Result	Reference range	
Diagnostics of Pompe Disease from Dried Blood			
alpha-glucosidase at pH 3.8	1.48	- 1,5 - 10	nmol/spot*21h
alpha-glucosidase at pH 7.0	11.31	1,8 - 17,1	nmol/spot*21h
alpha-glucosidase with inhibition	0.13	- 0,9 - 7,2	nmol/spot*21h

Evaluation
Dear colleague,
the activities of alpha-glucosidase at pH 3.8, with and without specific inhibition, are below their respective reference ranges. This is in agreement with Pompe disease. We recommend to verify the diagnosis in another dried blood specimen (if possible also in lymphocytes/fibroblasts). In addition, especially if enzyme replacement therapy is under consideration, a molecular genetic work-up should be carried out.
If you have any questions feel free to contact us anytime.

Dr. C Els
Linkwood Hospital
24 - 12th Avenue
Linksfield
2192
South Africa

Report of Molecular Genetic Testing

Vienna, 15.08.2013
Lab-ID: 13503

Patient Name: **Ewan GRIFFIONE** Birth Date: **29.09.2010**

Material tested: DBS Sample received: 01.08.2013 Indication: Pompe Disease

Analyses: DNA extraction, PCR and sequencing of all coding exons and flanking intronic regions
Official symbol: GAA
Gene ID: 2548
Reference sequence: NM_000152.3 (ENST00000302262)

Result: The following heterozygous mutation was detected:
c.[925G>A];[1634C>T] (p.[Gly309Arg];[Pro545Leu])

Interpretation:
Two missense mutations were detected in your patient. Both mutations have been reported in Pompe disease (Kroos MA, 1998; Hermans MM, 1994). The mutations confirm Pompe disease in the patient.

E.R.T. WITH MYOZYME

Alglucosidase alfa

Recombinant human

Treat as early as you can !

20 mg/kg every 2 weeks

High protein diet/ alanine/ beta agonists

Lumizime used in late-onset varieties

Pediatr Res. 2009 September ; 66(3) 329-335

N Engl J Med 326;15 April 15 2010

Genet Med 2009 ; 11(3) : 210-219

…

Now 3,5 years old

14,5 kg

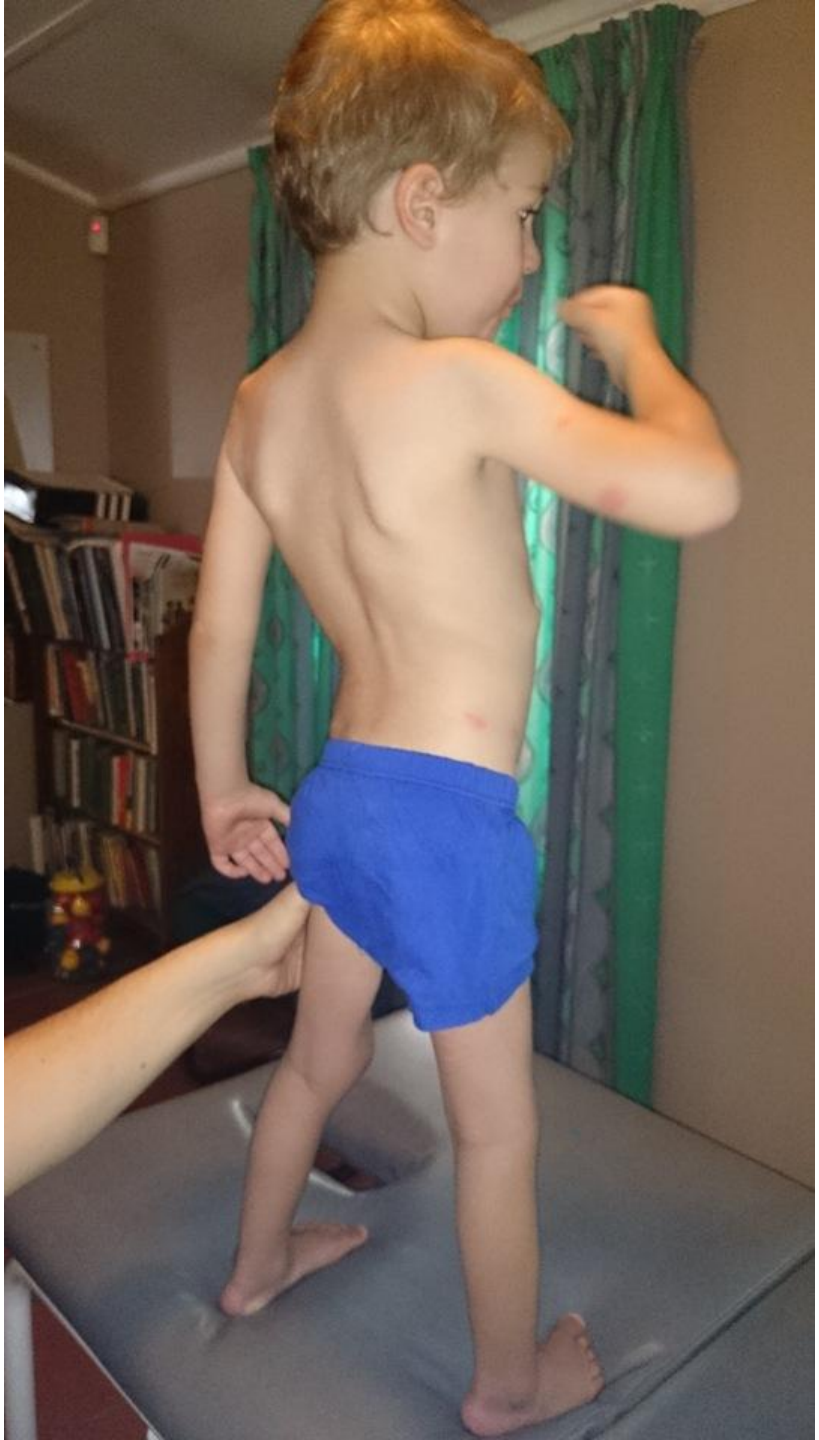
On ERT for 15 months

Heart normal still

Legs weaker , quads weakest
Can crawl well , shoulders fair ,
ankle DTR back ,
paraspinal muscles fair

Needs a walker

CK enzymes : halved from previous



Has a sister : 23 months

Her Pompe enzyme levels are low but 5 times those of her brother's (0,64 v 0,13)

Her CK : normal

Walked at 12 months and is else physically fine

Genotype not done , but will need to in order to determine the heterozygous carrier status

THERE ARE 111 PATIENTS IN THE UK WITH POMPE'S DISEASE ,
PESENTLY 5 CASES IN SA , 4 of them kids , last year lost 6 infants !

EXPRESSED IN HIGHLY VARIABLE PHENOTYPE -

MESSAGE IS : THINK , BIOPSY , ENZYME

QUESTION : HOW DOES HE DO IN THE 6 MINUTE WALK TEST ?

1/40 00 (compare SMA at 1/25 000 live births)
May 2013 Secretary of Health approved for "Recommended Uniform Screening"

GSD type 2 , the only lysosomal GSD (so not in the cytoplasm), A.R. ,
and it's a muscle Glycogenosis (up to type X111), described in 1932 by Dutch Pathologist J.C. Pompe
(not related to Pulmonary interstitial glycogenosis)

About 300 mutations described in the gene for acid-alpha-glucosidase (acid maltase)
the enzyme that breaks down / degrades glycogen to glucose , maps 17q25.2

For infants to manifest , the active enzyme level needs to be at < 1 %

Confusable with DANON'S disease , a more CMP disease with some myopathy.

E.O. or Infantile presentation (delineation is not perfect)

near complete deficiency in enzyme , begins in the first months of life and average age at death is 8.7 months,

floppy , feeding difficulties , head-lag , large heart , often large tongue , respiratory difficulties , enlarged liver , neuropathic bulbar weakness

NB : a hypertrophic CMP

Juvenile and later onset

from symptoms in first decade to 6th decade

heart usually not involved

late to walk is often first clue

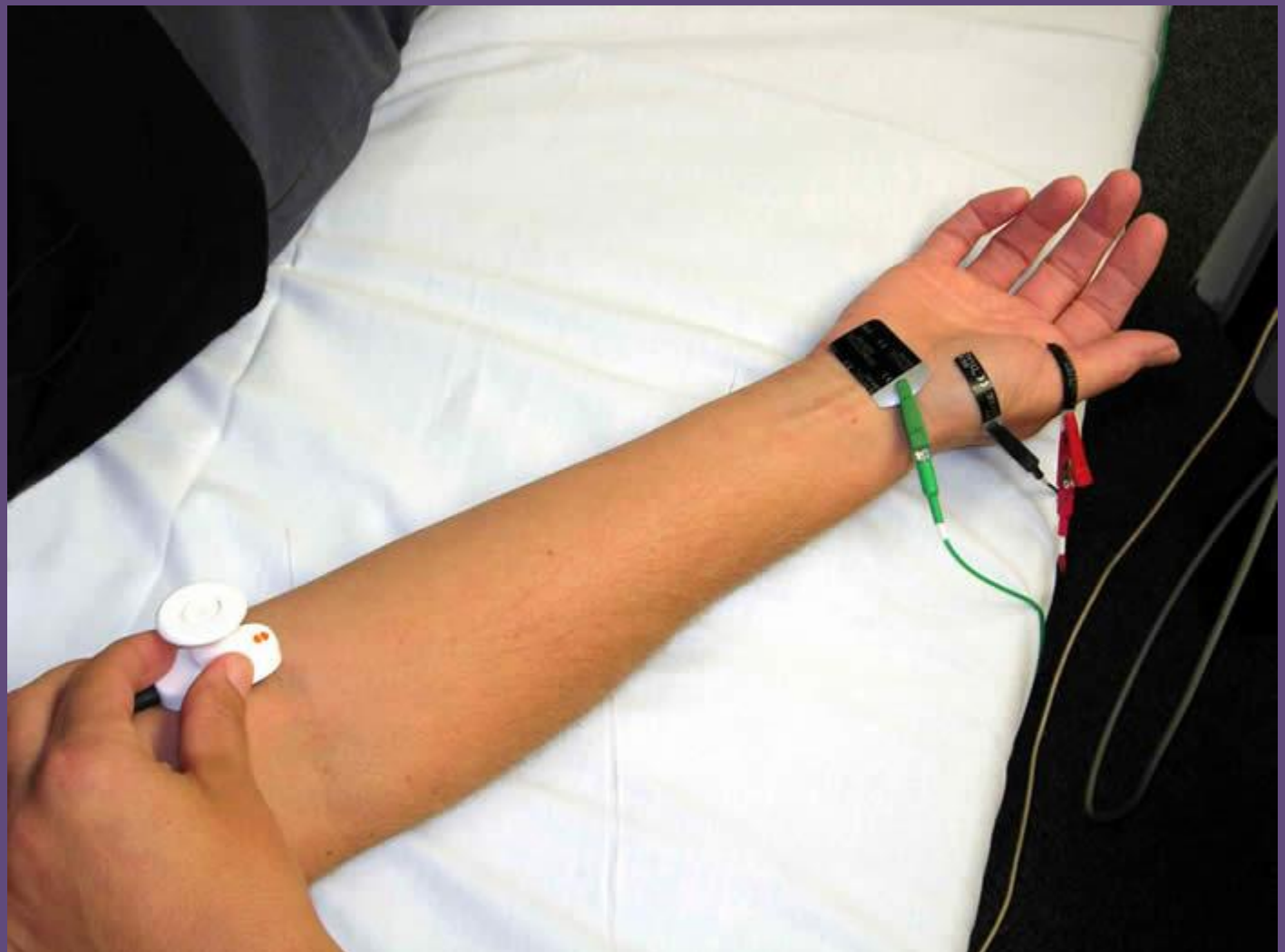
progressive weakness , of trunk and legs ,

breathing muscles quite affected (diaphragm)

MRI shows severe thinning of para-spinal muscles , wipe-out of hamstrings

EMG : myopathic excessive insertional irritability , pseudomyotonic discharges

in young patients may show neuropathic features too



WEAKNESS / MOTOR DYSFUNCTION / FLOPPINESS / LIMPNESS AND THE NEURAXIS CAUSES

Central ; cerebellar
Syndromic ; Prader-Willi , Down's , …. 40
Spinal cord ; myelodysplasias , brachial plexus root avulsions ,
Anterior horn cell ; polio , SMA , Hopkins ,
Neuropathic ; GBS , Krabbe and MCLD ,
Neuromuscular junction ; myasthenia
Myopathy ; dystrophies , congenital structural myopathies , myotonic dystrophies
Diverse ; botulism , hypermagnesemia , hypothyroidism ,

WEAKNESS / MOTOR DYSFUNCTION / FLOPPINESS / LIMPNESS AND THE NEURAXIS CLUES

Central ; also ataxia , cognition affected , brisk reflexes , small head

Syndromic ; dysmorphology

Spinal cord ; sensory levels , sphincters involved , cognition unaffected

Anterior horn cell ; very weak , absent DTR, fasciculation's , face not affected

Neuropathic ; nerve conduction velocities , CSF protein ,

Neuromuscular junction ; weaker face, weak cry and swallow , eyelid fatigue,

Myopathy ; weakness pronounced , girdle muscles , absent DTR , sens.norm

Diverse ; botulism (poor eye-movements , poor pupillary light reflex , constipation, bulbar w.)

MUSCLE WEAKNESS : GET A POWERFUL GRIP ON THIS ENEMY !


JUST BECAUSE YOU CAN'T
IMMEDIATELY SEE IT , DOES NOT
MEAN THAT IT'S NOT THERE !
PUO 74-36

LIMP BABIES … AND WEAK KIDS

Looooooook !

Get the DBS off !

DR M.M. LIPPERT