A

Appendices

Supplementary Tables

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Supplementary Tables

Neuromuscular diagnoses that can present with hyperCKemia and mild symptoms [53, 84, 87]

AD: autosomal dominant;
AR: autosomal recessive;
APR: Achilles tendon reflex;
BMD: Becker muscular dystrophy;
CK: creatine kinase;
DMD: Duchenne muscular dystrophy;
EMG: electromyography;
ER: exercise related;
ESR: erythrocyte sedimentation rate;
IHC: immunohistochemical staining of muscle tissue;
LGMD: limb girdle muscular dystrophy;
MMD: Miyoshi-type muscular dystrophy;
PA: histopathological analysis;
RRF: ragged red fibers;
WB: Western Blot analysis of muscle tissue; y: year

TABLE A Disorder	Gene	Inheritance	CK (U/L)	Asymptomatic hyperCKemia	CK in asymptomatic cases (U/L)	Myo-globinuria	Age presenting	Cramps	Exercise-intolerance	Calf hypertrophy
Musculardystrophies										
Dystrophinopathy	DMD	X-linked	very high to 100x	yes in carriers and sometimes in BMD	high	yes in BMD; in DMD in ambulant boys on steroid treatment	DMD childhood; BMD childhood-adult	yes, exercise related	possible	yes
LGMD 2B/MMD1	DYSF	AR	10-72x normal; up to to 27,000	yes	343-3000	occassional	generally 10 to 39 y			some
LGMD 1C	CAV3	AD	3-40x normal	yes; ♂>♀	478-2600		5- adulthood	yes, exercise related		yes
LGMD 2A	CAPN3	AR	nomal-80x normal; 190-11,000	yes			childhood-adult	no		no
Alpha-Sarco-glycanopathy	SGCA	AR	5x nomal, often>5000	yes	1000	yes	2-15 y			some
LGMD 2I	FKPR	AR	1000-8000	yes	8-26x normal	yes	variable; 61% less than 5 y	yes, late onset	yes	yes
LGMD 2L/MMD3	ANO5	AR	very high to 35,000	yes	3000-4000	yes	2nd-3rd decade		yes	yes
Myofibrillary myopathy with Desmin mutation	MFM1	AD/AR	338-1023; ♂>♀	yes	<1000		> 2nd decade			some

Limb girdle syndrome with Central cores	RYR1	AD	15x normal, may be normal	yes	may be normal	yes, following trigger	teens	yes	no	no
LGMD unspecified			elevated							
Facioscapulohumeral dystrophy	D4Z4 repeat retraction	AD	normal (25%) to<5 x normal		may be normal		congenital to late age; mean 3rd decade	no	no	no
Metabolic myopathies										
Carnitine palmitoyltransferase II (CPT2) deficiency	CPT2	AR	high at rhabomyolysis normal/ mildly elevated between episodes		<900	yes	adolescence-adult (mean 13 y; range 1-40 y)	yes	yes	
Myophosphorylase deficiency (McArdle)	PYGM	AR ♂predominance	to 12,000		5500	yes	usual<15		yes	yes
Phophofructokinase-deficiency	PFKM	AR ♂predominance	high			yes	2nd-4th decade	yes, proximal legs	yes	
Alpha-glucosidase deficiency (M. Pompe)	GAA	AR	< 10x normal, normal in 5% adults	yes			usual<15	yes, proximal		yes
Phosphorylase-b deficiency	PHKA1	X linked/AR	2-10x		<900	yes, occassionally	childhood-5th decade	yes	yes	
Adenylate-deaminase-deficiency	AMPD1	AR	normal to slightly elevated						yes	

Table A continued

Disorder	Gene	Inheritance	CK (U/L)	Asymptomatic HyperCKemia	CK in asymptomatic cases (U/L)	Myo-globinuria	Age presenting	Cramps	Exercise-intolerance	Calf hypertrophy
Mitochondrial myopathies										
with episodic HyperCKemia	MTTK	mitochondrial	200-11,000 (episodic) 67-320 (usual)				15-69 y			
with exercise intolerance and encephalopathy	MTCO3	mitochondrial, complex IV	high or normal			yes	4-20 y			
with myoglobinuria and exercise intolerance	MTCO1 MTCYB	mitochondrial; sporadic mitochondrial, complex III	CK normal at rest			recurrent yes	childhood-adult childhood	yes yes	yes yes	
Inflammatory myopathies										
Polymyositis		sporadic	up to 100x normal				>20 y			
Inclusion body myositis		sporadic; ♂predominance	2-5x normal				>50 y			
Macrophagic myofaciitis		sporadic	40% increased mildly to high				3th-5th decade			
Sarcoid myoparthy		sporadic; ♀predominance	moderately high				middle aged females			

Congenital myopathies										
Centronuclear	DNM2	AD/sporadic	rarely mildly high				variable: neonatal to adult			
Multicore	SEPN1	AR /sporadic	normal to slightly elevated				eearly delayed motor milestones			
Miscellaneaous										
Proximal myopathy with tubular aggregates		AD	normal-mildly high				5th-6th decade	yes	yes	
Proximal myopathy with tubular aggregates		sporadic /AR	normal-mildly high				teens	yes		
Thyroid disorder		sporadic; ♀predominance	high in hypothyroidism normal or low in hyperthyroidism				adult	yes		
Myotonia flucuans[125]	SCN4A	AD	2-4x normal				teens			
Myotonic dystrophy type 2 (PROMM)[126,127]	ZNF9	AD	mild< 10x normal	yes	up to 1400	yes	8-60y		yes	
Malignant hyperthermia[90,128]	RYR1	AD	in rest normal to mildly elevated; CK during hyperthermia very high up to 100,000			yes	related to exposure to volatile and depolarizing anesthetics			

TABLE B	Signs				Diagnostic tools			
Disorder	WEAKNESS PRESENTING	SPECIFIC	PRO-GRESS	CARDIAC INVOLVEMENT	LABORATORY	MUSCLE BIOPSY	IMMUNOLOGICAL STUDIES	GENE
Muscular dystrophies								
Dystrophino-pathy	proximal. first legs, later arms	presentation may be atypical with developmental delay, cognitive deficit, behavioral problems or cardiac failure	fast in DMD slower in BMD	yes,cardio-myopathy		dystrophy	DMD: IHC dys1,2,3 absent BMD: IHC dys1,2,3 reduced WB : in BMD different size or amount of dystrophin	DMD
LGMD 2B MMD1	limb girdle or distal gastrocnemius	posterior muscles; legs> arms asym-metry common later onset: varying phenotypes, also in same family	leg	no		dystrophy	IHC: dysferlin reduced or absent. WB: dysferlin absent or reduced	DYSF
LGMD 1C	proximal leg	also mutation specific distal myopathy has been described onset age 3rd-5th decade	usual-ly mild	mutation related		mild myopa-thic; fibrosis	WB: caveolin-3 reduced	CAV3
LGMD 2A	<12y shoulder; > 30y pelvic	weakness mild to se-vere in early onset	slow	no		myopathic with necrosis and regeneration	WB: Calpain-3 reduced	CAPN3
Alpha -Sarcogly-canopathy	proximal, progressive	late onset: less severe phenotype heterozygotes may have myalgia and scapular winging but normal CK	yes	occasionally		dystrophy	IHC: alpha sarco-glycan absent	SGCA
LGMD 2I	proximal> distal	exertional pain may be early symptom mild facial weakness in some	yes	cardiomy-opathy is common		dystrophy type 1 predominance	WB: reduced alpha dystroglycan	FKPR
LGMD 2L MMD3	proximal quadriceps; atrophy posterior lower leg	asymmetric weakness	slow	usually not		dystrophy	WB: reduced dystrophin and/or calpain-3	ANO5

Myofibrillary myopathy with Desmin mutation	posterior lower leg	cardiac failure may be presenting symptom; even sudden death	yes	frequently arrhythmia and heart failure		myopatic; subsarcolemmal & sarcoplasmic aggregates		MFM1
Limb girdle syndrome with Central cores	proximal symmetric	at risk for malignant hyperthermia following anaesthesia. During episode CK may be up to 100,000	slow			central cores		RYR1
LGMD unspecified	proximal symmetric		yes			dystrophy		
Facioscapulohumeral dystrophy	face (eye and/or lip closure); scapular muscles and biceps	often asymmetric rarely presentation with foot drop or lower limb proximal weakness	yes	arrhytmia and conduction block in 2-5%		varied fiber size, small angular fibers and hypertrophic type 2 fibers		D4Z4 repeat retraction
Metabolic myopathies								
CPT2 deficiency	no, in late stage weakness in some				acylcarnitineprofile			CPT2
Myophosphorylase deficiency	mild> 40 y. proximal > distal; arm >leg	second wind ; rhabdomyolysis; renal failure 10%; muscle wasting and hypertrophy are described			exercise test: reduced lactate		IHC: myophosphorylase absent	PYGM
Phophofructokinase deficiency	late onset fixed myopathy in some	second wind			exercise test: reduced lactate			PFKM
Phosphorylase-b deficiency	distal > proximal				exercise test: nl or reduced rise lactate			PHKA1
Adenylate deaminase deficiency	no weakness	no second wind			exercise test: reduced ammonia rise, normal lactate	normal morphology	IHC: AMPDA absent	AMPD1

Table B continued	Signs				Diagnostic tools			
Disorder	Weakness presenting	Specific	Pro-gress	Cardiac involvement	Laboratory	Muscle biopsy	Immunological studies	Gene
Mitochondrial myopathies								
with episodic HyperCKemia	proximal symmetric	episodic myalgia				SDH+ & COX- muscle fibers		MTTK
with exercise intolerance & encephalopathy	proximal in some patients	recurrent encephalopathy; migraine, myalgia and fatigue	improve-ment in teens		lactate acidemia	COX reduced	childhood: COX deficieny 20y RRF and COX+ fibers	MTCO3
with myoglobin-uria and exercise intolerance	no weakness (MTCO1 mutation)				serum lactate normal; low venous oxygen use at exercise test.	COX I&II reduced	COX deficieny; mild defects complex 1&III	MTCO1
	mild proximal (MTCYB mutation)				serum lactate high	RRF; SDH+/COX +	deficient com-plex III activity	MTCYB
Inflammatory myopathies								
Polymyositis	proximal >distal	dysphagia 40% arthritis/arthralgia 40%	slow	heart can be involved myocarditis		PA: inflammation		
Inclusion body myositis	proximal leg, distal wrist/finger flexor	in course often dysphagia	slow			PA: rimmed vacuoles/ inclusion bodies		
Macrophagic myofaciitis	mild proximal 43%	ESR elevated in 55%				PA: infiltration macrophages		
Sarcoid myopathy	proximal ± distal					PA: granuloma-tous myopathy		

Congenital myopathies							
Centronuclear	distal>prox	often dysphagia or ptosis/strabismus	slow			central nuclei	DNM2
Multicore		often rigid spine and scoliosis >10 y				multiple small cores	SEPN1
Miscellaneaous							
Proximal myopathy tubular aggregates AD	proximal	AD disorder; also known with younger onset with opthalmoplegia (limited upgaze) and high CK		no		tubular aggregates in type 2 fibres	
Proximal myopathy tubular aggregates sporadic /AR	proximal					tubular aggregates	
Thyroid disorder	mild proximal	hypothyroidsm: myxedema; APR absent; hyperthyroidism: brisk reflexes	resolving after treatment		TSH/Ft4	non-specific	
Myotonia fluctuans	no weakness	myotonia often delayed after exercise			needle EMG		SCN4A
Myotonic dystrophy type 2 (PROMM)	proximal leg> arm distal hand: flexors of thumb and fingers	often muscle pain/ stiffness	yes slow	cardiac arrhythmia		abnormal type 2 fibers	ZNF9
Malignant hyperthermia		Malignant hyperthermia can also be related to mutations in ion channel genes with transient weakness and normal or marginally elevated CK		yes, arrhythmia during episodes			RYR1

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Curriculum Vitae

Chiara Straathof was born on 6 December 1963 in Eindhoven. She grew up in Valkenswaard and in 1973 she moved to The Hague where she graduated from high school (Gymnasium β) at the Aloysius College in 1982. After this, she started her medical training at the Rijksuniversiteit Leiden. In 1987 she worked for six months as a research student at the Department of Neurology at the Johns Hopkins University, Baltimore, U.S.A. (prof. D.S. Zee) and studied the Optokinetic After-nystagmus in healthy subjects. The report was awarded a "Hippocrates studiefonds-prijs" in 1988. In 1990 she followed a clinical fellowship Neurology at the National Hospital for nervous diseases, Queen Square, London (dr. A.E. Harding) for three months. After obtaining her medical degree in May 1990 she worked as a house officer in Internal Medicine at "Ziekenhuis de Lichtenberg", at present Meander MC, in Amersfoort (dr. H.Ch. Hart).

From 1992 to 1998 she was resident in Neurology at the Dijkzigt Hospital, at present Erasmus MC, in Rotterdam (Prof. dr. F.G.A. van der Meché). In 1994 she received a research fellowship from the Dutch Cancer Society (de Nederlandse Kankerbestrijding) and did a research project on chemotherapy for malignant glioma in a rat model at the Daniel den Hoedkliniek in Rotterdam (Prof. dr J.H.M. Schellens, Prof. dr M.J. van den Bent), followed by an internship Neuro-oncology (dr. Ch.J. Vecht) in the same clinic.

As a neurologist she worked for six months at the Erasmus MC, at the departments of Neurology and Clinical Neurophysiology. From 1999 to 2002 she worked as a neurologist in the Bronovo Ziekenhuis in The Hague and since 2002 she is member of the clinical staff Neurology at the Leiden University Medical Center (LUMC). She received a clinical fellowship Neuro-myology from the Prinses Beatrix Spierfonds and was trained at the LUMC (Prof. dr. J.J.G.M. Verschuuren), the Academic Medical Center (Prof. dr. M. de Visser) and the University Medical Center Utrecht (Prof. dr. J. Wokke), followed by registration as neuromyologist in 2006.

In 2007 she started the studies for her PhD (Prof. dr. J.J.G.M. Verschuuren).

At present she is involved in the care of adult patients with neuromuscular disorders in the LUMC and participates in the multidisciplinary clinic for young adults with muscular dystrophies. Concurrently she is head of the Outpatient Department of Neurology since 2011.

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List of abbreviations

AD	Autosomal dominant
ADHD	Attention-deficit and hyperactivity disorder
AON	Antisense oligonucleotide
AR	Autosomal recessive
AxD	Axial diffusivity
BMD	Becker muscular dystrophy
CK	Creatine kinase
CPT2	Carnitine palmitoyltransferase II
DM1	Myotonic dystrophy type 1
DM2	Myotonic dystrophy type 2
DMD	Duchenne muscular dystrophy
DTI	Diffusion tensor imaging
ECG	Electrocardiography
EFNS	European federation of neurological societies
EMG	Electromyography
FA	Fractional anisotropy
FSIQ	Full scale intelligence quotient
HR- MCA	High resolution melting curve analysis
ICV	Intracranial volume
LDGA	Laboratory for Diagnostic Genome Analysis
LGMD	Limb girdle muscular dystrophy
MD	Mean diffusivity
MH	Malignant hyperthermia
MLPA	Multiplex ligation-dependant probe amplification
MMD	Miyoshi-type muscular dystrophy
MND	Motor neuron disease
M-PCR	Multiplex-Polymerase chain reaction
MRI	Magnetic resonance imaging
NPE	Neuropsychological examination
OCD	Obsessive-compulsive disorder
PROMM	Proximal myotonic myopathy
RD	Radial diffusivity
SD	Standard deviation
SDS	Standard deviation score
SDQ	Strengths and Difficulties Questionnaire
SEM	Standard error of the mean
SMA	Spinal muscular atrophy
SMN1	Survival motor neuron 1
TBV	Total brain volume
U/I	Units/liter
VBM	Voxel based morphometry
WB	Western Blot analysis
WCB	Wheelchair bound