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ORIGINAL COMMUNICATION

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Muscle computed tomography patterns in patients with the mitochondrial DNA mutation 3243A>G

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Abstract Computed tomography provides a sensitive method for investigating skeletal muscle changes in neuromuscular diseases, but this method has not been applied to mitochondrial myopathies. We characterized the pattern of muscle involvement in patients with the 3243A>G mutation in mitochondrial DNA (mtDNA), the common MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) mutation. Twenty-four patients, age 19–73 years, with 3243A>G were examined. Clinical evaluation included assessment of muscle strength and functional capacity. All the patients underwent muscle computed tomography, and muscle samples from 17 of them were examined for the presence of ragged red fibres and for the 3243A>G heteroplasmy. Venous blood lactate at rest and serum creatine kinase were determined. Clinical myopathy was found in six patients, while nine showed mild muscle weakness and nine had normal muscle function. The upper and lower limbs were equally affected, but the proximal muscles were more severely affected than the distal ones. CT revealed abnormalities in the muscles of 13 patients (54 %; 95 % confidence interval, 33–76 %), including the six with clinical myopathy and seven without clinical myopathy. Myopathic changes were found most frequently in the pelvic muscles, with predominant involvement of the gluteus maximus. These data show that CT reveals frequent abnormal findings in the muscle of patients with the 3243A>G mtDNA mutation. Muscle CT is a useful adjunct to clinical evaluation in these patients.

Key words myopathy · MELAS · muscle CT · myopathic pattern

Introduction

Imaging of muscles with CT (computed tomography), MRI (magnetic resonance imaging) and ultrasound has been shown to be a sensitive means for evaluating muscle involvement in various neuromuscular diseases [1, 3, 4, 14, 17, 19, 24, 27]. In primary myopathies, muscle CT reveal small, focal hypodense areas which may progress to form widespread areas of low attenuation. The most severe abnormalities of this kind have been observed in muscular dystrophies [24]. In neurogenic diseases, muscle CT can reveal atrophic changes, although muscles may also contain small punctate areas of decreased attenuation [24] or even severe hypodensity in hereditary neuropathies [17].

The muscles are commonly affected in diseases caused by mutations in mitochondrial DNA (mtDNA), and a muscle biopsy is still the cornerstone of any diagnosis, even if there are no signs or symptoms of myopathy [20]. The clinical manifestations of muscle involvement in these diseases include weakness, exercise

JON 1363

intolerance, muscle cramps and myalgia. Myopathy has been suggested as one of the most frequent clinical features in patients who harbour the 3243A>G mutation in the gene encoding $tRNA^{Leu(UUR)}$ (MTTL1) [5], which is the most common cause of the MELAS syndrome (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes).

Histological examination of muscle from patients with a mitochondrial disorder does not usually reveal signs of inflammation, muscle fibre degeneration, necrosis or atrophy [20], although dystrophic changes have been found occasionally [25]. Muscle lesions in metabolic myopathies are often dispersed. CT has been used to examine patterns of muscle involvement in several neuromuscular diseases, but not in mitochondrial myopathies, although it would be capable of showing the presence and extent of dystrophic or atrophic changes in the muscles of patients with mitochondrial diseases. We therefore performed muscle CT on 24 patients with 3243A>G in order to establish the frequency and type of muscle involvement.

Patients and methods

Patients

Twenty-four patients (8 men, 16 women) aged 19–73 (mean 46.7) years were examined. We have previously ascertained 11 pedigrees with the 3243A>G mtDNA mutation in a population-based screening in the province of Northern Ostrobothnia, Finland [16]. The patients in the present study were members of these families and each patient had been diagnosed with 3243A>G. Functional capacity was evaluated with a seven-item test, including assessment of gait, climbing stairs, rising from a chair, sitting from supine, standing from sitting, and functioning of the proximal and distal upper limbs [15]. Assessment of the global clinical severity of the disease was based on this functional evaluation and was scored in terms of the Modified Rankin scale (0–5). Physical activity and susceptibility to exercise intolerance were determined by means of a structured interview. Muscle strength was assessed bilaterally according to the modified MRC grading system (scale 0–5) [18] including the facial and mandibular muscles, shoulder abduction, flexion and extension of the neck, elbows, wrists, fingers, hips and knees, pronation and supination of the forearms and ankle dorsiflexion and plantar flexion. Entirely normal muscle examination gave a mean score of 5.00, while mean scores ≤ 4.50 were considered to indicate myopathy and scores between 4.50 and 5.00 were considered to indicate muscle weakness (Table 1). Other causes of myopathy were ruled out by clinical examination and laboratory tests. A biopsy of the vastus lateralis or anterior tibial muscle was obtained from 17 patients. Ragged red fibres (RRFs) were defined as present if at least one was confidently detected in the muscle specimen. The

Table 1 Clinical characteristics of 24 patients with the 3243A>G mtDNA mutation

Patient	Age (years)/Sex	Clinical features	Muscle diagnosis	CK (U/l)	HP (%)	RRF	MRC score (mean ± SD)	Rankin score (0–5)
1	46/F	none	normal	119	n. d.	n. d.	5.00±0.00	0
2	72/F	G, L, S	M	177	53	+	4.19±0.27	2
3	51/F	D, L, S, V	W	214	75	+	4.77±0.35	1
4	43/F	S+, V	normal	75	n. d.	n. d.	5.00±0.00	1
5	23/F	E, G, HA, L, P, S, SE	W	235	n. d.	n. d.	4.79±0.34	2
6	59/F	G, L	M	144	67	+	4.08±0.12	2
7	19/M	C, G, H, S	W	134	76	+	4.56±0.43	2
8	52/M	L	W	225	n. d.	n. d.	4.86±0.36	0
9	37/F	none	normal	141	59	–	5.00±0.00	0
10	57/M	A, D, G, L, N, P, S	M	358	72	–	4.13±0.21	3
11	67/M	C, D, G, H, L, N, S	M	188	70	+	4.41±0.37	3
12	21/F	E, G, HA, S	M	57	n. d.	n. d.	4.09±0.12	2
13	51/F	S	W	109	74	–	4.87±0.30	1
14	34/F	none	normal	124	76	–	5.00±0.00	0
15	63/F	D, G, L	normal	236	75	+	5.00±0.00	1
16	61/M	D, G, H	W	221	73	+	4.83±0.32	1
17	46/M	C, S	normal	69	86	+	5.00±0.00	2
18	73/F	D, G, S	W	93	n. d.	n. d.	4.77±0.59	1
19	38/M	C, D, G, H, L, S+	normal	133	89	+	5.00±0.00	2
20	36/F	B, C, D, G, H, L, R, S	normal	654	83	+	5.00±0.00	2
21	62/F	C, G, H, S	M	209	66	+	4.06±0.11	3
22	29/F	C, D, G, L	W	110	n. d.	n. d.	4.91±0.24	1
23	25/M	C, D, H, E, G, L, S, SE	normal	147	94	+	5.00±0.00	2
24	56/F	D, G, H, L	W	133	78	+	4.86±0.33	1

HP degree of mutation heteroplasmy in muscle; *RRF* ragged red fibres (+ = present, – = not present); *MRC* Medical Research Council scale (mean of all muscles examined on both sides); *A* ataxia; *B* basal ganglia calcifications; *C* cognitive decline; *D* diabetes; *E* epilepsy; *G* short stature; *H* cardiac hypertrophy; *HA* episodic headache; *L* lactic acidosis; *M* clinical myopathy; *N* peripheral neuropathy; *P* ptosis; *R* pigment retinopathy; *S* sensorineural hearing impairment (*S+* deafness); *SE* stroke-like episodes; *V* vitiligo; *W* weakness; *n. d.* not determined. Muscle diagnosis indicates the result of clinical evaluation

3243A>G mutation heteroplasmy in mtDNA was analysed in the muscle by restriction fragment analysis [12]. Venous blood lactate at rest (normal < 1.3 mmol/l) and serum creatine kinase (CK, normal < 150 U/l for women, < 270 U/l for men) were determined. The research was approved by the Ethics Committee of the Medical Faculty of the University of Oulu and all the examinations were carried out after obtaining informed consent from the patients.

Computed tomography of skeletal muscle

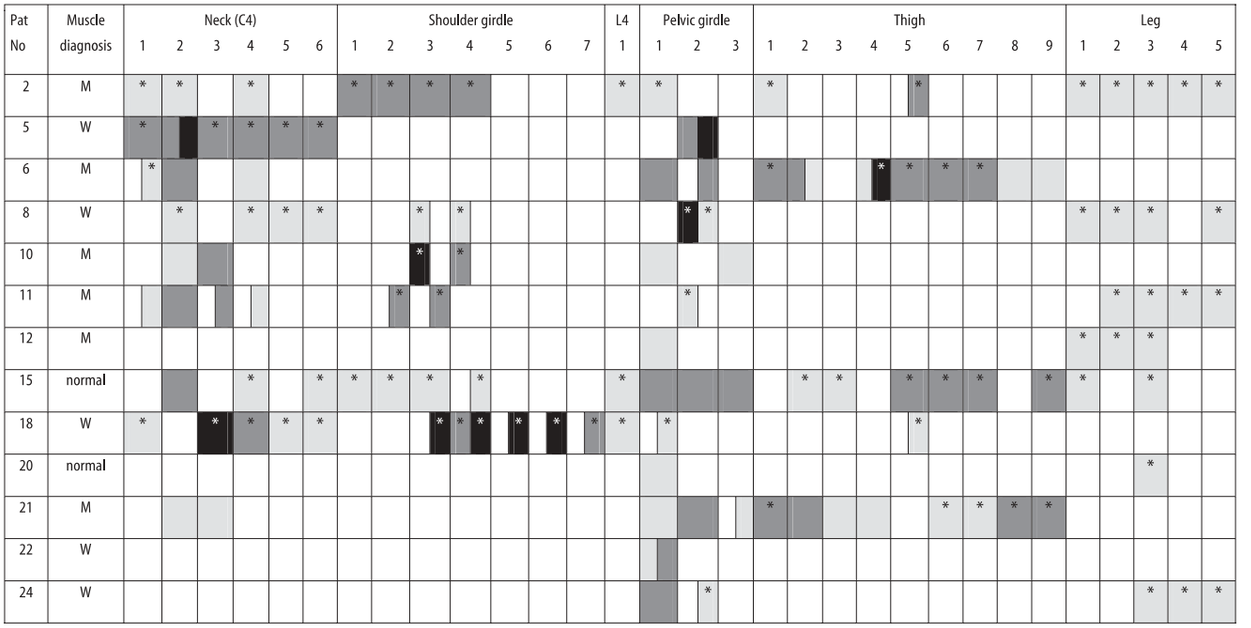
All patients underwent multi-slice computed tomography (Toshiba Aquilion, Nasu, Japan 2000, 4 x 5 mm slices, 120 kV, 150 mAs, 0.5 s rotation time, standard algorithm, 256 x 256 matrix) in the supine position. A total of 43 muscles (those indicated in Table 2 and the levator scapulae, pectoralis major, longissimus, ileocostalis, sartorius, gracilis, iliopsoas, gluteus minimus, anterior and posterior tibial and flexors of digitorum and hallucis longus) were visualised bilaterally at six transverse levels [1], including neck muscles (focusing on the fourth vertebra of the cervical spine), the shoulder girdle (middle of the fossa glenoidalis), lumbar muscles (the fourth vertebra of the lumbar spine), the pelvic girdle (5 cm above the symphysis), the thighs (midpoint between the greater trochanter and the centre of the knee joint) and lower legs (largest diameter of the lower leg). In addition, the gluteal region was scanned at three levels in four patients, three of them with clinical myopathy. Three healthy and physically active women (age 24, 40 and 53 years) and men (age 25, 41 and 51 years) were scanned as control subjects using the same protocol.

The CT images were evaluated with regard to intramuscular signal density and degree of muscle atrophy. Myopathic CT findings were graded in four categories [2, 24]: 0 = normal: a muscle with normal attenuation, 1 = spot-like: a muscle with several small hypodense areas, 2 = moth-eaten: a muscle with multiple patchy areas of low attenuation with little or no reduction in muscle area, and 3 = washed-out: a muscle with widespread low attenuation or complete replacement by low-attenuation tissue. Muscle atrophy was determined on the basis of the reduction in the cross-sectional area of the muscle and was also graded in four categories: 0 = no atrophy, 1 = mild; simple atrophy of muscle corresponding to a slight reduction in muscle size, 2 = moderate; simple atrophy corresponding to a 50 % reduction in muscle size, and 3 = severe; marked atrophy of the muscle or its disappearance accompanied by an increase in the subcutaneous tissue. The scans were analysed by two neurologists and one neuroradiologist, and a consensus was required.

Electromyography

A concentric needle EMG examination was performed for 12 patients on the same day as the CT. Twelve skeletal muscles were examined on the right side, including the anterior tibial, medial gastrocnemius, lateral vastus femoris, biceps femoris (short and long heads separately),

Table 2 Muscle CT findings in patients with the 3243A>G mtDNA mutation. Patients with normal muscle CT findings are not shown



Muscle diagnosis indicates the result of clinical evaluation. *M* clinical diagnosis of myopathy; *W* muscle weakness.
Muscles at neck level (C4): *1* sternocleidomastoid; *2* multifidus; *3* semispinalis cervicis; *4* semispinalis capitis; *5* splenius capitis; *6* trapezius.
Muscles at shoulder girdle level: *1* deltoid anterior; *2* deltoid medius; *3* deltoid posterior; *4* infraspinatus; *5* subscapularis; *6* serratus anterior; *7* rhomboid.
Muscles at lumbal level (L4): *1* multifidus.
Muscles at pelvic girdle level: *1* gluteus maximus; *2* gluteus medius; *3* tensor fasciae lata. Patient 2 had also moderate atrophic changes in the gluteus minimus.
Thigh muscles: *1* rectus femoris; *2* vastus lateralis; *3* vastus intermedius; *4* vastus medialis; *5* biceps femoris; *6* semitendinosus; *7* semimembranosus; *8* adductor magnus; *9* adductor longus. Patient 6 had also severe changes in the sartorius and gracilis.
Leg muscles: *1* peroneus; *2* extensor digitorum longus; *3* gastrocnemius medialis; *4* gastrocnemius lateralis; *5* soleus.
The severity of myopathic pattern and the degree of atrophic changes are shown in grey scale; white = normal; light grey = spot-like pattern or mild atrophy; medium grey = moth-eaten pattern or moderate atrophy; black = washed-out pattern or severe atrophy. Muscles with atrophic changes are marked with an asterisk. The right and left sides are shown separately if asymmetrical abnormalities were observed.

semitendinosus, semimembranosus, gluteus maximus, iliopsoas, trapezius, biceps brachialis, triceps brachialis and the first dorsal interosseus muscles. Owing to patient non-compliance, the hamstring muscles were not examined in six patients, the first dorsal interosseus muscle in three patients and the trapezius muscle in two patients. In addition, EMG results were available for four patients who had been examined previously (patients 2, 6, 10, 21). The gluteal and hamstring muscles had not been examined in these cases. For an electrophysiological diagnosis of myopathy it was required that myopathic findings should be detected in the EMG of at least one muscle.

Statistical analysis

The Fisher exact test, Mann-Whitney test and t-test were used for statistical analysis of the data.

Results

Clinical examination

The clinical phenotype was quite variable among the patients (Table 1). A definite myopathic weakness was found in the clinical examination of six patients (two men, four women), three of whom had a slight waddling gait and difficulty in climbing stairs and rising from a supine position as a consequence of gluteus maximus weakness. Nine patients (three men, six women) showed mild muscle weakness and two of them complained of exercise intolerance and myalgia. Muscle strength evaluation and functional assessment were normal in the remaining nine patients (three men, six women). Serum CK was mildly elevated in six women and one man (Table 1). Twelve patients had increased resting blood lactate values. The mean degree of 3243A>G mutation heteroplasmy in muscle was 73% ± 11%. RRFs were found in the muscles of 13 out of the 17 biopsied patients. Clinical examination showed the proximal muscles to be more severely affected than the distal ones, which in turn were affected equally as much as the facial and mandibular muscles. The upper and lower limbs were equally affected.

Muscle CT findings

A homogeneous density was seen in the muscles of the healthy controls, whereas the CT scans revealed abnormalities in the muscles of 13 patients (54%; 95% confidence interval, 33–76%) (Table 2), but were normal in the remaining 11 patients. No changes were detected in muscle density or cross-sectional area in nine out of the 43 muscles among all the 24 patients. A myopathic pattern was found most frequently in the pelvic muscles, with predominant involvement of the gluteus muscles (Table 2, Figs. 1, 2). The gluteus maximus was affected in 10 patients (42%). Muscle atrophy was common in the shoulder girdle and the legs, where the medial gastrocnemius was most commonly affected (seven patients, 29%), while the anterior tibial muscle was intact in all the patients. Marked atrophic changes could also be observed in the thighs (Fig. 3) and the neck. Almost all the

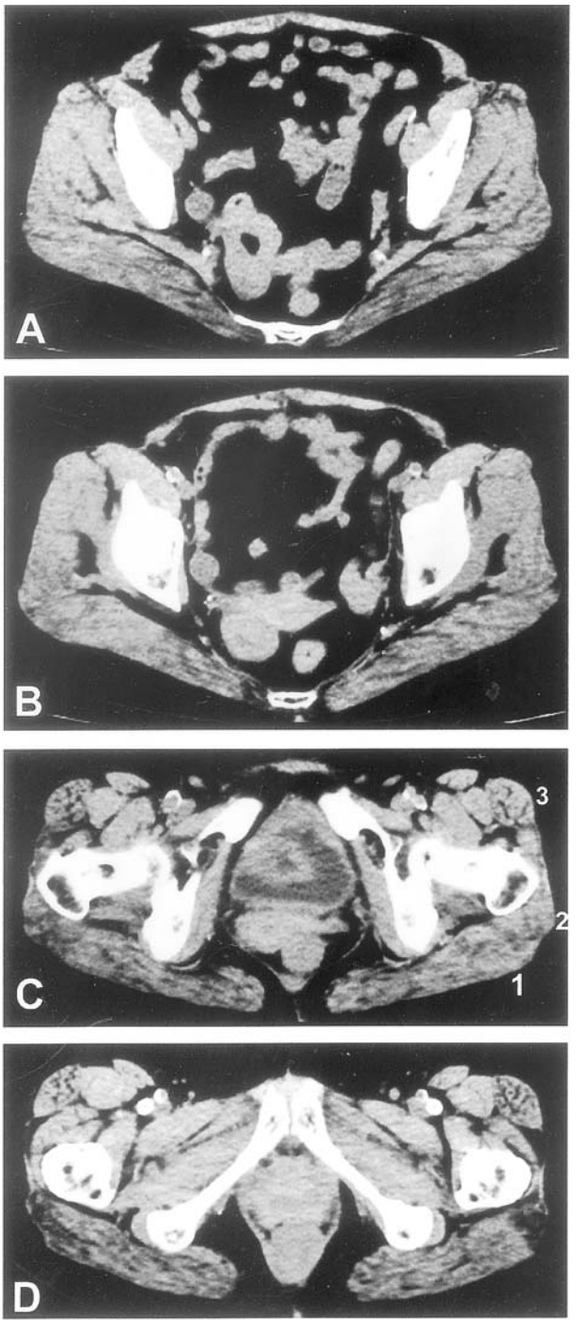


Fig. 1 Adjacent CT scans of the pelvic muscles in patient 15. The scans show a progressive increase in myopathic involvement in the craniocaudal direction (**A–D**) in the gluteus maximus (1), gluteus medius (2) and tensor fasciae latae (3)

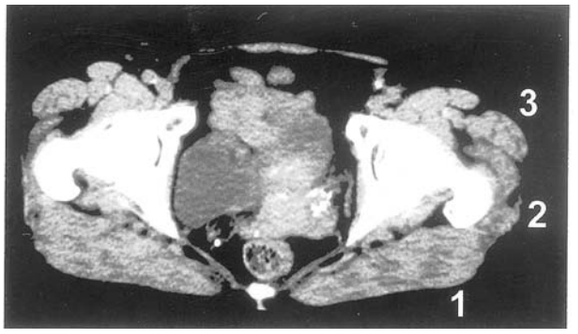


Fig. 2 Muscle CT scans at the pelvic level show patient 21, with clinical myopathy, to have bilateral severe fatty replacement of the gluteus maximus (1), gluteus medius (2) and tensor fasciae latae muscles (3)

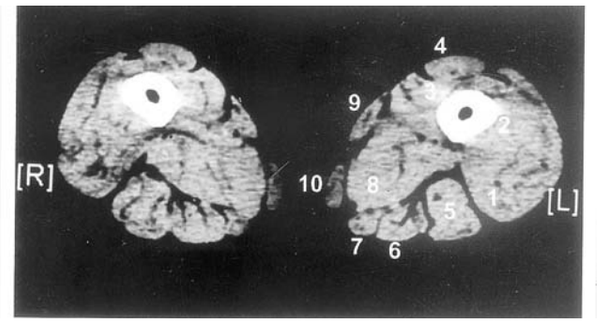


Fig. 3 Muscle CT scan of the thighs of patient 6. The gracilis muscle (10) is severely atrophic and almost entirely replaced by fat tissue. Moderate hypodensity is seen in the sartorius muscle (9). The right vastus lateralis muscle (1) shows marked atrophy, while the left one is less involved and the vastus medialis muscle shows severe atrophic changes (3). The rectus femoris muscle (4) is atrophic and markedly hypodense. The hamstrings, including the biceps femoris (5), semitendinosus (6) and semimembranosus (7), are moderately hypodense. The vastus intermedius (2) and adductors (8) have been mostly spared

muscle findings were symmetrical (Table 2) and no compensatory muscle hypertrophy was found. Variations in intramuscular density were seen in the gluteus maximus, gluteus medius and tensor fasciae lata muscles in adjacent CT scans of the pelvic region in four patients (Fig. 2).

Electromyographic studies

Twelve patients underwent a needle EMG. Short-duration, low-amplitude, polyphasic motor unit potentials were abundant in some muscles of six patients, the most frequently affected muscles being the gluteus maximus (three patients), trapezius (three patients), the short head of the biceps femoris (two patients) and the biceps brachialis (two patients). Fibrillation potentials were not detected, but complex repetitive discharges occurred in three myopathic muscles of patient 10. The EMGs of the four additional patients revealed myopathic findings in the biceps brachialis muscle of three cases. Two patients with myopathy (patients 10 and 11) had evidence of peripheral neuropathy in clinical and neurophysiological examinations (Table 1).

Correlation of clinical features and muscle CT findings

An association was found between the presence of myopathic findings in muscle CT and low MRC scores (Table 3), but the patients with myopathic findings and those without did not differ in gender distribution, age, functional capacity, myopathic findings in EMG, the presence of RRFs, the presence of cardiomyopathy, the severity of hearing impairment or the degree of mutation heteroplasmy in muscle.

Table 3 Comparison of the 3243A>G patients with and without abnormal CT findings

	Patients with abnormal findings	Patients without abnormal findings	p value
Men/women (n)	3/10	5/6	0.39
Age (years)	57 (21–73)	43 (19–61)	0.79
MRC score	4.55 (4.06–5)	4.91 (4.56–5)	0.009
Rankin score	2 (0–3)	2 (0–3)	0.50
Myopathic findings in EMG (n)	7	2	0.26
RRF (n)	7	6	0.57
Muscle heteroplasmy (%)	70 (53–83)	76 (59–94)	0.13
Cardiomyopathy (n)	6	2	0.31
BEHL (dB)	49 (13–63)	49 (6–106)	0.46

Fisher's exact test, Mann-Whitney test and the independent samples t-test were used to detect differences between the groups. *MRC* Medical Research Council scale; *RRF* number of patients with ragged red fibres; *BEHL* better ear hearing level over the frequencies 0.5, 1, 2 and 4 kHz in audiogram. Values are medians (range), except for MRC scores, which are means

Discussion

Clinical examination revealed a marked proximal muscle weakness in six patients with the 3243A>G mtDNA mutation, and skeletal muscle CT showed abnormal attenuation in each case. Furthermore, muscle weakness was found to some extent in nine patients, five of whom with changes in muscle CT. Nine patients showed no clinical signs or symptoms of myopathy, and only two of these had changes in muscle CT. These findings suggest that CT accurately detects skeletal muscle abnormalities in patients with a mitochondrial disorder. Interestingly, we found no correlation between muscle CT findings and other clinical features of mitochondrial diseases or the degree of mutation heteroplasmy in muscle.

Muscle weakness is not uncommon in patients with mitochondrial diseases [21, 23] and a meta-analysis of reported cases with 3243A>G has revealed myopathy in 53 % [5]. We found that 13 of our patients with 3243A>G (54 %) had myopathic and/or atrophic findings in CT scans of the pelvic muscles. The gluteal muscles were affected in all these patients, including the six with clinically definite myopathy. Gluteal CT abnormalities have also been reported in other myopathies such as polymyositis. In this disease gluteal CT abnormalities have been suggested to be due to a more severe disease process in the gluteal region than in other muscles [27]. The gluteus maximus is one of the principal gait ambulatory muscles, counteracting the tilting of the pelvis, which makes it active in an upright position, thus suggesting a high demand for aerobic metabolism. Interestingly, the posterior leg muscles were frequently involved in patients with 3243A>G, and the posterior group was also involved in the thigh and neck muscles. A similar pattern of posterior muscle involvement has been found in patients with primary myopathies [4, 14] and peripheral neuropathies [17].

We found the most frequent CT changes in the antigravity muscle group, including the neck, back and hip extensors and plantar flexors. Muscle fibres are diverse in their contractile and energetic properties, and can be classified on the basis of the activity of mitochondrial enzymes or on the basis of the expression of myosin heavy chain protein isoforms, into slow-twitch fibres, the type I fibres, and into fast-twitch fibres, the IIA and IIX fibres (previously designated as IIB fibres). The distribution of the fibre types varies from muscle to muscle and even in different parts of the same muscle [11]. Muscles primarily involved in maintaining posture, e. g. the plantar flexors, have a higher proportion of type I fibres [7]. Anatomically, the type I and IIA fibres lie in a deeper plane and are situated closer to the trunk or limb axis and are responsible for the sustained strong activity required by postural functions. They are also more densely populated with mitochondria and possess a higher activity of cytochrome oxidase than type IIX fibres [10]. In consequence, failure of energy production caused by a mtDNA mutation may lead to the pattern of clinical and radiological involvement observed in the proximal muscles of the patients with 3243A>G.

The distribution of myopathic findings in the patients with 3243A>G may also be explained by differences in the embryonic origin of the individual muscle. Even though the fate maps for the somitic origins of skeletal muscles are still incomplete, gluteal muscles are thought to originate from the sacral and coccygeal somites, while anterior thigh muscles, e. g. the sartorius, are derived from the rostralmost lumbar somites [8]. In addition it is known that some muscles receive myogenic precursor cells from as few as three contiguous somites, while others originate from as many as seven somites [8]. Precursor cells may contain different proportions of mutant mtDNA as a consequence of the sampling effect in the mitochondrial bottleneck during embryonic development and as a consequence of subsequent mitotic segregation. Extraocular muscles originate from preotic myotomes, which are thought to be derived from the three extreme rostral somitomeres [8]. The isolated involvement of extraocular muscles in chronic progressive external ophthalmoplegia (CPEO) may be partly explained by the embryonic origin of these muscles. On the other hand, these muscles contain many mitochondria, presumably related to the high demand of energy due to almost constant eye movements. Thus embryonic factors may also play a role in the selective distribution of muscle involvement in mitochondrial myopathies.

Dystrophic features have been observed in the muscle histology of some patients with mitochondrial myopathy [25] and we found here radiological features similar to those described in dystrophic muscle diseases [9]. Furthermore, we found radiological evidence for muscle atrophy in half of the patients with 3243A>G, although muscle atrophy is not common on histological examination. The parenchymal changes in atrophic muscles were often spotlike, which in the absence of neuropathy in these patients suggests that atrophy is myogenic in origin. Sparing of the gracilis and sartorius muscles has been reported in many myopathies, including dystrophies [9, 22, 24] and this probably reflects biochemical and functional differences in these muscles [22]. These muscles are characteristically of the fusiform, stretched-out type. In the case of mitochondrial myopathies, a particularly prominent fatty infiltration has been detected by MRI in the gracilis and sartorius muscles of five out of six patients with CPEO [6]. We found myopathic changes in the gracilis and sartorius only in one patient with clinical myopathy, while these muscles were spared in the other patients. These results reflect a selective involvement of muscles. Different, selective involvement has also been observed in muscle CT scans in limb-girdle muscular dystrophy, between sarcoglycanopathy

with proximal muscle involvement and dysferlinopathy with distal lower limb involvement [26].

EMG was consistent with myopathy in six out of the 12 patients, in agreement with a previous study on MELAS patients [23]. It is well known that many myopathic disorders, especially congenital and endocrine, affect the contractile properties of the muscle fibres without modifying their electric properties, and therefore a needle EMG does not produce detectable changes [28]. We observed that EMG abnormalities were more frequent in proximal muscles, although they occurred less abundantly than changes in CT scans. In the lower limbs, EMG abnormalities were mainly found in the gluteal and hamstring muscles, where CT changes were also seen most often. In the upper limbs, the EMG findings were more disperse, although there, too, they were proximal, occurring most often in the trapezius muscle. Myopathy may co-occur with peripheral neuropathy in patients with 3243A>G [13], and accordingly, we observed two patients with myopathic findings in EMG and abnormalities in the electrodiagnostic evaluation of the peripheral nerves.

We thus found that CT of skeletal muscle revealed frequent abnormal findings in patients with the 3243A>G mtDNA mutation, the pelvic muscles being more often affected than the others. The changes seen in muscle CT scans were both dystrophic and atrophic in nature and their presence was associated with more pronounced muscle weakness. Our findings suggest that imaging is a useful adjunct to clinical evaluation of these patients and aids to define the distribution of muscle involvement in mitochondrial myopathies.

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