Table 1 Patients with early presentation of the mitochondrial A8344G mutation

Age of onset	*Clinical features*	Cerebral MRI lesions	RRF	% Hetero-plasmy (tissue)	Post-mortem examination (brain)	Author (reference)
6 months	DD, hypotonia, stridor, asthma-like episodes, acute respiratory failure	Normal		90 (SM, L, B, K)	Lesions in midbrain, pons, medulla, dentate nucleus, white matter and spinal cord, myocarditis	Grattan-Smith (*J Child Neurol* 1990;5:137)
Infancy	DD, spastic diparesis, acute neurological deterioration		ND	92 (B)	Typical lesions of LS	Santorelli (*Ann Neurol* 1998; **44**: 962)
3 months	DD, hypotonia, episodes with hyperventilation, hypertrophic cardiomyopathy, died at 16 months			95 (SM)		Stratilova (*Cas Lek Cesk* 1999; **138**: 401)
1 week	DD, hypotonia, spastic quadriparesis	White matter		50 (SM)		Stratilova *(idem)*
18 months	DD, ataxia, hypotonia, hiccups, sleep apnea, dysphagia, myoclonus, tremor	Midbrain, medulla oblongata and tegmentum	Yes	NM		Yasaki (*Neuroped* 2001; **32**: 299)
Birth	DD, hypotonia, constipation, status asthmaticus, acute respiratory failure, neurological regression, PEO, ptosis, muscle weakness, hypertrophic cardiomyopathy, WPW, pancreatitis, sensorineural deafness, died at 23 months	Putamen, claustrum, thalamus, midbrain, medulla, spinal cord (at 20 months)	ND	100 (WBC)		Tsao (*J Child Neurol* 2003; **18**: 62)
Birth	DD, poor feeding, colicky abdominal pain, FT, died at 11 months		ND	100 (SM, H, L)	Lesions in cerebral cortex, subthalamic and cranial nerve nuclei, gray matter of spinal cord, histiocytoid cardiomyopathy, liver steatosis, retinal hypoplasia	Vallance (*Pediatr Cardiol* 2004; **25**: 538)
12 months	DD, feeding difficulties, frequent vomiting, growth retardation, ataxia, hypotonia, tremor, static encephalopathy	Putamen (bilateral) (at 4 years)	ND	75 (SM)		Orcesi (*J Child Neurol* 2006; **21**: 79)
2 months	DD, asthma-like episodes, FT, hypertension, hypotonia, abnormal breathing pattern	Midbrain, pons, medulla oblongata and cervical spinal medulla (at 11 months)	ND	95 (SM)		Scalais (2007)

DD, developmental delay; FT, failure to thrive; LS, Leigh syndrome; MRI, magnetic resonance imaging; ND, not detected; NM, not mentioned; PEO, progressive external ophthalmoplegia; RRF, ragged-red fibres in skeletal muscle; WPW, Wolff-Parkinson-White syndrome; SM, skeletal muscle; L, liver; B, brain; K, kidney; H, heart muscle.

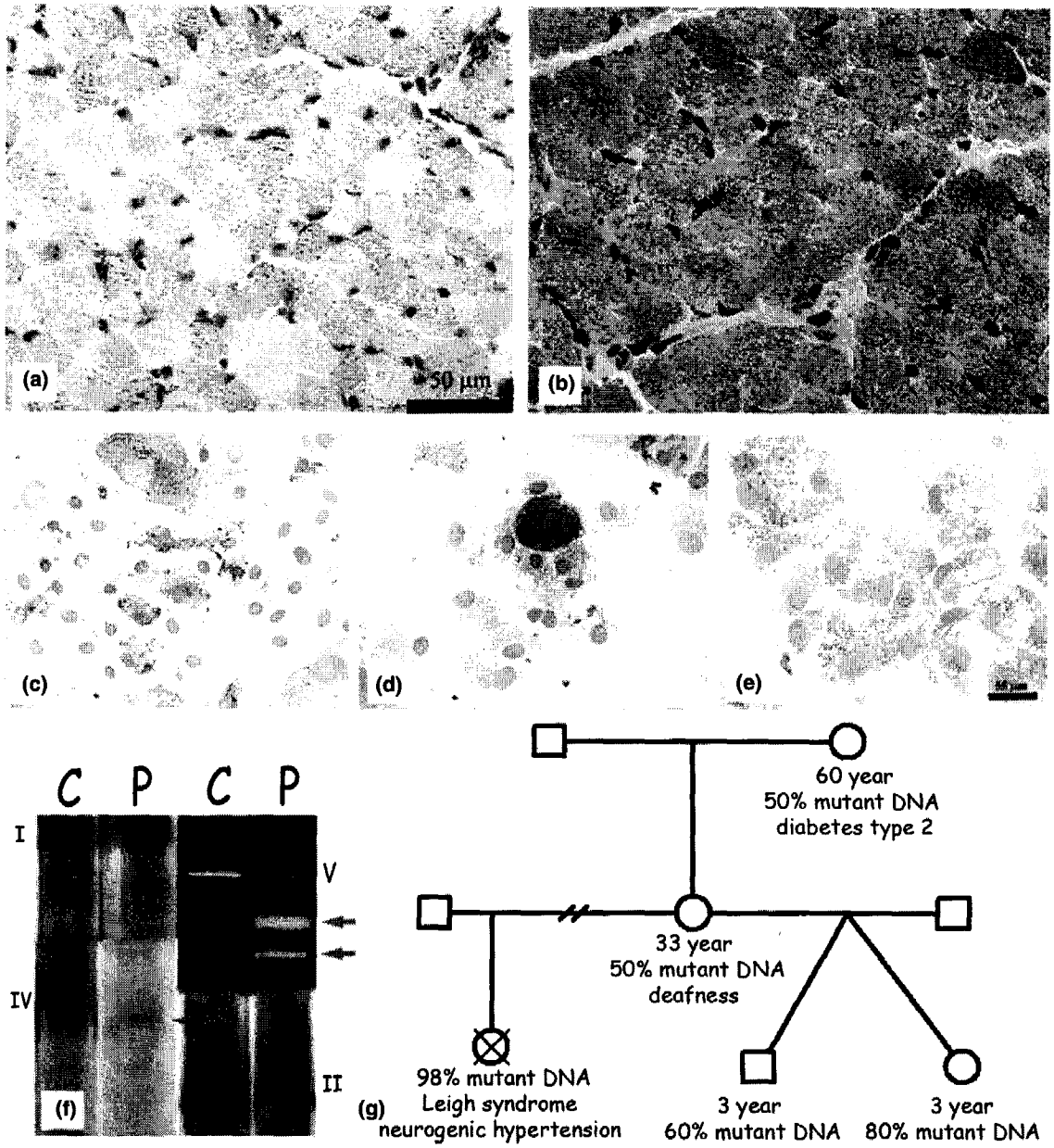

Figure 1 (a, b) Muscle: (a) Mosaic pattern of immunohistochemically stained OXPHOS constituents using an antibody against the 20 kDa subunit of complex I in muscle. (b) Homogeneous staining with an antibody against the alpha subunit of complex V. (c, d, e, f) Fibroblasts: Immunocytochemical staining of OXPHOS constituents (DAB, brown) with counterstained nuclei (haematoxylin, blue) using antibodies against complex subunits: (c) Mosaic type result for complex I (antibody against the 20 kD subunit), (d) similar mosaicism for complex IV (antibody against subunit I), (e) normal staining for complex V (antibody against the α-subunit). (f) Catalytic staining following BN-PAGE separation of the OXPHOS complexes (P: patient, C: Control). In the patient, catalytic staining decreased for complex IV, but normal for the complexes I and II. In the lane stained for complex V subcomplexes are detected (arrows). (g) Family pedigree of the proband showing maternal transmission of the A8344G somatic mutation, variability of the mutant mtDNA fraction, and of clinical signs. The proband has 98% of mutant mtDNA. In the mother with 50% of mutant mtDNA, the plasma lactate is normal as well as a cerebral MRI and MRI spectroscopy. The half-sib twins are in good health.

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LETTER TO THE EDITOR

Infantile presentation of the mitochondrial A8344G mutation

E. Scalais[a], C. Nuttin[a], S. Seneca[b], J. Smet[c], B. De Paepe[c], J.-J. Martin[d], R. Stevens[c], F. Pierart[c], O. Battisti[c], W. Lissens[b], L. De Meirleir[b] and R. Van Coster[c]

[a]*Division of Paediatric Neurology, Department of Paediatrics, Centre Hospitalier de Luxembourg, Luxembourg;* [b]*Center for Medical Genetics and Division of Paediatric Neurology, Academic Hospital of the Vrije Universiteit Brussel, Brussels;* [c]*Division of Paediatric Neurology and Metabolism, Department of Paediatrics, Ghent University Hospital;* [d]*Institute Born-Bunge, University of Antwerp, Antwerp; and* [e]*CHC, Clinique Saint-Vincent, Rocourt, Belgium*

Correspondence: Dr Emmanuel Scalais, Centre Hospitalier de Luxembourg, Rue Barblé 4, L 1210 Luxembourg (tel.: +35 2 4411 31 81; fax: +35 2 4411 64 66; e-mail: scalais.emmanuel@chl.lu).

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Sir,

Most patients carrying the A8344G mutation develop the MERRF phenotype characterized by myoclonic epilepsy, ataxia and myopathy and by the presence of ragged-red fibres (RRF) on histochemical examination in skeletal muscle. Patients with onset of symptoms before the age of 18 months are rare. Here, we report a patient with clinical signs starting in the first months of life and initially not suggestive for an underlying mitochondrial defect.

Case report

The proposita was the first child of non-consanguineous parents (Fig. 1g). At the age of 2 months, she presented with episodes of abnormal breathing initially interpreted as wheezing. At 7 months, failure to thrive and truncal hypotonia were noticed. Moreover systemic arterial hypertension (153/85 mmHg) was found. A left ventricular hypertrophy was observed on echocardiogram. At 9 months recurrent episodes of hyperventilation, sighing respiration and apnoea occurred. Clinical examination revealed a Babinski sign bilaterally. Lactate was increased in plasma (2.8 mM, normal < 2.2) and CSF (2.5 mM, normal < 2). Routine morphological and histochemical study of the skeletal muscle biopsy performed at 10 months was normal. RRF were not detected and the activities of the oxidative phosphorylation (OXPHOS) complexes were within the normal range. However, immunohistochemical staining showed a mosaic pattern when stained with specific antibodies against complex I subunits (Fig. 1a). In cultured skin fibroblasts, the catalytic activity of complex IV measured spectrophotometrically was decreased. Immunostaining of fibroblasts showed a mosaic pattern for both complex I and complex IV (Fig. 1c,d). In fibroblasts, subcomplexes of complex V were detected on BN-PAGE followed by activity staining (Fig. 1f). Cerebral MRI performed at 11 months revealed bilaterally necrotic lesions extending from the medulla oblongata to the mesencephalon prompting the diagnosis of Leigh syndrome (LS) supported also by the increased lactate concentrations in blood and CSF. The A8344G mutation was found in skeletal muscle (98% of mutant DNA). The girl died at 11 months of age due to respiratory failure. The mutation had been transmitted through two generations in the maternal line (Fig. 1g). The mother of the proband (50% of mutant DNA) has deafness and the maternal grandmother (50% of mutant DNA) diabetes type 2.

Discussion

In contrast to the large series of adult patients reported with the A8344G mutation only a few patients are on record with onset of symptoms before the age of 18 months (Table 1). The clinical presentation in these young patients is different from the common MERRF phenotype. The eponym 'MERRF' cannot not be used for the early onset disease because clinically these infants have neither myoclonic epilepsy nor RRF in skeletal muscle. Most of the reported patients with early presentation have developmental delay, hypotonia, failure to thrive or respiratory difficulties (Table 1). The clinical signs and the predominant involvement of the basal ganglia and brainstem are suggestive of LS instead.

Most patients with a pathogenic point mutation in the mtDNA, in general, do not become symptomatic before childhood or adulthood. The few with early onset of symptoms usually have a large fraction of mutant DNA (>90–95%), as was found in our proband (98% of mutant DNA).

The findings in this patient clearly underscore the interest of pursuing additional biochemical and molecular studies in young patients with possible encephalopathy when routine morphological and histochemical investigations are non-contributory. In particular, immunological staining techniques using specific antibodies against subunits of the OXPHOS complexes may be most informative [1]. When a mosaic pattern of staining for either complex I or complex IV is found a mtDNA defect should be suspected. Complex I and complex IV have indeed the largest number of mitochondrially encoded subunits. Any decrease of intramitochondrial protein synthesis will affect preferentially complex I and complex IV. The mosaic pattern of staining is the result of different degrees of heteroplasmy and of the threshold phenomenon. The detection of subcomplexes of complex V in a Blue Native PAGE gel may also point to a mtDNA defect. Complex V has only the subunits 6 and 8 that are mitochondrially encoded. They link the intramembranous segment to the globular segment of complex V. Decreased intramitochondrial translation causes more globular segment to become dissociated from the intramembranous segment (Fig. 1f). The diagnostic strategy used here may be applied successfully in other patients with atypical clinical findings.

Reference

1. De Paepe B, Smet J, Leroy JG, *et al.* Diagnostic value of immunostaining in cultured skin fibroblasts from patients with oxidative phosphorylation defects. *Pediatric Research* 2006; **59:** 1–5.