CASE REPORT

Classical MERRF phenotype associated with mitochondrial tRNA^{Leu} (m.3243A>G) mutation

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Abstract Myoclonic epilepsy with ragged red fibres (MERRF) and mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) are established phenotypes of mitochondrial encephalopathies. Nearly all patients affected by MERRF harbour a mutation in the mitochondrial tRNA^{Lys} gene. We report a 13-year-old patient who presented with the classical phenotype of MERRF but was found with the typical mutation of MELAS. The patient presented with myoclonic epilepsy beginning at 10 years of age, a muscle biopsy with ragged red fibres and some COX negative fibres and progressive bilateral MRI hyperintensitivities in the basal ganglia constituting MERRF syndrome but lacked clinical characteristics of MELAS. In particular, stroke-like episodes or lactic acidosis were not present. None of the tRNA mutations described in MERRF were found. However, further analyses showed the tRNA^{Leu} mutation m.3243A>G usually found in MELAS to be responsible for the condition in this

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Friedrich-Alexander-University of Erlangen-Nuremberg, Institute of Neuropathology, Erlangen, Bavaria, Germany patient. This report highlights the broad phenotypic variability of mitochondrial encephalopathies with juvenile onset. It shows that m.3243A>G mutations can cause classical MERRF and emphasises the significance of comprehensive genetic studies if mitochondrial disease is suspected clinically.

Keywords Mitochondriopathy · MELAS · MERRF · Epilepsy · Paediatrics

Introduction

Myoclonic epilepsy with ragged red fibres (MERRF) and mitochondrial encephalopathy, lactic acidosis and strokelike episodes (MELAS) are established phenotypes of mitochondrial encephalopathies. MERRF is a rare mitochondrial syndrome with juvenile onset characterised by progressive myoclonus epilepsy and the histopathological finding of ragged red fibres in skeletal muscle tissue. The vast majority of MERRF patients have a mutation in mitochondrial gene MTTK encoding tRNA^{Lys}. The remaining patients harbour a choice of other mitochondrial tRNA mutations. Single cases of other non-tRNA mitochondrial mutations or nuclear DNA defects and MERRF phenotype have been described [10]. MELAS, on the other hand, in the broad majority of cases is caused by the mitochondrial DNA mutation tRNA^{Leu}. Additionally, a number of other mitochondrial DNA defects are known to cause typical MELAS phenotype. Clinically, MELAS is characterised by stroke-like episodes and lactic acidosis as well as progressive encephalopathy (reduced consciousness, seizures, cognitive dysfunction) and additional symptoms like recurrent headache and vomiting (Table 1). Overlap syndromes of those syndromes have been described [7].

| MELAS |
|--|
| 'Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes' |
| m.3243A>G |
| Stroke-like episodes |
| Encephalopathy |
| Lactate acidosis |
| Recurrent nausea/headache |
| |

 Table 1
 Comparison of the major clinical and genetic characteristics

 of MELAS and MERRF syndrome

Case report

We report a patient who, after normal development until the age of 10 years, presented with proximal weakness and elevated serum creatine kinase levels. Diagnostic work-up including molecular genetic testing for dystrophinopathies did not reveal specific signs of neuromuscular or metabolic diseases. Yet, since laboratory anomalies and clinical manifestations were only mild, the family declined further investigations. Eight months later, the patient presented again with a first generalised tonic-clonic seizure. Interictal EEG showed primary generalised spike waves, while further neurophysiologic examinations (visual evoked potentials, auditory evoked potentials) were normal. Serum lactate and ammoniac levels measured regularly at routine consultations were within normal range, as were audiometric and ophthalmologic examinations. An initial cranial MRI showed no intracerebral abnormalities. During the following months, frequency of generalised tonic-clonic seizures dramatically increased. Seizure control was unsatisfactory indicating development of pharmaco-refractory epilepsy. Treatment with several antiepileptic drugs such as lamotrigine, levetiracetam, ethosuximide and topiramate which were used as mono- and polytherapy showed only temporary or incomplete improvements in seizure frequency. Finally, 12 months after manifestation of the primary generalised epilepsy, myoclonic episodes developed. These episodes were accentuated during morning hours and occurred daily.

Considering a possible interrelation between progressive myoclonic epilepsy and elevated creatine kinase levels, muscle biopsy taken from *m. vastus lateralis* was performed showing multiple ragged red fibres. Together with the detection of several muscle fibres with negative staining for cytochrom oxidase (COX) (Fig. 1a–b), mitochondrial disease was suggested. Therefore, biochemical analysis of mitochondrial respiratory chain enzymes I–IV was performed in muscle tissue. However, enzyme activities were found within the normal range (related to the activity of citrate synthase, a mitochondrial matrix enzyme). As ragged red fibres were present, further investigations were focused on molecular genetic analyses of mitochondrial DNA which did not show any of the typical mutations usually found in MERRF syndrome that was suggested clinically. Interestingly, comprehensive analysis revealed a tRNA^{Leu} mutation (m.3243A>G) which constitutes a well-known mutation in patients showing MELAS phenotype (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes). Degree of heteroplasmy was found to be 5–10% in peripheral blood and, of note, 60% in muscle tissue. No other mitochondrial tRNA mutation could be found. Further molecular testing was rejected by the parents. The patient's mother as well as the younger sister were asymptomatic without any signs of muscle weakness. The maternal creatine kinase level was within normal range.

Cranial MRI was repeated 2.5 years after initial brain imaging showing bilateral hyperintensities in T1-weighted MRI in the basal ganglia particularly putamen, caudate nucleus and thalamus with slight signs of calcification (Fig. 2a–d).

In addition to anticonvulsive therapy, supportive medication (carnitine, coenzyme Q) was recommended according to international guidelines. During an interval of 6 months, there was no obvious deterioration of muscle weakness, cognitive functions and seizure frequency; however, myoclonic and generalised tonic–clonic seizures still were present resistant to lamotrigine and topiramate.

Discussion

Present observation reinforces the clinical and genetic heterogeneity of mitochondrial overlap syndromes. Clinically, our patient fulfilled the major criteria of MERRF syndrome including histopathological, neurophysiological and neuroradiological findings. Signs of MELAS phenotype were not present either clinically or by cranial MRI. Of note, although seizures are observed in both conditions as a sign of encephalopathy [7], our patient did not show signs of the pathognomonic stroke-like episodes. While no specific brain imaging features could be defined for MERRF, the basal ganglia lesions in our patient fit to the changes regularly described for this condition: cerebellar or brain stem changes which have been reported as well were not present in our patient [6]. This goes in line with the lack of ataxic or cerebellar symptoms in our patient, although a clear correlation of radiological and clinical expression cannot be assumed. Diagnosis was impeded by the fact that neither lactic acidosis nor any other signs of a defect of energy metabolism were present. Therefore, only the findings of the muscle biopsy with proof of ragged red fibres gave way to further molecular diagnostics. Here, COX-negative fibres are rather uncommon in MELAS mutations [3].



The vast majority of patients with MERRF syndrome (80%) harbour the mitochondrial tRNA mutation m.8344A>G. Further, 10% of the patients fall to the mutations m.8356T>C, m.8363G>A, m.8361G>A and, respectively, m.611G>A and

m.15967G>A [1]. A single case of MERRF-like syndrome associated with a nuclear missense mutation in polymerase gamma gene (*POLG*), a polymerase involved in replication of the mitochondrial genome, has been reported [10].





In very rare cases of MELAS mutations, m.3243A>G MERRF-like phenotypes have been described. These pedigrees exhibited markedly variable phenotypic expressions and only two authors explicitly mention paediatric manifestations [2, 4, 5].

Family members of our patient are asymptomatic but, unfortunately, declined molecular genetic diagnostics. Therefore, carrier status cannot be ruled out. Differences in manifestation within one family and the peculiar phenotype of our patient may possibly be due to differences in heteroplasmy, mutational background of mitochondrial and nuclear DNA and epigenetic or environmental influences.

Although curative treatment is not available, exact diagnosis of a mitochondrial syndrome enables the attending physician to employ evidence-based treatment measures and to avoid treatment- and disease-associated complications. This includes consequent prevention of any kind of hypoxic or metabolic distress like seizures or fever episodes. Of special significance avoiding of medications which impair the respiratory chain function (e.g. valproic acid, phenobarbital, tetracyclines) is imperative. Furthermore, a variety of supplementary co-factors could be applied such as coenzyme Q10, carnitine or riboflavin according to international guidelines [8]. To prevent and treat stroke-like episodes in MELAS syndrome, arginine treatment has been suggested [9]. But still, efficacy of these therapeutic options has not been proven by controlled clinical trials.

This report highlights the broad phenotypic variability of mitochondrial encephalopathies with juvenile onset. The patient described here adds to the rare cases of mitochondrial m.3243A>G mutations associated with clinical MERRF syndrome and emphasises the importance of comprehensive genetic studies if mitochondrial disease is suspected.

Conflict of interest None of the authors has received financial support. There is no conflict of interest.

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