

Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome with hypothyroidism and focal segmental glomerulosclerosis in a paediatric patient

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Abstract Herein, we report on a paediatric patient with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) who was hospitalized for acute on chronic renal insufficiency, seizures and deterioration of the level of consciousness. She also had hypertension, hypothyroidism and nephrotic range proteinuria. Kidney biopsy revealed many sclerotic glomeruli and focal segmental glomerulosclerosis (FSGS). Glomerulopathy is rare in patients with MELAS, and FSGS has been reported only in a few patients. The histopathological features of the renal biopsy suggested that the aetiology of the FSGS may have been secondary to chronic renal injury rather than from a primary immunologic cause. Moreover, our case is unique in that, the coexistence of MELAS, hypothalamic hypothyroidism and FSGS has not been reported in the past. The purpose of this report is to increase the awareness of health-care professionals, especially in the fields of paediatrics, neurology, endocrinology and nephrology, regarding the manifestations and complications of MELAS.

Keywords FSGS · Hypothyroidism · MELAS · Nephrotic syndrome · Paediatrics

Introduction

Mitochondrial encephalopathy is a heterogeneous disorder with variable clinical presentations. Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is one of the most commonly described syndrome of mitochondrial encephalopathy with multi-system involvement. We describe a paediatric MELAS patient with the rare association of hypothyroidism and nephrotic syndrome secondary to focal segmental glomerulosclerosis (FSGS).

Case report

A 13-year-old Asian girl was transferred to our paediatric intensive care unit from a local hospital, where she had been admitted initially with fever, repeated vomiting, dehydration and acute renal insufficiency. Her serum creatinine upon admission was 1.9 mg/dl. She was initially diagnosed as having urosepsis and pneumonia, which was treated with a course of intravenously injected ceftriaxone and orally administered azithromycin. During hospitalization, she developed diarrhoea and progressive renal insufficiency,

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with a peak serum creatinine level of 5.1 mg/dl. She then developed progressive respiratory distress and was subsequently transferred to our intensive care unit due to a rapid deterioration in her level of consciousness.

She was the first child of the family, born to a 27-year-old Chinese woman with sensorineural hearing loss at 32 weeks by vaginal delivery. The birth weight was 2 lb and 9 oz, and no cause for the intrauterine growth retardation was obvious except for possibly maternal diabetes. She required oxygen for a short period of time but did not require any artificial ventilation. She was discharged home at the age of 1 month without any apparent respiratory or neurological injury secondary to prematurity. She had an uneventful childhood and was developmentally normal. She achieved her developmental milestones appropriately and attended school with reportedly good grades. She first came under medical attention at the age of 8 years for hypothyroidism, with low blood levels of thyroid-stimulating hormone (TSH) and free T4. She then had an episode of suspected seizure-like activity, with shaking of both hands without loss of consciousness at 9 years of age. Although the electroencephalogram findings at that time were inconclusive, she was started and maintained on phenobarbital. Initially, the seizures were relatively well controlled, with only a few brief breakthrough seizures. She then progressed to develop focal status epilepticus along with stroke and lactic acidosis (lactate level was 8 mEq/l; with normal range between 0.6 mEq/l and 2 mEq/l) at the age of 11 years. The seizure involved the right side of her body, with jerking movements of both the upper and lower limbs, with no loss of consciousness. Her seizure was aborted after treatment with phenobarbital and phenytoin in the hospital. During that hospitalization, she was noticed to have a decrease in her hearing acuity, residual right hemiparesis and progressive inability to walk. A neurological examination demonstrated mild psychomotor retardation and expressive dysfluency. There was generalized hypertonia and bilateral intention tremor. Her sensory functions were intact. Initial laboratory work-up for stroke revealed normal coagulation profile, angiotensin converting enzyme, anti-nuclear antibody

and anti-cardiolipin antibody. The results of a cerebral spinal fluid study were normal for cell counts and biochemistry and negative for culture. MRI of the brain showed an increase in signal intensity on T1-weighted scans in both of the basal ganglia, the putamen, part of the caudate nucleus and the globus pallidus (Fig. 1). There were similar hyperintensities of the peripheral gray and white matter in the inferior cerebellar hemispheres and inferior occipital cortices. There was also mild cerebellar atrophy and bilateral occipital encephalomalacia. The pituitary gland appeared to be normal. Mitochondrial DNA study done at the University of California San Diego by restriction fragment length polymorphism (RFLP) and reverse transcriptase-polymerase chain reaction (RT-PCR) showed the common MELAS mutation, base pair 3243 A → G in the mitochondrial DNA, at a level of 50% heteroplasmy. During her stay in hospital at that time, she later developed hypertension, microscopic haematuria and nephrotic range proteinuria (urine protein-to-creatinine ratio was 22) without peripheral edema. Her serum albumin and cholesterol levels were 1.6 mg/dl and 217 mg/dl, respectively. Renal function was normal at that time, with a serum creatinine

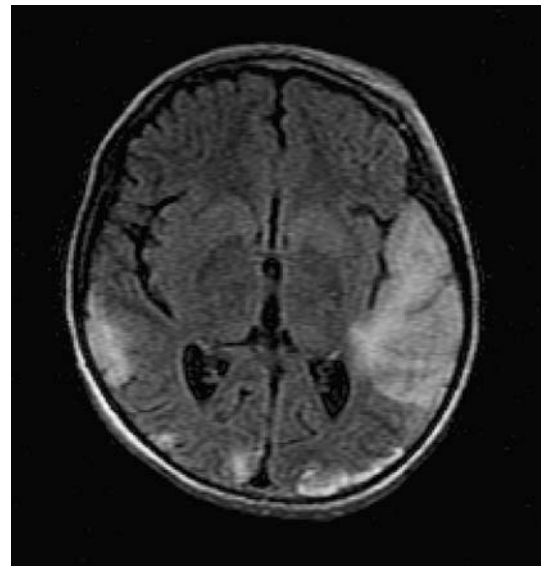


Fig. 1 Brain MRI of the patient, which shows bilateral basal ganglial calcifications and ischaemic changes in both temporal and parietal lobes

concentration of 0.4 mg/dl. Levels of liver transaminases were also within normal limits. Complement 3 and 4 levels were 159 mg/dl and 41 mg/dl. The anti-nuclear antibody titre, hepatitis B surface antigen and anti-streptolysin O titre were negative. Since all the work-up for nephrotic range proteinuria did not reveal any known cause of chronic glomerulopathy, the nephrotic range proteinuria was felt likely to be related to MELAS syndrome, and no renal biopsy was performed at that time. Subsequent to that, she had multiple hospital admissions with seizures and strokes. She also had progressive regression of her developmental milestones and required a G-tube for feeding. Her family history was significant for progressive hearing loss of unknown aetiology and insulin-dependent diabetes mellitus in her mother, who eventually died of colon cancer. The patient had a 2-year-old younger sibling who appeared to be healthy. Otherwise, there are no other family members known to have any endocrine or neurological disease. Her medications included co-enzyme Q, enalapril, phenobarbital, L-thyroxine, L-carnitine, vitamin E and aspirin.

Upon the current admission, she was afebrile, with an oral temperature of 36°C. Other vital signs included: a temperature of 36°C, weight of 22 kg (below the 3rd percentile), height of 119 cm (below the 3rd percentile), blood pressure of 132/88 mmHg, oxygen saturation of 98% in room air, heart rate of 150 beats per min and respiration rate of 31 per min. She was not in acute distress when first admitted to the intensive care unit. She had peripheral pitting oedema of all four limbs, but, otherwise, the results of the examinations of her ears, nose, throat, chest, cardiovascular region and abdomen were within normal limits. Neurological examination showed generalized hyperreflexia, presence of ankle clonus and positive Babinski signs bilaterally. Her initial arterial blood gas was as follows: pH 7.45, PCO₂ 39 mmHg, PO₂ 75 mmHg and bicarbonate of 27 mmol/l. Her other laboratory values are listed here: haemoglobin 10.8 g/dl, white blood cell count $10.1 \times 10^9/l$, platelet count $452 \times 10^9/l$, serum sodium 150 mEq/l, potassium 4.7 mEq/l, blood urea nitrogen (BUN) 48 mg/dl. Her serum creatinine progressively increased from 1.9 mg/dl

to 5.1 mg/dl, her serum total calcium was 6.8 mg/dl and phosphorus 6.1 mg/dl. Her TSH level was low at less than 0.01 μ IU/ml (normal range 0.35–5.5 μ IU/ml), and free thyroxine concentration was normal at 1.46 ng/dl (normal range 0.8–1.8 ng/dl). The electroencephalogram showed multi-focal and generalized spikes and waves that were consistent with diffuse epileptogenic brain abnormality. A chest X-ray showed left-sided pleural effusion. The echocardiogram showed mild left ventricular hypertrophy with normal function as well as mild mitral and tricuspid regurgitation. A renal biopsy was done during the hospitalization, and the histology was compatible with focal segmental glomerulosclerosis (Fig. 2). It showed advanced glomerular obsolescence of more than 60% of the glomeruli. Besides mesangial matrix expansion, there was marked glomerular basement membrane (GBM) wrinkling, tuft collapse and adhesion. Hyalinosis was identified in both glomeruli and arterioles. The tubules demonstrated moderate-to-severe atrophy, with evidence of resolving tubular necrosis. There was also chronic vasculopathy consistent with hypertensive nephropathy. Immunofluorescence staining showed moderate-to-heavy focal segmental or focal global staining for IgM and C3 in the sclerotic areas. No definite immune complexes or fibrillary type deposits were apparent under electron microscopy (Fig. 3). The mitochondria in the tubular cells were mildly swollen but did not display abnormal deposits or crystals, and the

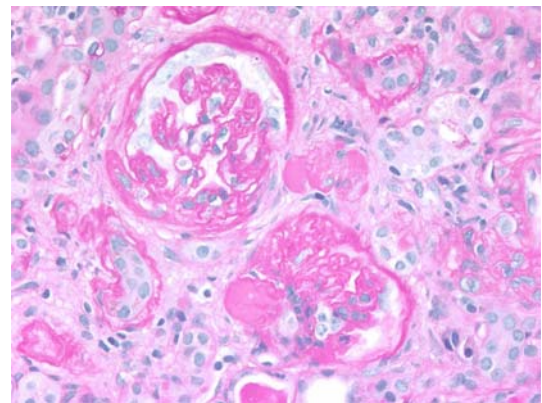


Fig. 2 Significant sclerosis and GBM wrinkling with moderate-to-severe tuft collapse and adhesions. Haematoxylin and eosin, $\times 200$

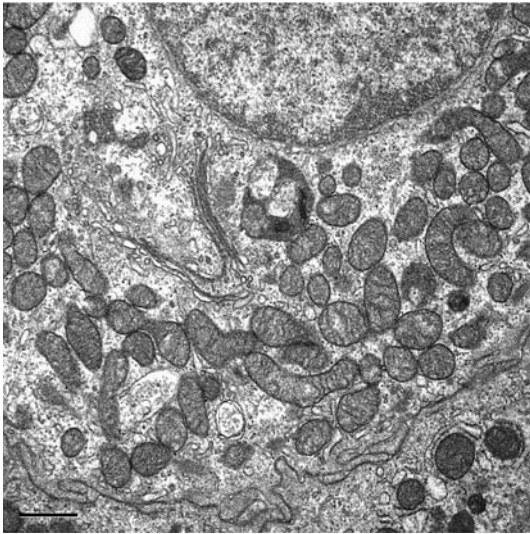


Fig. 3 Mildly swollen mitochondria in the tubular cells, and the internal cisternae are uniform and appear normal. (Electron microscopy, $\times 11,000$)

internal cisternae were uniform but appeared relatively normal.

Hospital course

The patient improved slowly in the hospital and was discharged home after 20 days. She was then admitted again 4 days later with acute worsening of consciousness, disseminated intravascular coagulopathy, hyperkalaemia with serum potassium at 7.6 mEq/l, elevated creatine kinase at 579 μ g/l, serum creatinine at 5.4 mg/dl, leucocytosis and severe pulmonary oedema. She rapidly went into multi-organ failure and died 1 week later.

Discussions

Since mitochondria are the power-houses of the cells, their proper function is vital to energy metabolism [1, 2]. Recent studies showed that mitochondria are also responsible for other tissue-specific roles in metabolism other than just merely providing ATP [3, 4]. The most common form of syndromic mitochondrial encephalomyopathy is the MELAS syndrome, characterized by stroke-like episodes and lactic acidosis. Patients

usually have migraine and repeated vomiting. Additional features may include deafness, diabetes, seizures, dementia, and cardiomyopathy [5, 6]. The stroke-like episodes are assumed to be due to metabolic perturbations rather than of vascular origin [7]; imaging such as CT and MRI typically show white matter and cortical lesions in the parieto-occipital regions. Unilateral or bilateral basal ganglia calcifications are also common [8].

In this report, we describe a MELAS patient with an adenine-to-guanine (A-to-G) mutation of the leucine transfer RNA gene [tRNA^{Leu} (UUR)] at position 3243, who first presented as a case of hypothalamic hypothyroidism before the onset of encephalopathy. Her clinical course was later complicated by renal dysfunction and glomerulonephropathy. The 3243 mutation was originally described only in patients with MELAS [9]; up to 84% of patients with MELAS have this mutation [10]. However, recent reports have shown that this mutation can also be found in patients with non-MELAS phenotypes. Mitochondrial diseases may present at any stage of life, and the number of organs involved and their severity usually increases with age. Even within the same family with the same mutation, the clinical presentation may be very diverse and heterogeneous [11]. In the family of our patient, her mother had severe hearing loss, diabetes mellitus and colon carcinoma without the encephalopathy, while her sister and maternal uncle were clinically unaffected. Sensorineural hearing loss ranging from mild to severe has been described in patients with MELAS [12], and successful restoration of auditory function by cochlear transplantation has been reported [13]. Endocrine problems other than diabetes mellitus are often found; patients may exhibit features of hypoparathyroidism and growth hormone deficiency. Thyroid involvement is distinctly rare, and hyperthyroidism and hypothyroidism have only been described in single case reports [14, 15]. Kidney involvement in mitochondrial encephalopathy is infrequent. The most common reported kidney diseases associated with MELAS are Fanconi syndrome [16,17] and nephrotic range proteinuria [18,19]. Although chronic renal insufficiency in MELAS syndrome has been described and has been attributed to

either chronic tubulo-interstitial nephritis or FSGS, glomerular disease associated with MELAS is rare [20] and has been described in only one child before [17].

The pathogenic mechanism of the A-to-G mutation at the 3243 position is still controversial; evidence supports the notion that the mutation leads to an alteration in a crucial step during the translation process of the mitochondrial ribosomes and a reduction in the incorporation of leucine into the mitochondrial oxidative phosphorylation system, thus affecting the mitochondrial structure and function [16]. As glomerular injury may potentially be secondary to mitochondrial malfunction and abnormal ATP supply, it is very suggestive that this renal histological change may be related to the mitochondrial mutation. However, the exact mechanism of this mutation leading to FSGS is still unknown. Accumulation of dysmorphic mitochondria exclusively in podocytes was observed in some patients. Any impairment of the energy supply may lead to podocyte dysfunction and development of FSGS [17].

Interestingly, FSGS has also been observed in non-MELAS diabetic patients that had the A 3243 G mutation [21, 22]. As glomerular injury may potentially be secondary to mitochondrial malfunction and abnormal ATP supply, it is very suggestive that this renal histological change may be related to the mitochondrial mutation. Patients with MELAS and mitochondrial malfunction are theoretically more susceptible to ischaemic damage. As vascular injury secondary to systemic hypertension may result in ischaemia to the parenchyma, the hypertension in our patient might have contributed significantly to the progressive deterioration of kidney function, since haemodynamic alterations in the renal parenchyma from hypertension can lead to FSGS [23].

Primary FSGS usually presents as overt nephrotic syndrome. Renal biopsy often shows generalized visceral epithelial cell/podocyte injury and all glomeruli express and exhibit similar epithelial cell damage. On the other hand, secondary forms of FSGS usually present with slowly progressive proteinuria, which may eventually progress to nephrotic range proteinuria and even the nephrotic syndrome. Hence, it is more

likely that our patient had secondary FSGS, and, in view of the lack of laboratory findings suggestive of any known cause of secondary FSGS except hypertension, the FSGS in our patient was very likely due to her MELAS.

Conclusions

We report on the first paediatric case of MELAS syndrome with the coexistence of FSGS and hypothalamic hypothyroidism. Although renal involvement in MELAS is rare, it is an important manifestation, since it could be a significant cause of morbidity. Although the pathogenesis of glomerulonephropathy associated with MELAS is still obscure, mutations leading to mitochondrial disease should be included in the aetiologies of secondary FSGS.

References

1. Srere PA (1987) Complexes of sequential metabolic enzymes. *Annu Rev Biochem* 56:89–124
2. Wallace DC (1999) Mitochondrial diseases in man and mouse. *Science* 283:1482–1488
3. Naviaux RK, McGowan KA (2000) Organismal effects of mitochondrial dysfunction. *Hum Reprod* 15 [Suppl 2]:44–56
4. Schatz G (1995) Mitochondria: beyond oxidative phosphorylation. *Biochim Biophys Acta* 1271:123–126
5. McFarland R, Taylor RW, Turnbull DM (2002) The neurology of mitochondrial DNA disease. *Lancet Neurol* 1:343–351
6. Tay SK, Shanske S, Crowe C et al (2005) Clinical and genetic features in two families with MELAS and the T3271C mutation in mitochondrial DNA. *J Child Neurol* 20:142–146
7. Leonard JV, Schapira AH (2000) Mitochondrial respiratory chain disorders II* neurodegenerative disorders and nuclear gene defects. *Lancet* 355:389–394
8. Schapira AH, Cock HR (1999) Mitochondrial myopathies and encephalomyopathies. *Eur J Clin Invest* 29:886–898
9. Tanaka M, Ino H, Ohno K et al (1991) Mitochondrial DNA mutations in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). *Biochem Biophys Res Commun* 174:861–868
10. Goto Y, Nonaka I, Horai S (1990) A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 348:651–653

11. Hammans SR, Sweeney MG, Brockington M et al (1991) Mitochondrial encephalopathies: molecular genetic diagnosis from blood samples. *Lancet* 337:1311–1313
12. Oshima T, Ueda N, Ikeda K (1999) Hearing loss with a mitochondrial gene mutation is highly prevalent in Japan. *Laryngoscope* 109(2 Pt 1):334–338
13. Rosenthal EL, Kileny PR, Boerst A (1999) Successful cochlear implantation in a patient with MELAS syndrome. *Am J Otol* 20:187–190
14. Yang CY, Lam HC, Lee HC et al (1995) MELAS syndrome associated with diabetes mellitus and hyperthyroidism: a case report from Taiwan. *Clin Endocrinol (Oxf)* 43:235–239
15. Balestri P, Grosso S (2000) Endocrine disorders in two sisters affected by MELAS syndrome. *J Child Neurol* 15:755–758
16. Campos Y, Garcia-Silva T, Barrionuevo CR et al (1995) Mitochondrial DNA deletion in a patient with mitochondrial myopathy, lactic acidosis, and stroke-like episodes (MELAS) and Fanconi's syndrome. *Pediatr Neurol* 13:69–72
17. Mochizuki H, Joh K, Kawame H et al (1996) Mitochondrial encephalomyopathies preceded by de-Toni-Debre-Fanconi syndrome or focal segmental glomerulosclerosis. *Clin Nephrol* 46:347–352
18. Ban S, Mori N, Saito K et al (1992) An autopsy case of mitochondrial encephalomyopathy (MELAS) with special reference to extra-neuromuscular abnormalities. *Acta Pathol Jpn* 42:818–825
19. Yoneda M, Tanaka M, Nishikimi M et al (1989) Pleiotropic molecular defects in energy-transducing complexes in mitochondrial encephalomyopathy (MELAS). *J Neurol Sci* 92:143–158
20. Yanagihara C, Oyama A, Tanaka M et al (2001) An autopsy case of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes syndrome with chronic renal failure. *Intern Med* 40:662–665
21. Nakamura S, Yoshinari M, Doi Y et al (1999) Renal complications in patients with diabetes mellitus associated with an A to G mutation of mitochondrial DNA at the 3243 position of leucine tRNA. *Diabetes Res Clin Pract* 44:183–189
22. Hotta O, Inoue S, Miyabayashi S et al (2001) Clinical and pathologic features of focal segmental glomerulosclerosis with mitochondrial tRNA^{Leu} (UUR) gene mutation. *Kidney Int* 59:1236–1243
23. Petermann AT, Pippin J, Durvasula R et al (2005) Mechanical stretch induces podocyte hypertrophy in vitro. *Kidney Int* 67:157–166