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Mitochondrial DNA 3252A>G mutation presenting as MERRF/MELAS overlapping syndrome: A case report

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Abstract

We report a case of 25 years old male presented with a complex phenotype of myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) harbouring m.3252A>G mutation in the mitochondrially encoded tRNA leucine 1 (UUA/G) [MT-TL1] gene encoding the mitochondrial transfer ribonucleic acid (tRNA) for leucine. He presented with frequent myoclonus seizure, stroke-like episodes, elevated blood lactate with muscle biopsy showed numerous ragged-red fibers suggestive of a mitochondrial disorder. Whole mitochondrial genome sequencing revealed no mutations other than the A-to-G transition at nucleotide position 3252. This case report is the first to describe the m.3252A>G mutation in association with the MERRF/MELAS overlap syndrome.

Keywords: Myoclonic epilepsy with ragged red fibers (MERRF), Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), point mutation m.3252A>G, mitochondrial DNA

INTRODUCTION

The mitochondrial deoxyribonucleic acid (mtDNA) m.3252A>G mutation is one of the uncommon pathogenic mtDNA variants that has been described in MELAS.[1] It was first identified in a patient with mitochondrial encephalomyopathy, pigmentary retinopathy, dementia, hypoparathyroidism, and diabetes mellitus in 1993, which found heteroplasmy in blood (30%) and muscle (76%) for a mutation at nucleotide 3252 in the MTTL1 gene[1]. Its prevalence in general population is not known. Mitochondrial related disease is highly complex and variable, ranging from asymptomatic to lethal phenotypes, depending on the level of and distributions of m3252A>G heteroplasmy across the cells and tissue. To date, there is still no effective treatments for mitochondrial DNA-related diseases; only supportive interventions are available. Therefore, understanding the genetics, molecular mechanisms and phenotypes of the m.3252A>G mutation is important for early clinical recognition, genetic counselling, and enabling the prevention of m.3252A>G inheritance. We describe a patient showed overlap features of both MERRF and MELAS syndromes with m.3252 A>G mutation. Point mutation of m.3252A>G has not been reported in patient with MERRF/MELAS overlap syndrome previously.

CASE REPORT

A 25-year-old Chinese gentleman born from a non-consanguineous family, presented with psychomotor regression at 14 years old. He presented to us at the age of 17 years with multiple episodes of myoclonus seizure accompanied by impairment of consciousness. He was intubated twice for status epilepticus. He was initially treated for myoclonus epilepsy and was given sodium valproate and levetiracetam. However, the seizure was not well controlled. Subsequently, he had 2 episodes of transient hemiparesis which he did not seek any medical advises and both episodes resolved spontaneously within a few days. His elder sister was born premature with childhood developmental delay and epilepsy. No other significant family history.

Neurological examinations revealed bilateral ptosis with no external ophthalmoplegia. His deep tendon reflexes were exaggerated and muscle

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strength was reduced especially over the proximal muscle. The myoclonus could be induced by sudden buckling of limbs. Cerebellar sign was negative.

Laboratory examination revealed increased level of resting serum lactate acid which ranged from 2 mmol/L to 21mmol/L (normal <2.5mmol/L). Fundus photography examination revealed no papillary edema or optic nerve atrophy. His nerve conduction study was normal and electromyography revealed myopathic pattern in bilateral upper limbs and lower limbs. His creatinine kinase was slightly elevated (276 U/L). His electroencephalography showed diffuse theta slowing. Brain magnetic resonance imaging (MRI) showed generalized cerebral atrophy with proportionate bilateral hippocampus and amygdala volume loss. (Figure 1) Lumbar puncture was done with normal cerebrospinal fluid (CSF) studies include negative autoimmune encephalitis panel. Plasma amino acid showed elevation of alanine may indicate chronic lactic acidosis.

Muscle biopsy of left deltoid muscle was performed which showed variation in fiber size, marked atrophied and necrotic fibers, increased ragged red fibres (RRFs) with positive for succinate dehydrogenase-reactive stained vessels (SSVs) and cytochrome c oxidase (COX) negative fibers. (Figure 2) These results are suggestive of mitochondrial disease. Further genetic study detected the m.3252A>G mutation with 30 percent heteroplasmy in the blood. This variant was not found in his parents' blood sample.

His was diagnosed to have MERRF/MELAS overlap syndrome with m3252A>G point mutation. His echocardiography was normal. He was started on Coenzyme Q10 and riboflavin. His seizure achieved good control with levetiracetam, topiramate and clonazepam.

DISCUSSION

Mitochondria are indispensable organelles that generate around 90% of cellular energy via oxidative phosphorylation (OXPHOS).[2] The mitochondrial genome is a circular double stranded DNA molecule with 37 genes: 13 genes encode a component of electron transport chain, 22 encode mitochondrial t-RNAs, and 2 encode mitochondrial ribosomal RNAs. Electron transport chain complexes are composed of many subunits. Mitochondrial DNA (mtDNA) encodes only part of the electron transport chain. The remaining subunits are encoded by nuclear genes. Hence, mitochondria are unique as they contain their own DNA. It has a central role in the energy production for the cell. Hence, any cell that depends on oxidative phosphorylation for energy can be affected by mitochondrial disease.[3] The organ systems with high energy requirement such as brain, heart, and muscle are more often and more severely affected.

MERRF and MELAS are well established phenotypes of mitochondrial encephalomyopathy. MELAS is mainly characterized by stroke-like episodes, episodic headache and vomiting, lactic acidosis, and skeletal myopathy; it is most commonly caused by the A3243G mutation in the mitochondrial tRNA Leu (UUR) gene.[4] On the other hand, MERRF is characterized by myoclonic seizures, cerebellar ataxia, myopathy, and ragged-red fibers on muscle biopsy. A8344G mutation in the tRNA lysine gene happen in approximately 80% of the cases.[5]

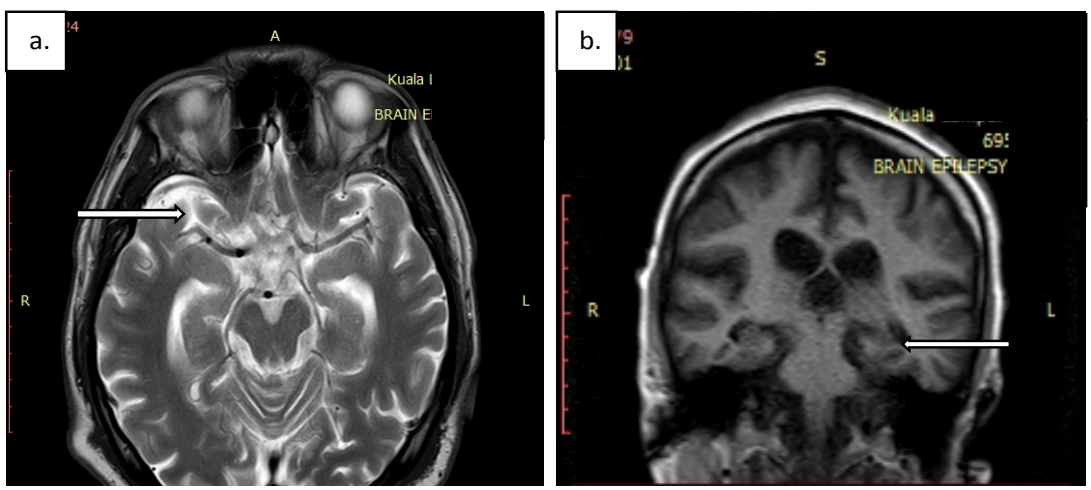

Figure 1. a, MRI in axial T2-weighted image. b, MRI in coronal T1-weighted image. Both a and b showed generalized cerebral atrophy with proportional hippocampus and amygdala volume reduction (arrow).

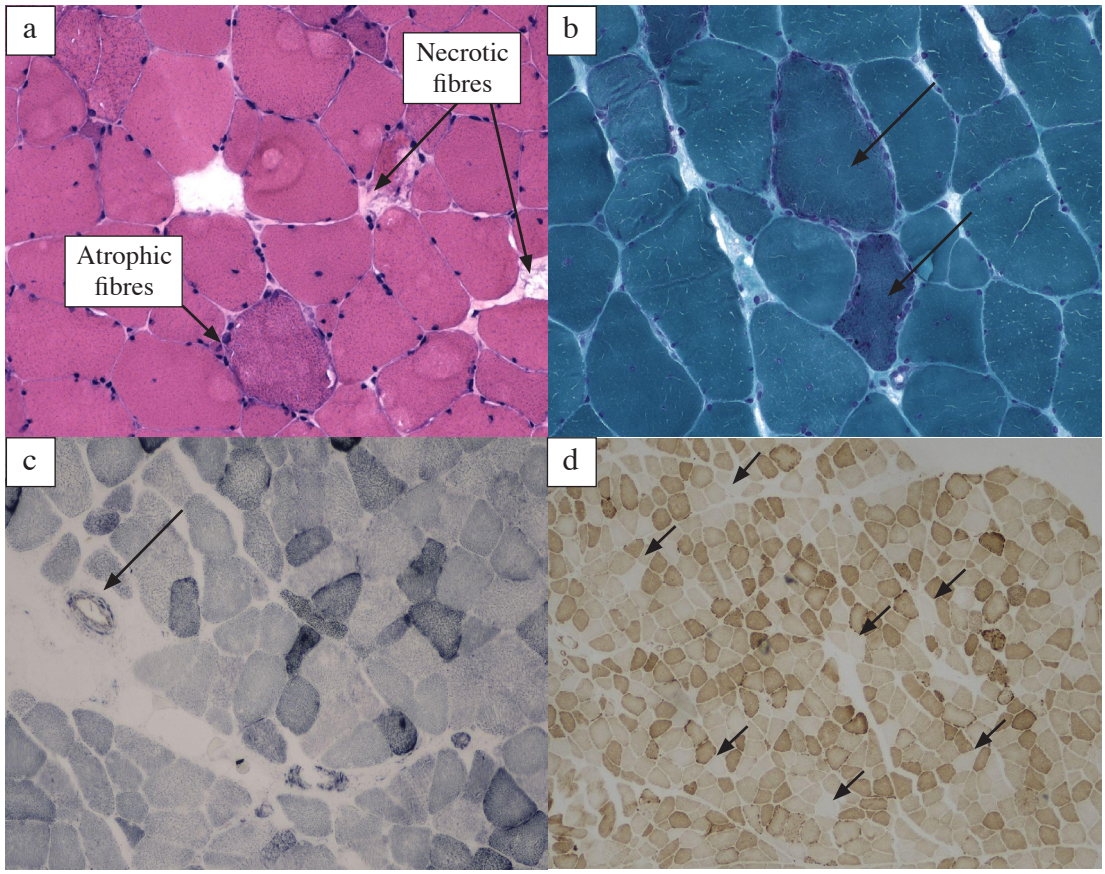

Figure 2. Histopathology observed in left deltoid muscle biopsies in the proband. a, b, c and d are pairs of adjacent sections stained as indicated. a, Hematoxylin and eosin (H&E) stain showed a marked variation in fibre size. b, Numerous scattered ragged red fibres (RRFs) were observed with Modified Gomori Trichrome (MGT) stain (arrowhead). c. Succinate dehydrogenase (SDH) stain showed succinate dehydrogenase-reactive blood vessels (SSVs) (arrowhead). d. Cytochrome c oxidase (COX) stain showed scattered COX negative fibres (arrowhead).

This patient's clinical manifestations of progressive cognitive decline, frequent myoclonus seizure, transient hemiparesis which suggest stroke-like episodes, myopathy together with elevated resting blood lactate acid, RRFs, SSVs and COX-deficient fibres in muscle biopsy, suggest the presence of a MERRF/MELAS overlap syndrome. He appeared to express some features of both MERRF and MELAS but did not fulfil the cardinal full spectrum of MELAS/ MERRF. Cortical atrophy is nonspecific finding seen in many mitochondrial diseases.[6] Typical MRI findings of ischemic lesions not conforming to a vascular territory was not seen in this case as it was not done during the stroke like episodes.

The MERRF/MELAS overlap syndrome is a rare occurrence and has been reported in several sporadic cases. The associated mtDNA point mutations that have been reported include m.8356T>C[7], m.3243A>G[8], m.13042G>A[9], m.7512T>C[10] and m.3291T>C[11] mutation. The mitochondrial mutation of 3252A>G is first described in a 1993 in a case of mitochondrial encephalomyopathy.[1] It comprises of 5 percent of cases in MELAS and it has not been reported in MERRF or MERRF/ MELAS syndrome. The full spectrum of phenotype and complexity of mitochondrial disease caused by m3252A>G mutation is probably far from complete understanding. His mother demonstrated negative mitochondrial gene sequencing from blood. Thus, it appears that this is a sporadic case. However, we are unable to completely rule out the possibility that she may also carries the same mitochondrial DNA variant because of variable heteroplasmy level in different tissues and so far we have not performed the genetic screening except on her blood.

Diagnosis of a mitochondrial disorder can be very challenging due to a wide spectrum of clinical manifestations. This is the first case report describe the MERRF/ MELAS overlapping syndrome phenotype in rare MT-TL1 m.3252A>G mutation, further expanding the clinical spectrum in association with m.3252A>G mutation. Future researches will be helpful in understanding the complexity of the disease.

DISCLOSURE

Ethics: Written consent from patient for publication including the radiological images and histopathology findings were obtained.

Conflict of interest: None

REFERENCES

1. Morten KJ, Cooper JM, Brown GK, Lake BD, Pike D, Poulton J. A new point mutation associated with mitochondrial encephalomyopathy. *Hum Mol Genet* 1993;2(12):2081-7. doi: 10.1093/hmg/2.12.2081.
2. Nunnari J, Suomalainen A. Mitochondria; in sickness and in health. *Cell* 2012; 148(6): 1145-59. doi:10.1016/j.cell.2012.02.035.
3. Gorman GS, Chinnery PF, DiMauro S, *et al*. Mitochondrial diseases. *Nat Rev Dis Primers* 2016; 2:16080. doi: 10.1038/nrdp.2016.80.
4. Goto Y, Nonaka I, Horai S. A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 1990;348:651-3. doi: 10.1038/348651a0.
5. Yoneda M, Tanno Y, Horai S, Ozawa T, Miyatake T, Tsuji S. A common mitochondrial DNA mutation in the t-RNA(Lys) of patients with myoclonus epilepsy associated with ragged-red fibers. *Biochem Int* 1990;21:789-96.
6. Russel P, Seth D, Dennis W. Neuroimaging of mitochondrial disease. Mitochondrion.2008 Dec; 8(5-6): 396-413.
7. Nakamura M, Yabe I, Sudo A, et al. MERRF/MELAS overlap syndrome: a double pathogenic mutation in mitochondrial tRNA genes. *J Med Genet* 2010;47: 659-64. doi: 10.1136/jmg.2009.072058.
8. Campos Y, Martin MA, Lorenzo G, Aparicio M, Cabello A, Arenas J. Sporadic MERRF/MELAS overlap syndrome associated with the 3243 tRNA(Leu(UUR)) mutation of mitochondrial DNA. *Muscle Nerve* 1996;19:187-90. doi: 10.1002/(SICI)1097-4598(199602)19:2<187::AID-MUS10>3.0.CO;2-S.
9. Naini AB, Lu J, Kaufmann P, *et al*. Novel mitochondrial DNA ND5 mutation in a patient with clinical features of MELAS and MERRF. *Arch Neurol* 2005;62:473-6. doi: 10.1001/archneur.62.3.473.
10. Nakamura M, Nakano S, Goto Y, *et al*. A novel point mutation in the mitochondrial tRNA(Ser(UCN)) gene detected in a family with MERRF/MELAS overlap syndrome. *Biochem Biophys Res Commun* 1995;214: 86–93. doi: 10.1006/bbrc.1995.2260.
11. Liu KM, Zhao H, Ji KQ, Yan CZ. MERRF/MELAS overlap syndrome due to the m.3291T>C mutation. *Metab Brain Dis* 2014; 29:139-44. doi: 10.1007/s11011-013-9464-5.