HK J Paediatr (new series) 2022;**27**:264-270

Case Report

A Case of Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like Episodes Caused by m.1630A>G Mutation with Initial Presentation of Chronic Kidney Disease and Gradual Progressive Predominant MNGIE-like Gut Dysmotility Features

CTW ***Wong***, JCK ***Chow***, BWM ***But***

Abstract Mitochondrial diseases related to mutations of the mitochondrial $tRNA^{Val}$ (MT-TV) gene are not common. We present the clinical features and disease course of the third reported case, as well as the first Chinese case, of mitochondrial disease with m.1630A>G mutation of the MT-TV gene that added to the phenotype spectrum of this particular variant. Our patient had an initial presentation of renal failure, and eventually development of stroke-like episode, followed by progression into significant MNGIE-like gastrointestinal dysmotility symptoms. We highlight the importance of recognising mitochondrial disease as one of the differential diagnosis when approaching children with chronic kidney disease or other renal disorders of unknown cause as it could be one of the first manifestations.

Key words *Chronic kidney disease; MELAS syndrome; Mitochondrial disease*

Introduction

Mitochondrial disease is a group of heterogeneous genetic disorders that causes defective oxidative phosphorylation. Often mitochondrial disease has a multisystem involvement that could present with a variable combination of features, while some manifest as a recognised clinical syndrome. Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is one of the most common syndromes among the others. The hallmark feature is the occurrence of stroke-like episodes, together with symptoms such as focal or generalised seizure, short stature, encephalopathy and muscle weakness. The m.3243A>G is the most common mutation that accounts for 80% of MELAS cases. On the other hand, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare syndrome caused by mutation in the nuclear TYMP gene. It has cardinal features of gastrointestinal dysmotility, cachexia, peripheral neuropathy, myopathy, ptosis, ophthalmoparesis and leukoencephalopathy. An entity related to it, called MNGIE-like disease, is labelled as patients do not fulfil all clinical features of MNGIE, in particular without leukoencephalopathy nor mutation of TYMP gene being identified. It has been associated with a number of nuclear and mitochondrial gene mutations.[1,2]

Here we present a case of mitochondrial disease with mutation m.1630A>G detected in the mitochondrial $tRNA^{Val}$ (MT-TV) gene. This mutation was reported in two cases before, with a phenotype of MELAS and MNGIE-like syndrome respectively. Our patient had presenting

Department of Paediatrics, Queen Elizabeth Hospital, 30 Gascoigne Road, Jordan, Kowloon, Hong Kong SAR, China

CTW **Wong**（黃梓慧） *FHKAM (Paediatrics), FHKCPaed*
JCK **Chow**（周芷君） *FHKAM (Paediatrics), FHKCPaed*
BWM **But**（畢慧文） *FHKAM (Paediatrics), FHKCPaed, FRCPCH*

Correspondence to: Dr CTW **Wong**
Email: wtw371@ha.org.hk

Received April 8, 2021

features predominant of chronic kidney disease, followed by development of stroke-like episode about 1.5 years after onset of symptoms, and progressive evolution to more prominent MNGIE-like gastrointestinal dysmotility features several years on.

Case

A 12-year-old girl, who was the only child born to non-consanguineous Chinese parents at 36 weeks gestation with a birth weight of 2.2 kg. Her perinatal course was unremarkable except a transient heart murmur, with echocardiogram showed trivial pulmonary incompetence only. She had normal growth and development up to one year of follow up after birth. She first presented at 7 years and 11 months old with sudden onset of disorientation evident by confused or unintelligible speech without associated neurological deficits. Symptoms resolved soon after admission spontaneously. Computed tomography of the brain performed upon admission and electroencephalogram were normal. Blood and urine tests were unrevealing on metabolic aspect except a mildly elevated lactate level at 3.8 mmol/L (normal range 0.5-2.2 mmol/L) and alanine level at 521 umol/L (normal range 159-472 umol/L) which both normalised on second samples. Acylcarnitine profile, ammonia, pyruvate level and urine organic acids were all normal. The exact cause of disorientation was not identified. However, she was found incidentally to have hypertension (blood pressure readings up to 130/90 mmHg), hyperkalaemia (highest at 6.2 mmol/L), normal anion gap metabolic acidosis (worst with pH 7.12 and base excess of -15.1) and a persistently deranged renal function of elevated creatinine and urea level (up to 91 umol/L and 18.6 mmol/L respectively despite adequate hydration) and an eGFR of down to 58 ml/1.73 m^2/min. She had normal urine output with no proteinuria nor microscopic haematuria all along. She subsequently underwent further investigations for her stage 3A moderate chronic kidney disease (CKD) and hypertension. Notable findings from the investigations include a left ventricular concentric hypertrophy on echocardiography, which was thought to be secondary to the hypertension at that time, a mild generalised increase in echogenicity in both kidneys without evidence of renal arteries stenosis from ultrasound and also a mildly decreased uptake in lateral aspect in upper third of right kidney without volume loss from DMSA scan. She was started on hydrochlorothiazide for her hypertension and hyperkalaemia, supplemented with oral sodium bicarbonate and was discharged with follow up for her chronic kidney disease.

She was admitted the second time at nine years old for episode of focal seizure presented with intermittent twitching of right fingers and a fluctuating Glasgow Coma Scale (GCS) level range from 10-15/15, preceded by nausea, vomiting and epigastric pain for two days. Magnetic resonance imaging (MRI) and magnetic resonance (MR) arteriography of the brain performed after admission showed a large acute left parieto-occipital infarct with no steno-occlusive lesions in the neck or intracranial vessels to account for the presentation. An MRI brain and MR spectroscopy repeated about 10 days later showed gyral swelling and T2-hyperintensity in left posterior parietal and occipital regions, and posterior aspect of bilateral thalami, with decreased N-acetylaspartate (NAA), elevated choline and presence of lactate peak at left occipital region (Figures 1 & 2). Mitochondrial disease in particular MELAS was suspected. She was found to have an elevated CSF lactate of 5.5 mmol/L with normal paired serum lactate of 1.9 mmol/L. In fact, her serum lactate and alanine level remained normal throughout her stay. Her renal impairment remained static, and her eye examination was unremarkable. She was found to have bilateral severe sensorineural hearing loss confirmed by pure tone audiometry. In retrospect, mother recalled a worsening of hearing since about eight years old. Echocardiogram showed a progressive biventricular hypertrophy that could not be explained by hypertension alone. She was diagnosed to have hypertrophic cardiomyopathy likely related to her suspected mitochondrial disease. Electroencephalogram revealed diffuse cerebral dysfunction without epileptiform discharge. Renal biopsy was performed, which showed a mild to moderate global glomerulosclerosis, moderate tubular atrophy with thyroidisation pattern and moderate to marked interstitial fibrosis, suggestive of chronic tubulointerstitial nephritis. Upon further questioning, mother reported that maternal grandmother suffered from recurrent symptoms of ileus or intestinal obstruction and died at the age of 63 from complications associated with her abdominal surgery. Mother remained healthy and asymptomatic all along. During this admission, the patient was treated with a course of arginine infusion followed by oral arginine and coenzyme Q10 supplement. She recovered from the stroke-like episode with no neurological deficits. She was also started on atenolol for her hypertrophic cardiomyopathy.

We had proceeded with genetic studies to investigate the underlying mitochondrial disease. Initial testing on eight common mitochondrial hot spot mutations (including m.3243A>G, m.3252A>G, m.3271T>C, m.8344A>G, m.8356T>C, m.8361G>A, m.8363G>A, m.8993T>G and m.8993T>C) were negative. Targeted next generation sequencing for renal diseases panel was also performed and found no clinically significant variants. Long-range polymerase chain reaction did not show large deletions or structural rearrangement in mtDNA. Eventually next generation sequencing of the mitochondrial genome was performed and detected the pathogenic variant m.1630A>G in both proband and her mother. The heteroplasmy levels for the proband and her mother were 92% and 24% in blood, and 99% and 66% in urine respectively. Whole exome sequencing was also performed for both of them, and reported no significant variants identified. Targeted analysis on nuclear genes associated with mitochondrial diseases were also unrevealing for both patient and her mother.

Over the years, the patient did not have florid neurological symptoms but very mild proximal muscle weakness, minimal upward gaze palsy and subtle cognitive decline only. There was no recurrence of seizure after the stroke-like episode. However, she ran a downhill clinical course characterised by worsening of her hypertension with stage 4 severe CKD and hypertrophic cardiomyopathy. Her eGFR deteriorated to 25-30 ml/1.73/m^2 and her left ventricle mass increased from 157.1 g/m^2 at diagnosis to 226.6 g/m^2 by 12 years 10 months old. In addition, she developed growth failure around 10 years of age and became progressively more cachexic with a BMI of 11.8 kg/m^2 latest. Initially she had a dropping body weight

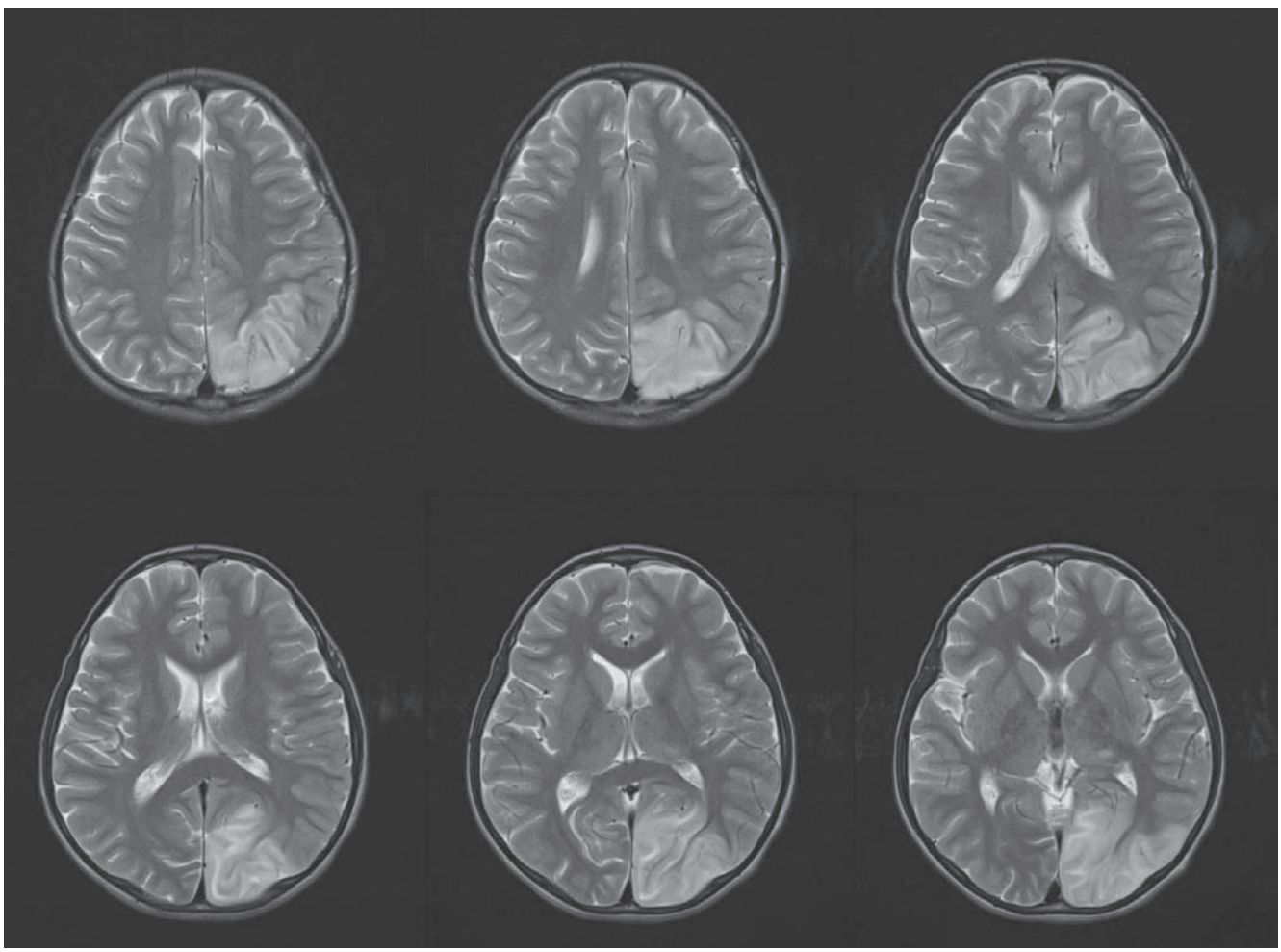

Figure 1 Magnetic resonance imaging showing gyral swelling with T2-hyperintensity over left posterior parietal and left occipital regions. Involved gyri show hyperintense signal on diffusion weighted imaging and hyperintense-to-isointense signal on ADC map.

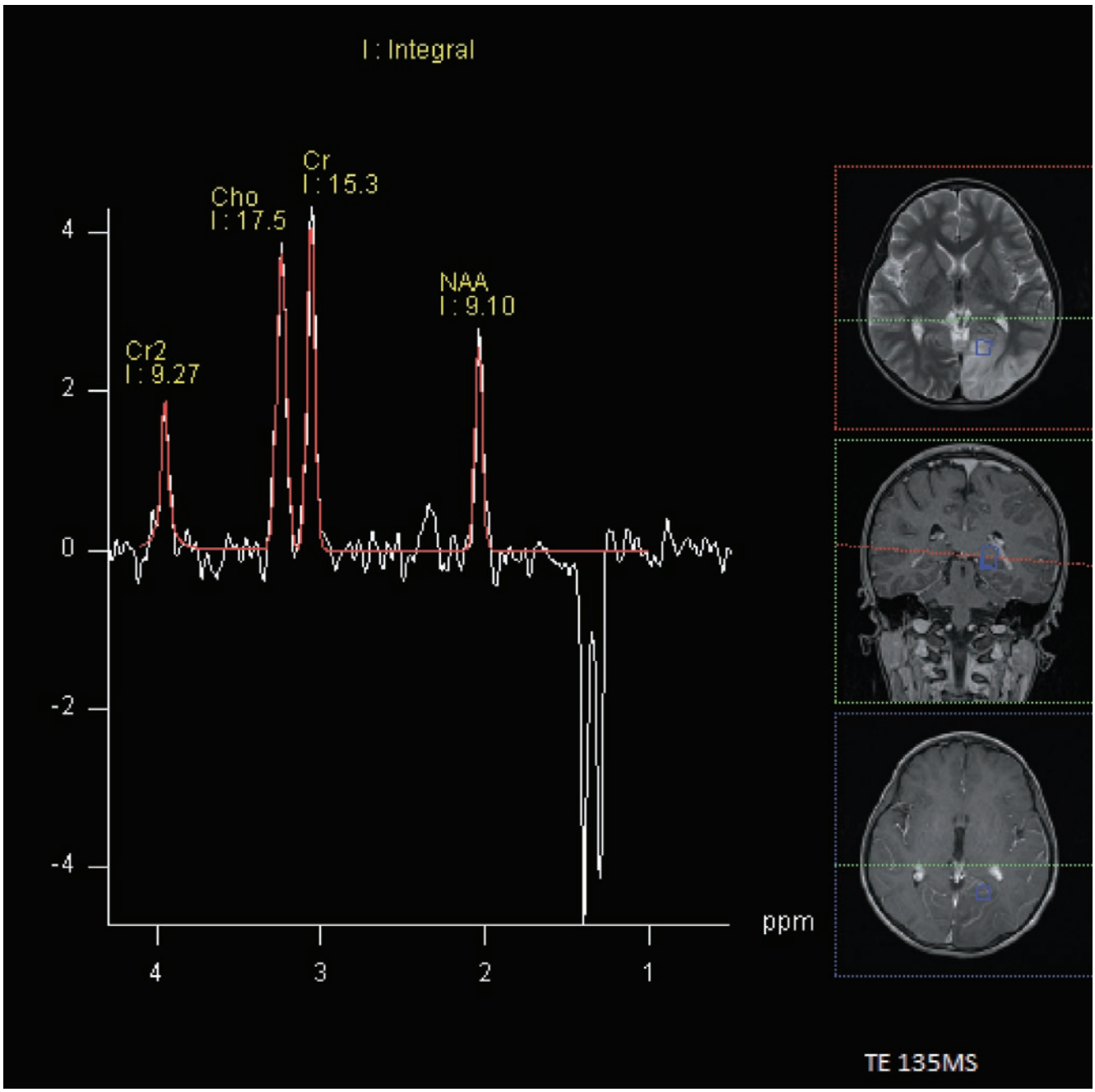

Figure 2 MR-spectroscopy showed decreased NAA, elevated choline and presence of lactate peak at left occipital region.

despite normal oral intake, but eventually developed prominent symptoms from feeding intolerance and gut dysmotility by 12 years 6 months old. She had very significant ileus and pseudo-obstructions of her bowel that rendered her parenteral nutrition dependence.

Discussion

We report a case of mitochondrial disease from a heteroplasmic mutation m.1630 A>G detected in mt-tRNA^{Val} with an initial presentation of CKD, followed by MELAS phenotype and subsequently developed more predominant MNGIE-like features.

tRNA^{Val} is a transfer RNA encoded by mitochondrial MT-TV gene. This gene is a 69 nucleotide RNA, located in position 1602-1670 bp in the mtDNA. Its function is to insert the amino acid valine to suitable locations in order to assemble proteins that are involved in oxidative phosphorylation.[3] Mitochondrial diseases related to mutations of the MT-TV gene are not common. There were 11 mutations reported to-date, and associated with a range of phenotypes including MELAS, Leigh syndrome, Chronic progressive external ophthalmoplegia, MNGIE and hypertrophic cardiomyopathy.[3]

This particular variant of m.1630A>G that we identified in our patient had been reported in two other cases before, with functional studies performed to prove its pathogenicity. The first case was reported by Horvath et al in 2009,[4] with a clinical phenotype of MNGIE-like syndrome. Muscle biopsy was obtained and demonstrated a severe combined deficiency of complexes I and IV in skeletal muscle and myoblasts. The second case was reported by Glatz et al in 2011,[5] with a clinical phenotype of MELAS. Functional study was performed by creating cybrid lines using the patient's fibroblast mtDNA and demonstrated a reduction in electron transport subunit COXI activities and an impairment in oxygen consumption. From the analysis of secondary structure of MT-TV, the m.1630A>G mutation was predicted to interfere with tRNA folding by disrupting a conserved base-pairing in the anticodon stem, resulting in instability of MT-TV.[4] Often there may not be a clear genotype-phenotype correlation in mtDNA mutations. It could be explained by a number of factors, such as the heteroplasmy levels, presence of modifiers in nuclear genes, various tissue distribution of the mutation and the mtDNA haplotype. However, there are a number of similarities noted between our case and the other two reported case of m.1630A>G (Table 1). Compared to the two other cases, our patient had a higher heteroplasmy level in blood and urine and an earlier onset of disease. She did not suffer from much neurological symptoms but instead she had more predominant clinical features of significant hypertrophic cardiomyopathic, chronic renal failure and gut dysmotility symptoms. Her gastrointestinal dysfunction gradually became the most symptomatic and significant among organs involved.

We would like to highlight the atypical initial presentation in our patient predominated by CKD with hypertension, hyperkalaemia and metabolic acidosis. To the best of our knowledge, only a few cases of paediatric-onset mitochondrial disease have been reported to initially present with renal involvement[6,7] and they were diagnosed as Fanconi syndrome or tubular dysfunction. Indeed, it was considered to be rather uncommon for children with mitochondrial disease to have renal disorder as the first manifestation. It was reported in two paediatric studies where only 2%[8] and 0%[9] of their cohort had renal disorder as the presenting symptom, while in the same studies, eventually 25% and 50% respectively developed renal involvement during their disease courses. There is now an increased awareness of renal involvement in a number of mitochondrial cytopathies, and its wide range of renal features, such as proteinuria/nephrotic syndrome, hypercalciuria, cystinuria, haematuria, nephrocalcinosis, glycosuria, Bartter-like syndrome as well as Fanconi syndrome. Nevertheless, when approaching children who have renal disorder without an underlying cause identified, unlike other patients with unexplained neurological symptoms, mitochondrial disease is rarely on the list of differential diagnosis. This illustrates the importance of increasing the familiarity of this uncommon yet devastating multi-systemic disease in other subspecialties apart from metabolic physicians and neurologists, as well as the involvement of nephrologists in the multidisciplinary management of mitochondrial disease.

Conflict of Interest

Authors report no conflict of interests to disclose.

Table 1 Comparison of clinical features of three reported m.1630A>G cases

Features	Our patient	Horvath et al's patient (2009)	Glatz et al's Patient (2011); Updated report by Uittenbogarrd et al (2019)[10]
Age of diagnosis	9 years old	16 years old	15 years old
Stroke-like episodes	Once, over left posterior parietal and occipital regions and no subsequent recurrence to date	No	Yes, over right occipital and posterior temporal lobes at diagnosis. Reported 2 additional infarcts by 24 years old
Sensorineural hearing loss	Yes, require hearing aids	Yes	Yes, on hearing aids
Seizure	Focal seizure during SLE, put on antiepileptic drug transiently	Focus in left parieto-occipital cortex in EEG	Status epilepticus at presentation, and subsequently seizure under control
Cognitive	Attended normal school, with subtle decline after diagnosis	Mild psychomotor delay	In age-appropriate education requiring support in math at diagnosis. Reported cognitive function younger than age by 24 years old
Other neurological symptoms	Mild proximal muscle weakness at diagnosis, and developed mild upward gaze palsy by 11 years old	Hyperopia, astigmatism, generalised hypotonia without weakness	Myopia at presentation. Reported ataxia, headache, tinnitus, unsteady gait, weakness, positive tremor, ankle clonus, loss of peripheral vision, upward gaze palsy, nystagmus on extreme right gaze by 24 years old
Growth	Height at 75th and weight at 50th centile at diagnosis, progressed to cachexia with BMI 11.8 by 12 years 10 months old	Cachexia, BMI 14.4	Short stature given GH supplement and delayed puberty
Lactic acidosis	Transient and mild only during decompensation	Yes (3.1-3.6 mmol/L)	Yes (6.4 mmol/L at presentation)
Renal involvement	Chronic kidney disease, eGFR ~60-70 ml/1.73 m^2/min at diagnosis and declined to ~25-30 ml/1.73 m^2/min by 12 years 10 months old		By 24 years old, reported chronic renal failure and underwent renal transplant
Cardiomyopathy	Hypertrophic cardiomyopathy LV mass 150 g (157.1 g/m^2) at diagnosis, progressed to 247g (226.6 g/m^2) by 12 years 10 months old		LV hypertrophy reported by 24 years old
Gastrointestinal symptoms	Asymptomatic at diagnosis, progressed to significant gut dysmotility and TPN dependent since 12 years 6 months old	Chronic motility problem, ileus, abdominal pain, megacolon	Reported GERD and bloating by 24 years old
Heteroplasmy	Blood 92% Urine 99%	Skeletal muscle >90% Blood 70% Myoblasts 80%	Blood 75%, Urine 95%, Fibroblast 60% at diagnosis; Fibroblast 89.63% at 24 years old
Maternal heteroplasmy	Blood 24% Urine 66% Mother asymptomatic	Blood 60% Mother asymptomatic	Blood 93%, Urine 98% in 2011; Fibroblast 94.8% in 2019 Mother asymptomatic

SLE: Stroke-like episode; EEG: Electroencephalography; BMI: Body mass index; LV: Left ventricular; eGFR: estimated glomerular filtration rate; GH: Growth hormone; GERD: gastroesophageal reflux disease

Acknowledgements

We thank Dr Liz Yuen, Dr Stella Leung and Dr Hoi Ning Cheung for support on genetic testing and results. We also thank Dr Wing Hung Lau for pathology support.

References

1. Chang TM, Chi CS, Tsai CR, Lee HF, Li MC. Paralytic ileus in MELAS with phenotypic features of MNGIE. Pediatr Neurol 2004; 31:374-7.
2. Tang S, Dimberg EL, Milone M, Wong LJC. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)-like phenotype: An expanded clinical spectrum of POLG1 mutations. J Neurol 2012;259:862-8.
3. Gallardo ME, Galera T, Garesse R, Bornstein B. Mitochondrial tRNA Valine in Cardiomyopathies. In: Branched Chain Amino Acids in Clinical Nutrition. Springer New York; 2015;p89-101.
4. Horváth R, Bender A, Abicht A, et al. Heteroplasmic mutation in the anticodon-stem of mitochondrial tRNA Val causing MNGIE-like gastrointestinal dysmotility and cachexia. J Neurol 2009;256: 810-5.
5. Glatz C, D'Aco K, Smith S, Sondheimer N. Mutation in the mitochondrial tRNAVal causes mitochondrial encephalopathy, lactic acidosis and stroke-like episodes. Mitochondrion 2011;11: 615-9.
6. Mochizuiki H, Joh K, Kawame H, et al. Mitochondrial encephalomyopathies preceded by de-Toni-Debre-Fanconi syndrome or focal segmental glomerulosclerosis. Clin Nephrol 1996;46:347-52.
7. Kuwertz-Bröking E, Koch HG, Marquardt T, et al. Renal Fanconi syndrome: First sign of partial respiratory chain complex IV deficiency. Pediatr Nephrol 2000;14:495-8.
8. Pérez-Albert P, de Lucas Collantes C, Fernández-García MÁ, et al. Mitochondrial disease in children: The nephrologist's perspective. JIMD Rep 2018;42:61-70.
9. Martín-Hernández E, García-Silva MT, Vara J, et al. Renal pathology in children with mitochondrial diseases. Pediatr Nephrol 2005;20:1299-305.
10. Uittenbogaard M, Wang H, Zhang VW, et al. The nuclear background influences the penetrance of the near-homoplasmic m.1630 A>G MELAS variant in a symptomatic proband and asymptomatic mother. Mol Genet Metab 2019;126:429-38.