

## Case report

# MELAS syndrome associated with diabetes mellitus and hyperthyroidism: a case report from Taiwan

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### Summary

**MELAS syndrome is a form of mitochondrial myopathy with manifestations of seizure, stroke-like syndrome, lactic acidosis, ragged red muscle fibres and mitochondrial encephalopathy. The syndrome has been reported in association with a variety of endocrine and metabolic disorders including diabetes mellitus (DM), hypothalamo–pituitary hypofunction, hypothalamic growth hormone deficiency and delayed puberty. Mitochondrial DNA (mtDNA) point mutation may be the major pathological defect. However, association of MELAS syndrome with hyperthyroidism has not previously been reported. A case is reported from Taiwan of a 32-year-old woman suffering from MELAS syndrome with associated DM and hyperthyroidism. When the latter was diagnosed in April 1988, the patient underwent subtotal thyroidectomy. There was no family history of thyroid disease. Because of repeated seizures, she had computed tomography (CT) and magnetic resonance imaging (MRI) of the brain which showed focal, low-density lesions over the cerebral hemispheres. Both serum and cerebral spinal fluid lactic acid levels were elevated. Mild elevations of serum T4 and T3 and a high titre of TSH receptor antibody were still present. Hyperglycaemia was noted during hospitalization and DM confirmed by oral glucose tolerance test. Muscle biopsy showed ragged red fibres. DNA**

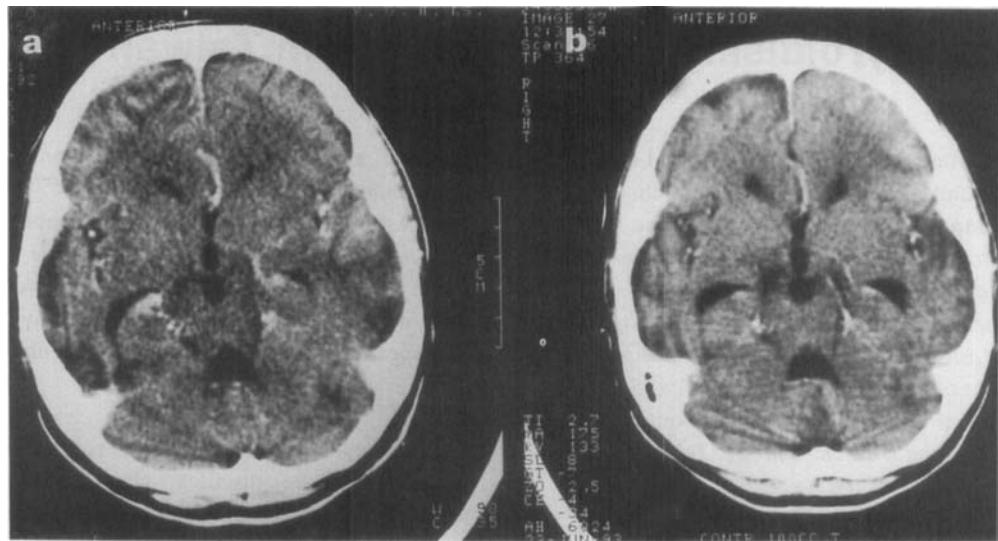
analysis showed an A-to-G transition at the 3243rd nucleotide position of the tRNA<sup>Leu(UUR)</sup> gene of the mtDNA from the patient. Quantitative polymerase chain reaction (PCR) and restriction analysis revealed that about 60% of the blood mtDNA was of mutant type. The patient received antithyroid drugs for hyperthyroidism, diet control for DM and anti-epileptic drugs for seizure.

The mitochondrial encephalomyopathies are hereditary neurodegenerative disorders characterized by multiple features and are usually divided into three clinical subgroups: (1) chronic progressive external ophthalmoplegia (CPEO) including Kearns–Sayre syndrome; (2) myoclonic epilepsy associated with ragged red muscle fibres (MERRF); and (3) MELAS syndrome (Rowland *et al.*, 1983). MELAS syndrome is an unusual form of mitochondrial disorder with manifestations of mitochondrial myopathy, encephalopathy, ragged red fibres, lactic acidosis and stroke-like syndrome (Pavlakis *et al.*, 1984). Children and young adults are most often affected. Patients are usually asymptomatic in infancy and have normal early development. Most patients are short and have recurrent epileptic seizures which are partial or generalized. Headache, vomiting, hemiplegia or hemianopia may also be present. Maternal inheritance has been found because human sperm contain only few mitochondria which do not penetrate the egg (Maertens & Dyken, 1992). The major defect is point mutation of the tRNA<sup>Leu(UUR)</sup> gene in the mitochondrial DNA (mtDNA) with heteroplasmic A-to-G transition at nucleotide position 3243 (80%) and T-to-C mutation at nucleotide position 3271 (10%) (Goto *et al.*, 1990). MELAS syndrome has been reported to be associated with a variety of endocrine and metabolic disorders, including diabetes mellitus (Onishi *et al.*, 1993), hypothalamo–pituitary hypofunction (Ishii *et al.*, 1991), hypothalamic growth hormone deficiency (Matsuzaki *et al.*, 1991) and short stature (Pavlakis *et al.*, 1984). However, the association of MELAS syndrome with hyperthyroidism has not previously been reported. We describe a case of MELAS syndrome associated with Graves' hyperthyroidism and DM.

### Case report

A 32-year-old Chinese woman presented with frequent episodes of facial jerking. Her family history was unremarkable, apart from the death of a younger brother at age 26

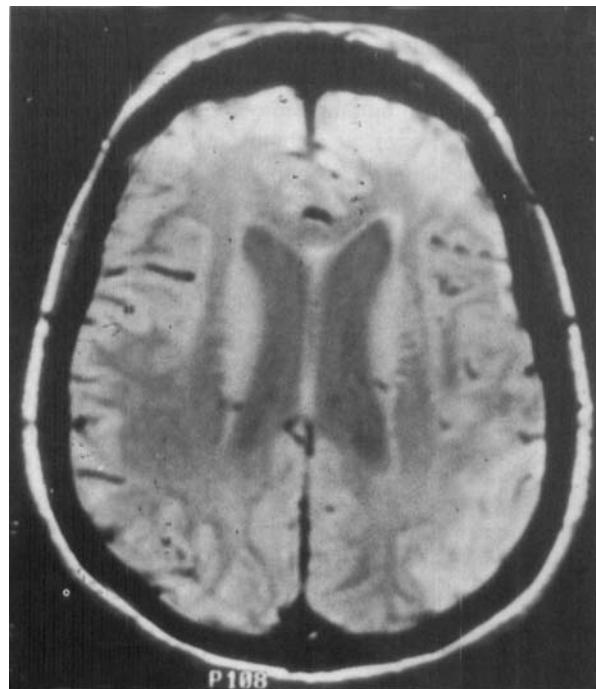
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**Fig. 1** Brain CT showing a, in Dec. 1992, low-density lesions over the postero-temporal regions bilaterally and right frontal region, with gyral enhancement and mild mass effect; b, in June 1993, prominence of a left-sided frontal sulcus with gyral enhancement. Resolution of the lesions in the postero-temporal regions can be seen.

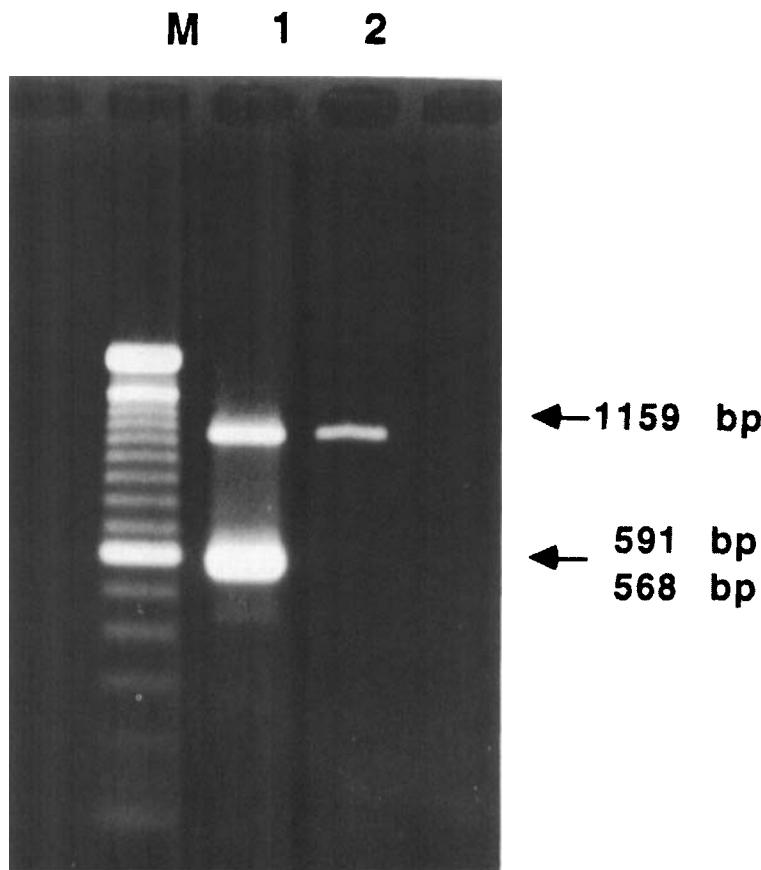
following several episodes of cerebral infarction. Her birth and developmental histories were unremarkable. Graves' disease with hyperthyroidism had been diagnosed in April 1988, and subtotal thyroidectomy was performed in another medical centre. There was no family history of thyroid disease. During the previous 4 years, her condition had been stable. In April 1992, she began to suffer from seizures and was admitted to a local hospital, but a specific diagnosis was not made. In December 1992, the patient was admitted to our unit because of focal motor seizures and bizarre behaviour of one week duration. Brain CT showed low-density areas over the postero-temporal and right frontal regions (Fig. 1a). Carotid angiography revealed hyperaemic changes in the right frontal region.  $^{99m}$ Tc HMPAO brain SPECT showed decreased uptake in the left occipital region, and marked uptake in the right frontal and left temporo-parietal-occipital regions. IQ testing (Wechsler Adult Intelligence scale) showed moderate mental subnormality (Verbal IQ 48, Performance IQ 46, Full IQ 44). She was discharged in a stable condition after 24 days of hospitalization. However, 6 months later, the patient was re-admitted because of persistent facial jerking. On examination, the patient was obtunded, and under weight (30.5 kg, height 155 cm). Her intelligence was impaired. Reduced muscle power and mutism were noted. Frequent twitching of the right side of her face and trunk was noted during the first few days of hospitalization.

Laboratory tests revealed normal haematology and biochemistry profiles except for elevated CSF lactate



**Fig. 2** Brain MRI, axial section: proton density image (FSE 2100/17) showing high signals over both frontal and left temporo-parietal regions.

**Fig. 3** Restriction analysis of mtDNA from the blood cells of the patient with MELAS. Lane 1 shows Apa I-digested PCR fragments amplified from the patient's blood cell mtDNA, lane 2 is a negative normal control. For restriction analysis with Apa I, a 1159-base-pair DNA fragment encompassing the putative mutation site (nucleotide position 3243) was amplified by PCR using a pair of primers L2678-2696 and H3817-3836, and then digested with 10 units of Apa I overnight under the conditions recommended by the manufacturers. The digest was subjected to electrophoresis on 1.5% agarose at 100 V for 40 min. The DNA bands were visualized under UV light illumination after staining with ethidium bromide for 20 min at 25°C. The only possibility for a new Apa I restriction site was the G-to-A transition at nucleotide 3243.



(110 mmol/l (normal <25)) and serum lactate (33 mmol/l (normal 5–19)) concentrations. Brain CT showed focal low density over the left frontal region with partial recovery of the previously noted low-density areas (Fig. 1b). MRI showed diffuse, high-signal cerebral lesions over both frontal and left temporo-parietal regions (Fig. 2). A muscle biopsy from the right vastus lateralis muscle was stained with modified Gomori-trichrome and showed ragged red fibres. DNA analysis was performed as previously described (Chen *et al.*, 1993). Restriction analysis of muscle and blood DNA showed an A-to-G transition at the 3243rd nucleotide position in the mtDNA, and about 60% mutant type mtDNA was present in the blood cells of the patient as estimated by scanning densitometry of the DNA bands in the agarose gel (Fig. 3).

Endocrine studies revealed mild hyperthyroidism (T3 3.6 nmol/l, normal range 1.3–2.3; T4 166 nmol/l, normal range 77–154; FT4 52 pmol/l, normal range 12–22, measured by radioimmunoassay; TSH <0.15 mU/l, normal range 0.5–4.0, measured by immunoradiometric assay) and positive thyroid antibodies (TSH receptor antibody 47%, normal <10%, measured by radioreceptor

binding assay; antimicrosomal antibody 230 IU/ml, normal <155, measured by ELISA). Hyperglycaemia was noted during hospitalization and an oral glucose tolerance test showed diabetes mellitus (plasma glucose 5.3, 10.1, 10.9, 13.0 and 13.9 mmol/l at 0, 30, 60, 90 and 120 min, respectively). The patient was treated with a simple diabetic diet and received propylthiouracil for recurrent hyperthyroidism, diphenylhydantoin and phenobarbitone for seizure control, and  $\alpha$ -tocopherol and ubiquinone for the mitochondrial respiration defect. After 30 days in hospital, she was discharged in a stable condition.

#### Discussion

MELAS syndrome was first described in 1984 (Pavlakis *et al.*, 1984), but the clinical criteria for diagnosis have recently been revised (Hirano *et al.*, 1992). A point mutation at nucleotide position 3243 within the tRNA<sup>Leu(UUR)</sup> gene of mtDNA was found in 80% of MELAS patients and another mutation at nucleotide position 3271 in 10% (Goto *et al.*, 1990; Goto, 1993). It has been shown recently that such mutations may cause progressive inhibition of the

mitochondrial respiratory function (Hayashi *et al.*, 1993). The defects in oxidative phosphorylation and respiratory chain function may result from a deficiency of the electron transport protein cytochrome C oxidase (Hagino *et al.*, 1993; Muller-Hocker *et al.*, 1993), and deficiencies of NADH dehydrogenase (Muller-Hocker *et al.*, 1993), NADH coenzyme Q reductase (Kobayashi *et al.*, 1987) and pyruvate dehydrogenase (Nagai *et al.*, 1992). The proportion of mutant mtDNA varied between different tissues and organs (Hamazaki *et al.*, 1993; Love *et al.*, 1993). MELAS syndrome is therefore a multisystem disease that involves multiple organs, including non-endocrine and endocrine (Hirano *et al.*, 1992). Hence it is not surprising to find that MELAS syndrome has been reported to be associated with both type 1 and type 2 DM since DM may be one of the heterogeneous features of a mtDNA point mutation (Gerbitz, 1992; Reardon *et al.*, 1992; Gerbitz *et al.*, 1993). Some patients with diabetes and the MELAS mutation have been reported to have negative islet cell antibodies which supports the hypothesis that the DM is related to mitochondrial defects (Reardon *et al.*, 1992; Onishi *et al.*, 1993), but serum islet cell antibodies in our patient were not checked. The association of MELAS syndrome with hyperthyroidism and DM has not been reported before. However, Kearns-Sayre syndrome (KSS) has been reported in association with thyroid disease and DM (Harvey & Barnen, 1992). Since KSS and MELAS syndrome belong to the same group of mitochondrial defects, it is not surprising to find a patient suffering from both MELAS syndrome and hyperthyroidism. Gerbitz (1992) has proposed that mtDNA mutation may lead to an abnormality in MHC-restricted immune response, resulting in a pathogenetic mechanism similar to that found in autoimmune type I DM. Since Graves' hyperthyroidism is also an autoimmune disease, the same mechanism may be responsible for the pathogenesis of hyperthyroidism in this patient.

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