IMAGE OF THE MOMENT

Initially identified as a cause of myopathy, mitochondrial dysfunction is now recognized as a relatively common cause of multisystem disease, affecting not only the central and peripheral nervous system but also other organs. Some of the characteristic clinical, pathological and molecular findings are summarized and illustrated below.

NEUROLOGICAL FEATURES

- Chronic progressive external ophthalmoplegia (CPEO)
- Pigmentary retinopathy
- Optic atrophy
- Epilepsy (myoclonus)
- Dementia
- Encephalopathy
- Leigh's syndrome
- Stroke-like episodes
- Deafness
- Movement disorder
- Myopathy
- Neuropathy

NON-NEUROLOGICAL FEATURES

- Cardiomyopathy
- Cardiac conduction defects
- Diabetes mellitus
- Short stature
- Endocrine dysfunction
- Gut hypomotility
- Hepatic failure
- Fanconi syndrome
- Lipomatosis

Mitochondrial cytopathy

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(a)

(b)

Figure 1 Chronic progressive external ophthalmoplegia.

CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLÉGIA

The patient is first looking ahead (Fig. 1(a)) and then attempting to look to the far left (Fig. 1(b)), but the range of movement is limited. Ptosis is slowly progressive and may be asymmetric (myasthenia gravis is an important differential diagnosis). Extraocular movements become increasingly restricted and may eventually be lost completely. Despite sometimes obvious axis deviation, diplopia is uncommon (unlike myasthenia).

PIGMENTARY RETINOPATHY

The pigmentation starts in the extreme periphery, and may be difficult to see without pupillary dilatation (Fig. 2). It rarely causes visual symptoms. Optic atrophy may also be seen, and in Leber's hereditary optic neuropathy is associated with severe visual impairment.

BASAL GANGLIA CALCIFICATION

This is relatively common, but usually less dramatic than this example, on brain CT (see Fig. 3).

Figure 2 Pigmentary retinopathy.

Figure 3 Basal ganglia calcification (arrows).

MYOPATHOLOGY

The most characteristic finding (but it is occasionally absent) is the presence of ragged red fibres – due to accumulation and abnormal distribution of mitochondria.

Some fibres may lack cytochrome oxidase staining.

Paracrystalline inclusions within mitochondria may be seen by electron microscopy. See Figs 4,5,6 and 7

MITOCHONDRIAL DNA

Mitochondrial DNA (mtDNA) is maternally inherited. Mitochondrial cytopathies associated with mtDNA point mutations are maternally inherited – these include the MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes) and MERRF (myoclonus epilepsy, ragged red fibres) syndromes and Leber's hereditary optic neuropathy. (Fig. 8.)

Figure 4 Ragged red fibres (arrows) seen in a muscle biopsy (Modified Gomori trichrome stain).

Figure 5 A mitochondrion.

Figure 6 Cytochrome oxidase negative fibres (arrows) shown on muscle biopsy.

Figure 7 Paracrystalline inclusion on electromicroscopy of muscle

Figure 8 Blot from a case of chronic progressive external ophthalmoplegia showing two populations of mtDNA – normal DNA of 16.6kb, and DNA of 11.5kb due to ~ 5kb deletion.