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Mitochondrial disease

inside

The authors

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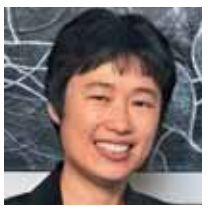

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Background

MITOCHONDRIAL disease can be a debilitating, life-threatening condition in its severest forms. It is caused by a loss of mitochondrial function and is often associated with genetic mutations in either mitochondrial or nuclear DNA. Recent studies have shown that at least one in 250 Australians are at risk of developing mitochondrial disease during their lifetime.

Severe or fatal forms of mitochondrial disease are more frequent in children than in adults, but adult patients often have chronic multisystem clinical manifestations that require constant surveillance and symptomatic treatment for the rest of their lives.

Because patients with the chronic, less severe forms of mitochondrial disease are more likely to present to GPs, this article focuses predominantly on the treatment of adult forms of mitochondrial disease.

Mitochondrial medicine represents a newly established, complex and evolving field. The first case of mitochondrial disease was described in 1962, but since then a multitude of clinical syndromes and disorders has been added to this subcategory of diseases.

Initially thought to be a rare group of conditions, it is recognised that mitochondrial disease now represents the most common subgroup of inherited metabolic diseases.

Prevalence of mitochondrial disease

Pathogenic mitochondrial DNA (mtDNA) mutations occur frequently in the general population.

The first true population-based study was performed in Australia and showed that a common mtDNA mutation, known as m.3243A>G (causing mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes [MELAS syndrome]), was found in one in 500 in the general community.[1] All individuals over 50 with the mutation were oligosymptomatic, in that none had all the clinical features diagnostic of MELAS syndrome.

The population prevalence of another point mutation — m.1555A>G (originally associated with antibiotic-induced hearing loss) — was similarly found in one in 500 subjects, indicating that a combined prevalence of these two point mutations alone was one in 250 persons.[2,3]

This prevalence was confirmed in a further study, which examined the prevalence of 10 common mtDNA point mutations and found a combined population prevalence of more than one in 200 live births.[4]

It should be noted that while mutation carriers may not develop full syndromic features of mitochondrial disease, they are at risk of developing any or all the symptoms associated with the specific mtDNA mutation they carry.[5]

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Pathogenesis

MITOCHONDRIA are the organelles that produce most of the energy for the cell. Energy in the form of adenosine triphosphate is made via the respiratory chain, a series of multi-enzyme complexes that are located in the mitochondrial membrane. The respiratory chain is comprised of proteins that are encoded by both mitochondrial and nuclear DNA.

With the advent of molecular biology and the discovery that mutations in the mtDNA caused mitochondrial disease, mitochondrial disorders can now be classified on genetic grounds. The first reports of pathogenic mutations being associated with human mitochondrial disease were published in 1988. Now more than 100 pathogenic mtDNA mutations have been reported in the literature (see MITOMAP database under Online resources, page 33).

Mutations in the nuclear genome (nDNA) have more recently been reported to cause mitochondrial disease. Affected adults are more likely to have mutations in mtDNA, whereas affected children may have mutations in either genome. Mutated nuclear genes are involved in mtDNA synthesis, repair or replication and thus may cause multiple deletions (missing bits) in, or depletion (reduced amount) of, mtDNA, which impairs mitochondrial function. (A list of the common mtDNA and nDNA mutations is available on request.)

Pathogenic mtDNA mutations may be categorised into point mutations, large-scale rearrangements (single deletions, duplications or multiple deletions), as well as mtDNA depletion. Despite the large number of pathogenic mtDNA mutations in humans, only a few of them occur frequently in various human populations, in particular those associated with the MELAS, myoclonic epilepsy ragged-red fibre (MERRF), neurogenic ataxia retinitis pigmentosa (NARP), and Leber's hereditary optic neuropathy (LHON) syndromes. The clinical manifestations of these syndromes are outlined in table 1.

MtDNA mutations are usually maternally transmitted, but single deletions often occur sporadically (table 2).

Table 1: Summary of common phenotypes of mitochondrial disease

Mitochondrial disease/syndrome	Main clinical manifestations
MELAS syndrome	Mitochondrial myopathy Encephalopathy Lactic acidosis Stroke-like episodes Short stature Hearing loss Diabetes
MERRF syndrome	Myoclonus epilepsy Ragged-red fibres Hearing loss Systemic lipomas Cerebellar ataxia Peripheral neuropathy
Aminoglycoside-induced hearing loss	Aminoglycoside-induced hearing loss Congenital hearing loss Maternally transmitted hearing loss
Kearns–Sayre syndrome/ CPEO/ Pearson's syndrome	Ptosis External ophthalmoplegia Retinal pigmentary changes Proximal myopathy Cardiac arrhythmia Cardiomyopathy Diabetes Cerebellar ataxia Hearing loss
Leigh's disease/ NARP syndrome	Bilateral striatal lesions on brain imaging Neuropathy Ataxia Retinal pigmentary change Basal ganglia lesions
Leber's hereditary optic neuropathy (LHON)	Bilateral optic neuropathy
Autosomal dominant PEO	Ptosis and progressive external ophthalmoplegia Proximal myopathy
Autosomal recessive PEO	Ptosis and progressive external ophthalmoplegia Proximal myopathy
MNGIE	Ptosis Progressive external ophthalmoplegia Gastrointestinal dysmotility Muscle weakness Cachexia
POLG/SANDO	Seizures (particularly exacerbated by sodium valproate) Cerebellar ataxia Hepatopathy Peripheral neuropathy Ptosis Proximal muscle weakness

MELAS = mitochondrial encephalopathy, lactic acidosis and stroke-like episodes syndrome
MERRF = myoclonic epilepsy ragged-red fibre syndrome
CPEO = chronic progressive external ophthalmoplegia
NARP = neurogenic ataxia retinitis pigmentosa syndrome
MNGIE = mitochondrial myopathy, neuropathy, gastrointestinal encephalopathy syndrome
SANDO = sensory ataxic neuropathy, dysarthria and ophthalmoparesis

Table 2: Inheritance patterns of mitochondrial disease and approach to sample selection for diagnosis

Genetic abnormality	Inheritance pattern	Best sample to perform DNA analysis
mtDNA point mutation	Maternal (may appear 'sporadic')	Muscle Hair follicles (especially if known mutation in family) Urine NB: Blood is not ideal (see text)
mtDNA deletion	Sporadic (rarely maternally transmitted)	Muscle tissue
mtDNA multiple deletions or mtDNA depletion	Autosomal recessive or autosomal dominant	Muscle tissue is best to detect deletions. Blood is satisfactory for nuclear gene sequencing

Clinical assessment

MITOCHONDRIA are present in the cells of almost every tissue (except for red blood cells), so they can potentially affect any organ in the body. Therefore, patients with mitochondrial disease can present with a diversity of clinical manifestations affecting multiple organ systems. Given that the mitochondrion's main function is to produce energy for the cell, tissues that need the most energy are most commonly affected. These typically include brain, muscle, heart, retina and cochlea.

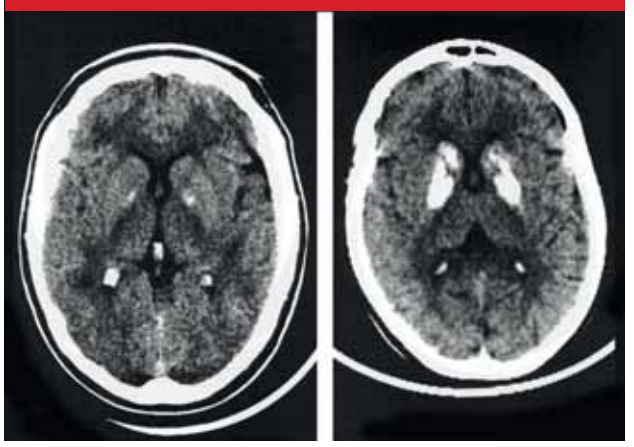
Symptoms may not appear for years after birth, even when the condition is inherited. Why identical pathogenic mutations cause disease at different ages is unknown, but presumably it involves mechanisms such as:

- The tissue distribution of mtDNA mutations (ie, heteroplasmy, when some mitochondria may have more mutant mtDNA than others [figure 4, page 32]).
- Threshold effects of the tissue at the time.
- Environmental stressors.
- Underlying nuclear genetic factors.

Clinical manifestations associated with adult mitochondrial disease include:

- Hearing loss (sensorineural hearing loss).
- Ophthalmological abnormalities (such as retinal pigmentary changes, ptosis, progressive external ophthalmoplegia, optic atrophy and rarely, retinitis pigmentosa).
- Muscle weakness (especially proximal weakness, exercise intolerance, dysphagia, dysarthria).
- Neurological involvement (focal neurological deficits, migraine, seizures).
- Cardiac manifestations (cardiac arrhythmia, hypertrophic cardiomyopathy, conduction block).
- Gastrointestinal system abnormalities (pseudo-obstruction, constipation).
- Endocrine abnormalities (diabetes, short stature and, rarely, hypoparathyroidism and hypogonadism).
- Renal involvement (renal tubular acidosis/Fanconi syndrome, glomerulo-nephritis).

Figure 1: Cerebral CT scan showing mild thalamic (left panel) and marked basal ganglia calcification (right panel), often seen in mitochondrial disease.



For some clinical manifestations, particular features may alert the clinician to the diagnosis of a mitochondrial disorder, although these are not invariably present. At other times it is the combination or cluster of clinical symptoms that can lead to the diagnosis of a mitochondrial disorder. Particular clinical features that should alert the clinician to the diagnosis of a mitochondrial disorder are summarised in table 3.

Diagnosis and management of mitochondrial disease involves a four-step process:

- Confirming the diagnosis.
- Assessing the illness.
- Treating the symptoms.
- Implementing preventive strategies.

Confirming the diagnosis

If the clinical history and examination is suggestive of the diagnosis of mitochondrial disease, a panel of investigations to confirm this clinical

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Table 3: Clinical features suggestive of a mitochondrial disorder

Clinical manifestation	Features suggestive of a mitochondrial disease
Sensorineural hearing loss	Asymmetrical onset Young age of onset History of partial recovery after an auditory insult High frequencies affected first
Focal neurological deficits	Young age of onset Preceded by clinical prodrome* Non-vascular territory on neuroimaging Predominantly grey matter affected Associated basal ganglia calcification Good clinical recovery Neuroradiological changes out of proportion to clinical deficit Associated focal seizures or status epilepticus Raised CSF lactate
Seizures	Sudden-onset status epilepticus Recurrent physiological triggers# Severe episodes of seizures with good interictal periods (requiring no anticonvulsants for control interictally) Worsened by sodium valproate
Ptosis	Asymmetrical onset Slowly progressive with little diurnal variation Accompanying progressive external ophthalmoplegia or retinal pigmentary changes
Retinal pigmentary changes	Perimacular distribution No drusen Non-vision threatening
Diabetes	No associated diabetic retinopathy or peripheral neuropathy related to the length of diabetes onset Easily controlled with oral hypoglycaemics with respect to duration of the diabetes

*A typical prodrome may include nausea, vomiting, headache, drowsiness, fever or seizures

#Physiological triggers may include fevers, systemic illness such as viral infection, bacterial infection, sleep deprivation, anxiety or excessive emotional stress

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suspicion is warranted.

Unfortunately, there is no one diagnostic test that is abnormal in all patients with mitochondrial disease, and confirmation of the diagnosis may require a number of investigations. Those that may be appropriate are listed in table 4.

Ideally, non-invasive investigations should be performed before invasive ones. It should be noted that mtDNA mutations are usually maternally transmitted, but single deletions often occur sporadically. Given that nuclear gene mutations may follow Mendelian inheritance patterns (ie, autosomal dominant or autosomal recessive), a careful extensive family history is also crucial in the clinical work-up of mitochondrial disease (see table 2).

Diagnostic investigations

Two diagnostic investigations require special mention: muscle biopsy and mtDNA analysis.

Muscle biopsy

The pathological hallmark of mitochondrial disease is known as the 'ragged-red fibre', traditionally seen on muscle biopsy tissue using the modified Gomori trichrome stain (figure 3A, next page). This histological stain shows subsarcolemmal aggregates of proliferating mitochondria that stain 'red' against green-stained muscle fibres, giving the abnormal muscle fibre a ragged appearance around the edge.

Muscle morphological changes can be seen on other 'specific' mitochondrial stains such as cytochrome c oxidase (COX) and succinate dehydrogenase (SDH) staining (figure 3B).

These abnormalities are seen in muscle fibres that have mitochondrial proliferation in the subsarcolemmal regions of the muscle fibre.

Electron microscopy can also identify abnormal mitochondria as well as electron-dense inclusions that indicate abnormal mitochondrial function.

Although any or all of these histological features may be found in the muscle of patients with mitochondrial disease, it is now known that not all patients with mitochondrial disease will have these abnormalities. Furthermore, ragged-red fibres and COX-negative fibres can be seen in several other non-mitochondrial diseases (such as drug-induced myopathies, inclusion-body myositis and muscular dystrophies).

Mitochondrial DNA analysis

Detection, quantification and characterisation of mtDNA mutations have become an important step in the diagnosis of mitochondrial disease. Several properties of mtDNA should be emphasised to improve the physician's understanding of the genetic tests required to diagnose this condition.

Human mtDNA is a double-stranded circular genome that has three specific properties:

- Maternal inheritance.
- Heteroplasmy.
- Mitotic segregation.

Maternal inheritance. At conception, essentially all surviving mtDNA is derived from the mother's ovum. Thus a pathogenic mutation in an affected mother is transmitted to all her offspring, but only her daughters will transmit the mutation to their progeny. Hence, a disease that is expressed in both sexes but not transmitted from male to male is highly suggestive of an mtDNA defect.

Heteroplasmy. Heteroplasmy is the coexistence of both normal (wild-type) and abnormal (mutant) mtDNA within the same cell (figure 4, page 32). Because there are multiple mitochondria within any given cell, the percentage of mutant mtDNA may vary between zero and 100%. This is in contrast to nuclear genetics, where cells may contain two normal genes (0% mutant), one abnormal gene (50% mutant or heterozygote), or two abnormal genes (100% mutant, homozygote or compound heterozygote — two different mutations, one on each chromosome of a pair).

In general, the higher the mutational load of mtDNA within the tissue or cell, the greater the level of mitochondrial dysfunction.

A minimum number of mutant genomes are required for the expression of disease, a phenomenon referred to as the threshold effect.

The threshold effect is a relative concept, because the critical percentage of mutation necessary to cause impaired mitochondrial function will vary depending on the relative metabolic requirements of the tissue or cell at any given time and the particular mtDNA mutation involved.

Typically, higher proportions of mutant mtDNA have been observed in more severely affected patients.

Mitotic segregation. Given that there may be many hundreds of mitochondria within any given cell, the proportion of mutant DNAs passed on to the daughter cell at cell division may vary between zero and 100%, depending on the proportion of mutant mtDNAs that are transmitted. Hence, the percentage of mutant mtDNA may change rapidly from parent to daughter cell.

This phenomenon, in part, explains why some family members may be more severely affected than others and also how some patients might have different clinical manifestations at different ages.

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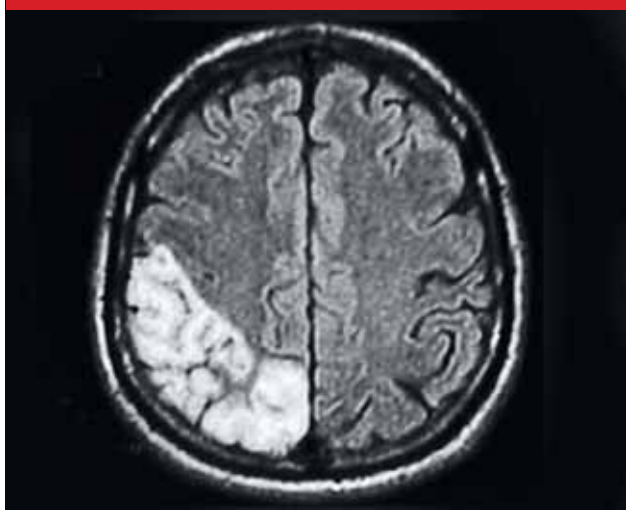
Table 4: List of investigations that may be helpful in the diagnosis and assessment of mitochondrial disease

Non-invasive investigations	Comments
Baseline blood test to exclude alternative (potentially treatable) diagnoses	FBC, electrolytes, LFTs, inflammatory markers, autoimmune markers, serum immune electrophoresis, B12, red cell folate, thyroid function tests
Serum or urinary lactate	May be elevated in mitochondrial disease, but normal values do not exclude the diagnosis
Serum creatine kinase	May be elevated in mitochondrial disease, but is not specific (ie, may indicate other muscle disease) and normal values do not exclude the diagnosis
Blood sugar level/oral glucose tolerance test	Patients with mitochondrial disease have a tendency for insulin resistance, which is non-specific. It needs to be documented with an oral glucose tolerance test in which both insulin and blood glucose levels are measured. Impaired glucose tolerance can also be seen
Cerebral CT scan	Basal ganglia calcification is often seen (figure 1), particularly at a younger age Hypodense lesions can be seen in some mitochondrial disorders such as MELAS White matter involvement can be seen in some mitochondrial disorders such as KSS and MERRF
Cerebral MRI (with MR spectroscopy)	Most commonly cortical T2 hyper-intensities are seen. Often they involve only grey matter In MELAS, cortical lesions can be migrating, crossing vascular territory in the temporal, parietal and occipital lobes (figure 2) May have cerebral or cerebellar atrophy late in the course of illness MR spectroscopy may show a lactate peak in the brain parenchyma or ventricles
Nerve conduction study	Often normal. Peripheral neuropathy may be present, with most disorders having sensory > motor axonal neuropathy Less commonly demyelinating neuropathies can be seen
Electromyography	May show mild to severe myopathic changes. In conditions such as MNGIE, NARP and SANDO, patients may have evidence of neurogenic change
Electroencephalogram	Usually normal. Slowing in patients with encephalopathy during an acute exacerbation. Can have epileptiform changes in eg, MELAS and MERRF syndrome or with *POLG* mutations (patients with *POLG* have an occipital predilection)
Audiogram	Symmetrical or asymmetrical sensorineural hearing loss affecting higher frequencies first. May be of young onset. Occasionally is reversible or partly reversible
Gastric emptying and colonic transit studies	Tendency to have slow colonic transit. Some patients have delay in gastric emptying. Gastroesophageal reflux is also common
ECG/Holter monitor	Atrioventricular and intraventricular conduction disturbances may be seen
Echocardiography	Can have left and right ventricular hypertrophy or dilatation, restrictive or dilated cardiomyopathies
Urine metabolic screen	Useful to exclude other metabolic conditions* — should be normal in mitochondrial disease
Urinary purines and pyrimidines	High urinary thymidine and deoxyuridine levels are diagnostic of MNGIE syndrome
Retinal photos	Retinal pigmentary changes are present in a large number of patients with mitochondrial disease but are only appreciated on dilated fundoscopy. Optic atrophy may occur in some mitochondrial diseases such as KSS, LHON and MERRF. Glaucomatous changes can also occur
Invasive investigations	
Muscle biopsy and histology	Pathological hallmark is the 'ragged-red fibre' (or sub-sarcolemmal accumulation of mitochondria). Other histological changes include cytochrome c oxidase-deficient (COX-negative) fibres, 'ragged-blue fibres' (as seen on succinate dehydrogenase stains) Muscle biopsy changes become more prominent with age and severity of the muscle weakness
CSF lactate	May be normal or elevated. Often elevated during acute stoke-like episodes
Additional investigations (non-rebatable)	
Mitochondrial DNA analysis for point mutations and deletions	mtDNA point mutations can be performed on muscle tissue, hair follicles, urinary epithelial cells or blood. Mutations may be lost from blood (particularly with increasing age), so analysis in other tissues is preferable Deletions should be tested for in muscle tissue (not blood)
Mitochondrial respiratory enzyme analysis	Respiratory chain enzyme-complex deficiency (this investigation is performed on muscle tissue, cultured fibroblasts or liver and is more helpful in children than in adults)
Nuclear gene mutations	Molecular analysis of nuclear genes is not freely available in Australia. Common mutations in some genes (eg, the *POLG* gene) can be performed at a reasonable cost. However, the cost of sequencing this entire gene and other genes is usually prohibitive

*Phenylketonuria (PKU), maple syrup urine disease (MSUD), homocystinuria, histidinaemia, galactosaemia, biopterin deficiency, histidinaemia

Figure 2: Cerebral MRI from a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and srtroke like episodes (MELAS sydrome) showing a high signal lesion that involves a non-vascular territory (lesion involves areas supplied by both the posterior cerebral artery and middle cerebral artery territories, and thus unlikely to be due to a single, large intracerebral vessel occlusion).



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It should also be noted that most pathogenic mtDNA mutations are heteroplasmic (ie, there is a mixture of mutant and normal mtDNA in any given cell) and that the mutational load of each tissue may vary within an individual. Therefore, the choice of tissue that is analysed is important (see table 2).

Unlike nuclear genetic disorders in which gene abnormalities are present in each cell, blood (specifically white blood cells) is not the ideal tissue to subject to mtDNA analysis.

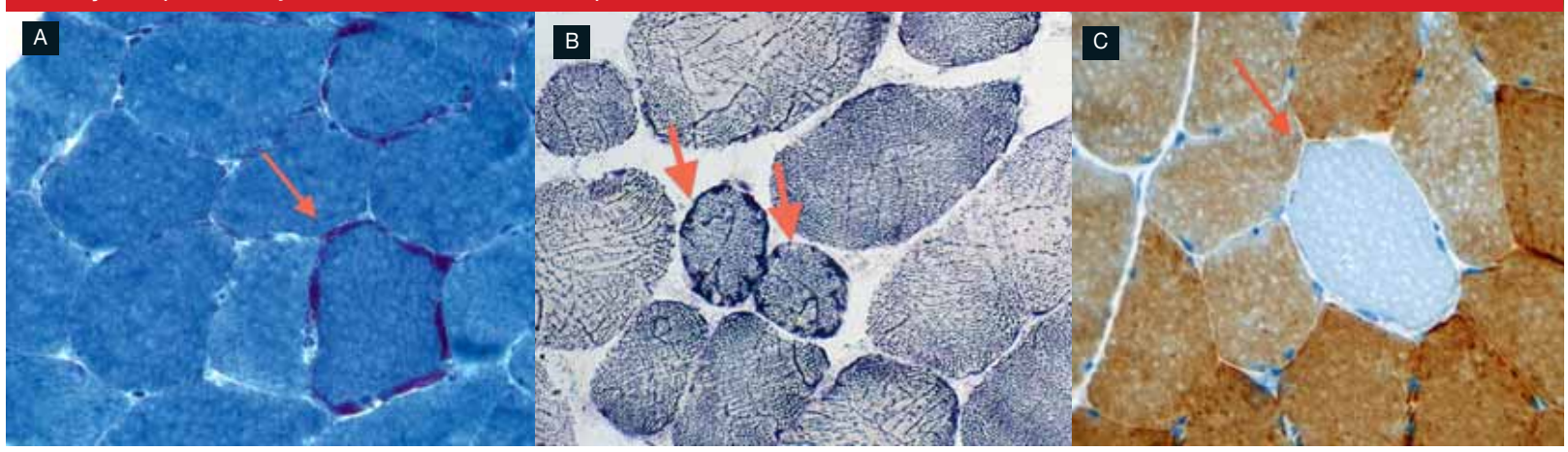
This is because mtDNA mutations typically disappear from blood with advancing age, as white cells have a high energy requirement and those with mtDNA mutations tend to be selected out. The preferred tissues for mtDNA genetic analysis include muscle, urine, or hair follicles. Muscle, as a post-mitotic tissue, is often best but may not be easily available, given the invasive nature of a muscle biopsy. Muscle can be used to identify point mutations as well as rearrangements and depletion.

Urine and hair follicles are readily available tissues for mtDNA analysis.

However, mutations may not always be present and not enough DNA is available in these types of samples to reliably detect deletions or depletion.

In addition, in our experience, mutational loads in hair or urine do not reliably correlate with clinical severity.

Figure 3 A: Muscle biopsy showing a typical 'ragged-red fibre' (arrow) on the modified Gomori trichrome stain. (Photo courtesy of Janice Brewer and Hwei Choo Soh.)
B: Muscle biopsy showing typical 'ragged-blue fibres' (arrows) on the SDH stain. (Photo courtesy of Roger Pamphlett.)
C: Muscle biopsy showing combined COX (brown) and SDH (blue) stain. When a muscle fibre is COX-negative (arrow), the underlying blue colour from the SDH stain can be clearly seen. (Photo courtesy of Janice Brewer and Hwei Choo Soh.)



Assessing the illness

If investigations are suggestive or diagnostic of a mitochondrial disorder, further assessment of the illness may be necessary. This may include review by a consultant neurologist, ophthalmologist, cardiologist, endocrinologist or gastroenterologist. Neurological manifestations such as stroke-like episodes, seizures, encephalopathy or muscle weakness may require further evaluation to confirm the diagnosis or exclude other causes.

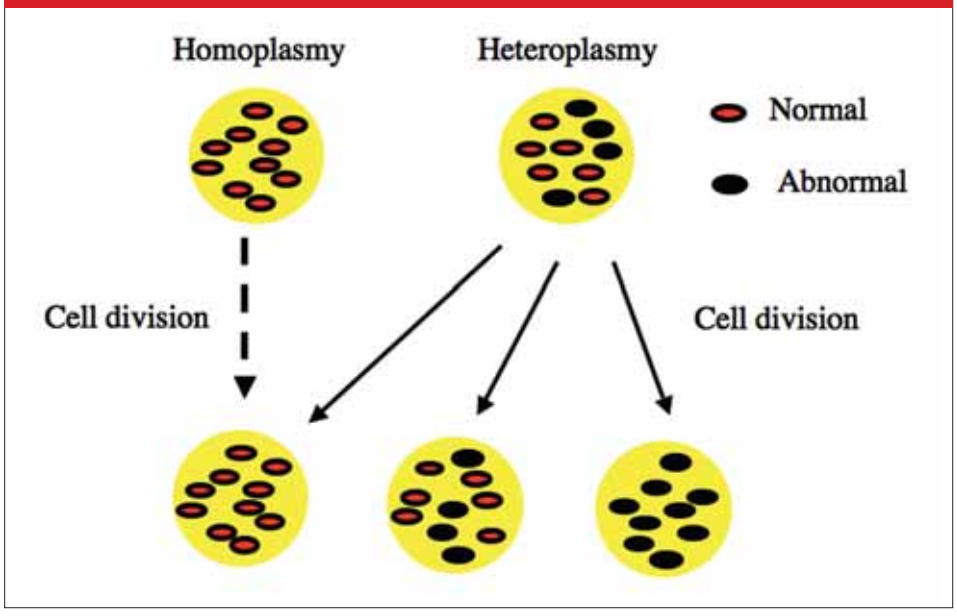
Confirming the presence of typical retinal pigmentary changes is very helpful for confirming the diagnosis of mitochondrial disease, but this usually does not require treatment, as these changes rarely lead to visual impairment.[5] Cardiological evaluation may be required to determine whether a cardiac arrhythmia is present and whether it requires treatment with antiarrhythmic agents or a pacemaker.

If cardiomyopathy is detected, other treatable or reversible causes (such as ischaemia) should be excluded.

Similarly, endocrinological review should evaluate the cause of the diabetes and exclude the presence of any other endocrinopathies.

Gastroenterological review with endoscopy to exclude other causes of upper or lower GI obstruction may be necessary before treating the motility problems seen in mitochondrial disease.

Figure 4: Schematic of cells with homoplasmic (normal) and heteroplasmic (abnormal) mtDNA. Mitochondria with normal mtDNA are represented in red and mitochondria with abnormal (mutant) mtDNA are represented in black. In the setting of homoplasmy, daughter cells will only contain normal mitochondria after cell division (dotted line). In the setting of heteroplasmy, daughter cells may contain different mutant loads from the parent cell after cell division (solid lines). This is referred to as mitotic segregation. Mutational load may change with cell division and thus be 'selected out' from some tissues (eg, blood) during life (see text).



Management

Symptomatic treatment

ONCE the diagnosis of mitochondrial disease has been made, symptomatic treatment can be started.

Neurological treatment

Stroke-like episodes are the most severe neurological manifestation of mitochondrial disease. They may be preceded by a clinical prodrome such as nausea, vomiting, headache, drowsiness, fever or seizures. Often metabolic stressors (eg, sleep deprivation, viral or bacterial infection, emotional stress, constipation) can be identified. Educating patients to recognise the beginning of a clinical prodrome and implementing lifestyle modifications to avoid or reduce these precipitating metabolic factors is helpful and may reduce the frequency of these attacks.

Prophylactic L-arginine has been reported to reduce the frequency of stroke-like episodes and is also useful in acute attacks.[6] Seizures may require treatment with anticonvulsants, but sodium valproate, and, to a lesser extent, phenobarbitone and phenytoin are contraindicated and best avoided.

Supervised tailored exercise programs may help symptoms of muscle fatigue. Regular physiotherapy may help optimise mobility, but there is little to offer patients that improves muscle strength.

Figure 5: Patient with mitochondrial disease showing bilateral ptosis (left panel) treated with silicon slings to correct ptosis (right panel).

Figure 6: Patient with mitochondrial disease showing external ophthalmoplegia resulting in skew deviation before (left panel) and after (right panel) treatment with surgical resection and retraction of extraocular muscles to correct alignment of the eyes. (Photos courtesy of Kimberly Tan.)

Eye symptoms

The most common ophthalmological abnormality is ptosis. Surgical correction is helpful to improve vision and reduce muscle strain (and subsequent development of headaches) from overactivity of the frontalis muscle. Correction with insertion of silicon slings (figure 5) is preferable to blepharoplasty, as it seems that patients develop fewer long-term complications (keratopathy or corneal ulceration) after surgery. Regular toileting with high-cellulose-content artificial tears is important to reduce the risk of corneal dryness or ulceration, particularly in the setting of ptosis or external ophthalmoplegia.

Diplopia from external ophthalmoplegia is present in up to 50% of patients with chronic progressive external ophthalmoplegia and may be corrected by fixation and alignment of the extraocular muscles (figure 6). While eye movement may be compromised during this procedure, only eye movement resulting in dysconjugate gaze is sacrificed.

Regular monitoring of intraocular eye pressure is recommended if optic neuropathy is noted on ophthalmological examination. Retinal pigmentary changes are typically asymptomatic, but if noticeable loss of dark/light adaptation is noted, protective eyeware (eg, sunglasses) should be used.

Hearing loss

Hearing loss is the most common clinical manifestations in adult patients with mitochondrial disease. If mild to moderate, digital hearing aids are helpful, but if hearing loss progresses to a profound level, insertion of cochlear implants may restore functional hearing, assuming that there is no central component to the hearing loss.

Cardiac manifestations

Cardiac arrhythmias can potentially be life-threatening, so regular (at least annual) electrocardiographs and Holter monitoring are mandatory if a patient has symptoms of palpitations. Patients with mitochondrial disease may also have hypertrophic or dilated cardiomyopathy. Cardiac failure should be treated on its own merits

and echocardiography should be performed annually if symptoms of cardiac failure are present.

Gastric dysmotility

Patients with mitochondrial disease often have constipation and may even present with pseudo-obstruction of the bowel. Motility studies will demonstrate which patients have impaired motility in the upper GI tract, lower GI tract or both. If gastric emptying studies indicate gastric dysmotility, agents such as domperidone may be helpful. For delays in colonic transit, treatment with osmotic laxatives such as magnesium salts (Epsom salts), lactulose (if not diabetic) and Macrogol 3350 (Movicol) are the most effective. Affected patients should avoid surgery for 'obstructive' symptoms, even if pseudo-obstructive episodes are prolonged, as bowel rest followed by gentle reintroduction of fluids prior to an oral diet usually resolves symptoms in even the severest of cases. However, other obstructive causes should be excluded, particularly if symptoms are severe.

Diabetes and insulin resistance

Diabetes mellitus due to mitochondrial disease is typically due to insulin resistance in the first instance. Although not specific, insulin resistance — as demonstrated by elevated levels of insulin to maintain normal blood sugar levels during an oral glucose tolerance test — is found in many patients before progression to overt diabetes.

A low-glycaemic-index diet or oral hypoglycaemic agents are usually adequate to treat diabetes mellitus in the early stages. However, metformin should be avoided in patients with mitochondrial disease, as it can induce lactic acidosis. Mitochondrial-related diabetes is not usually accompanied by the diabetic retinopathy seen in other longstanding or poorly controlled diabetic patients. Adult patients with mitochondrial diabetes often only require insulin in the advanced stages (with the exception of patients with Kearns–Sayre syndrome).

Metabolic

Patients may have lactic acidosis. This may be present at rest or during acute episodes of illness. Elevated lactate levels in the CSF (as detected by magnetic resonance spectroscopy) are associated with more severe clinical disease, but there is little treatment to offer patients with this condition. Trials with dichloroacetate showed that this agent could effectively reduce CSF lactate, but unfortunately this agent could not be tolerated due to the development of a severe peripheral neuropathy.[7]

Preventive strategies

There are no current treatments to stop the progression of, or cure, mitochondrial disease. Many agents, such as co-enzyme Q10, carnitine, vitamins C, D, E and K, riboflavin and idebenone, have been trialled with varying degrees of success. However, patients can adopt preventive strategies to minimise disease progression.

Tailored, judicious aerobic exercise is not only effective in improving symptoms of muscle fatigue and improving muscle energy supplies but may also improve muscle performance and delay the progression of insulin resistance to diabetes.

Given that hearing loss is a common clinical manifestation, our clinic at Royal North Shore Hospital recommends avoidance of occupational or excessive recreational noise exposure and regular use of ear protection.

Educating patients to recognise the clinical prodrome for stroke-like episodes and subsequently implementing lifestyle modifications to avoid or reduce these precipitating factors may be helpful to reduce the frequency of these attacks.

Given the chronic and sometimes unpredictable nature of this disorder, regular surveillance and monitoring of known and predictable complications can add to the wellbeing of the patient with mitochondrial disease.

Summary

MITOCHONDRIAL disease may present to clinicians of any medical speciality. The diagnosis of mitochondrial disease relies on the accurate assessment of clinical manifestations, family history, investigations (both supportive and diagnostic) and genetic studies. Mitochondrial genetic analysis may not be available at all centres, but is important for diagnosis and genetic counselling issues.

Given that mitochondrial disorders may follow maternal, autosomal dominant, autosomal recessive, X-linked and sporadic inheritance patterns, accurate diagnosis of the causative genetic mutation may be crucial for family planning issues. Prenatal genetic diagnosis may be helpful in families with disorders that follow Mendelian traits, but, given the transmission of mtDNA mutations can be unpredictable and that even small mutational loads can sometimes result in clinically severe disease, prenatal genetic diagnosis is fraught with danger in disorders caused by mutations in mtDNA.

Authors' case studies

Recurrent stroke-like episodes in an older woman

ALICE, 69, is a Caucasian woman who presented with recurrent stroke-like episodes. After noticing one week of increased somnolence, worsening of hearing loss, cognitive slowing, disorientation and progressive unsteadiness of gait, she developed difficulties with speech. Cerebral MRI showed a T2 high signal in the left parieto-temporal region. There was also evidence of old, small right temporal and left frontal infarcts, and mild to moderate cerebellar atrophy. MR spectroscopy showed an increased lactate peak in the right cerebellum.

Alice has a known history of progressive hearing loss since her 40s, poor balance since her 50s, and lifelong problems with intermittent constipation. She had a previous stroke-like episode four years earlier, having presented with dysarthria, ataxic gait, decreased level of consciousness, and complex partial seizures.

She has five children; the second child died from a stroke-like episode at age 45, while the other four children were oligosymptomatic, with clinical symptoms of hearing loss, muscle weakness and fatigue to varying degrees. Alice and all her children were found to carry the m.3243A>G mutation.

She remained encephalopathic with a decreased level of consciousness for the next three months, requiring supportive care in the high-dependency unit. Her hospital admission was complicated by hypothermia, metabolic acidosis, seizures and pseudo-obstruction of the bowel.

She required treatment with clonazepam, levetiracetam and lamotrigine for her seizures, intravenous L-arginine for her stroke-like episode, IV fluids and bowel rest for her intestinal pseudo-obstruction. She required total parenteral nutrition for six weeks before slow transition to nasojejunal feeds and thickened fluids.

On discharge she was wheelchair bound and required high-level assisted care. Over the next six months she began to mobilise, initially with the assistance of her husband, but one year after this exacerbation is now able to walk independently for short distances.

Comment

Alice had typical features of MELAS syndrome. Although classically this disorder presents at an earlier age, it is now well recognised that MELAS syndrome can present at any age, even well into late adulthood. Alice developed the typical clinical prodrome of increased drowsiness, worsening of hearing loss and neurological deterioration for a week before the onset of her focal neurological deficit.

An appropriately located lesion in the dominant temporo-parietal region was identified on neuroimaging. The clinical course required treatment with hospital admission and a high level of clinical care, but functional recovery occurs more often than not if patients are treated early enough and for long enough to allow neurological recovery.

Alice's family history is highly suggestive of a mitochondrial disease, with all maternally related relatives being affected to varying degrees. Most m.3243A>G mutation carriers remain oligosymptomatic, with only the minority (if any) of family members developing the full spectrum of severe mitochondrial disease.

Seizures in a young woman

Mary, a 21-year-old Caucasian university student, developed intractable, right-sided focal seizures involving the face, head, neck and thumb, hours after partying all night and drinking 30g of alcohol. Her non-consanguinous parents were both healthy. She was the youngest of five children. Her oldest brother had died at age seven from seizures and encephalitis.

On examination she had:

- Mild ptosis.
- External ophthalmoplegia.
- Dysarthria.
- Nystagmus.
- Proximal weakness.
- Dysdiadochokinesis.
- Past pointing in the upper and lower limbs.
- An ataxic gait, associated with hyporeflexia and mild sensory loss in the lower limbs.

Cerebral MRI/MR spectroscopy at the time showed fluctuating high signals on T2/FLAIR images in the grey and white matter in the occipital and parietal lobes, and pre- and post-central gyrus, associated with a large lactate peak on MR spectroscopy in the precentral gyrus. Serum lactate was just above the upper limit of normal. EEG initially showed occipital epileptiform discharges.

Nerve conduction studies revealed a sensorimotor peripheral neuropathy, with no evidence of a myopathy, and muscle biopsy of the vastus lateralis showed normal histology.

Mary was electively intubated for nine days, and multiple agents, including clonazepam, sodium valproate and levetiracetam, were used in an attempt at seizure control. Sodium valproate exacerbated the seizures. She was eventually discharged after a three-month admission, requiring multiple anticonvulsants to control her seizures.

Muscle strength and co-ordination slowly improved with extensive long-term rehabilitation. Mary initially required two walking sticks to mobilise, and continued to slowly improve over the subsequent two years, eventually achieving independence in mobility. Her anticonvulsant therapy was slowly reduced to small doses of clonazepam and levetiracetam.

Comment

Mary has a cluster of clinical manifestations suggestive of mitochondrial disease caused by mutations in the polymerase gamma (*POLG*) gene. The sudden onset of seizures, (presumably exacerbated by sleep deprivation and alcohol intake), the decline after treatment with sodium valproate, and associated ataxia, peripheral neuropathy, ptosis and external ophthalmoplegia are typical of this disorder.

These features may also be observed in mtDNA-related mitochondrial disease, but the family history of unaffected parents and one out of the other four siblings is suggestive of an autosomal recessive disorder, rather than a maternally transmitted one.

Mary will need constant monitoring of her anticonvulsant therapy and will need to reduce/avoid metabolic stressors that may exacerbate her acute onset of seizures. Patients with *POLG* mutations who have been admitted to intensive care units for intubation often have intractable epilepsy and require lifelong treatment with anticonvulsants.

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Further reading

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- Sue CM, et al. Mitochondrial gene mutations and diabetes mellitus. *Lancet* 1993; 341:437-38.
- Kaufmann P, et al. Cerebral lactic acidosis correlates with neurological impairment in MELAS. *Neurology* 2004; 62:1297-302.
- Trenell MI, et al. Aerobic exercise and muscle metabolism in patients with mitochondrial myopathy. *Muscle and Nerve* 2006; 33:524-31.

Online resources

- MITOMAP: A compendium of polymorphisms and mutations of the human mitochondrial DNA: www.mitomap.org

GP case

PROVIDED BY THE AUTHORS

Case study

A 34-YEAR-old mechanic recently moved into the area and is seeking a new GP. He lives with his new partner and her daughter and does not have children of his own. He has aspirations to join the Army Reserve.

The first thing you notice is his bilateral ptosis, which, on history, does not deteriorate much over the course of the day, and is not associated with dysarthria, dysphagia or other significant muscular weakness. Developmentally, he was born normal and was well as a child. He ran and sprinted well, but noticed by late high school years that his exercise endurance was poor.

He was noted to have an in-turned right eye at age 18 and had operations for medial and lateral recti adjustments at about 26 and again at 30. He has diplopia of objects at a certain distance, and finds that he sometimes has to close one eye when he rides his motorbike, which is his favourite hobby. Otherwise, he is able to run 3km, with just 2-3 short periods of walking in between.

He noticed in the last 1-2 years that his arm would fatigue with brushing his teeth at times. He has no bulbar or respiratory symptom, and no diarrhoea or constipation. He denies any hearing problem or migraine. There is no family history of others with ptosis or ophthalmoplegia, and his two younger brothers aged 33 and 31 are both well.

On examination he is a muscular man, with right-sided asymmetrical ptosis exceeding that on the left side. In the primary position the ptosis is obscuring half his right pupil and is just to up to the edge of the left pupil. Pupils are equal and reactive to light, and fundoscopy is normal through undilated pupils.

His extraocular movements are restricted: the left eye can adduct and look down, but has very limited up-gaze, and almost no abduction. The right eye can abduct and look down well but has even more limited up-gaze, and minimal adduction.

Tone, power and reflexes of his upper and lower limbs are normal and symmetrical, with no proximal weakness detectable. Gait is normal and he is able to hop on alternate feet, tip-toe, heel, tandem and squat fully. Reflexes are symmetrical and normal. Sensation to cold and vibration as well as co-ordination are intact.

Initial investigations showed a CK of 394 U/L (normal range 1-174 U/L). He has been seen by a number of ophthalmic surgeons, who raised the possibility of a mitochondrial disorder as the underlying cause.

Questions

Is this a typical presentation for mitochondrial disorders?

Yes, patients with isolated ophthalmic signs of ptosis, and ophthalmoplegia are likely to have chronic progressive external ophthalmoplegia (CPEO).

How would you investigate this patient for a possible underlying mitochondrial disorder?

Investigations would involve baseline studies to screen organ systems that can be commonly affected by mitochondrial dysfunction: baseline metabolic screen with electrolytes, LFTs , FBC, CK, lactate; ECG and echocardiogram for cardiac involvement, and ongoing ophthalmic review.

Referral to a neurologist may also help further discussion as to whether nerve conduction studies and/or electromyogram and muscle biopsy for further investigation might be warranted, given his exertional-related muscle fatigue.

How would you advise him on the chances of potentially passing the condition onto his children?

This is difficult. In the absence of a family history, isolated CPEO is most likely due to a sporadic deletion in the mitochondrial DNA, which will not be passed on to his offspring. However, both mitochondrial and nuclear mutations can be the culprit, and without a genetic diagnosis, we cannot be sure of the risk.

How would you advise him on his aspirations to join the Army Reserve and on his driving?

We would advise on lifestyle modification in the first instance, and discuss with the patient the potentially unpredictable involvement of other organ systems with time, although mitochondrial conditions are generally chronic and very slowly progressive. Joining the Army Reserve may not be easy, given the existing symptom of muscle fatigue already.

As for driving, we will be recommending further ophthalmological review to advise on whether it is safe to continue driving with his existing ptosis and ophthalmoplegia.

How to Treat Quiz

Mitochondrial disease — 25 March 2011

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

ONLINE ONLY

www.australiandoctor.com.au/cpd/ for immediate feedback

1. Which TWO statements are correct?
a) Severe or fatal forms of mitochondrial disease (MD) are more frequent in children than in adults
b) Patients with the chronic, less severe forms of MD are more likely to present to GPs
c) MD is very rare
d) MD is caused exclusively by mutations in mitochondrial DNA (mtDNA)

2. Which TWO statements are correct?
a) Mutations in mtDNA can be maternally transmitted to offspring of either sex
b) Mutations in mtDNA can be passed on by males
c) Mutations in nuclear DNA resulting in MD can be inherited in an autosomal recessive or autosomal dominant pattern
d) MD tends to affect only one organ in an affected individual

3. Which TWO statements are correct?
a) The most commonly affected organs in MD include brain, muscle, heart, retina and cochlea
b) The clinical onset of an inherited form of MD is usually in infancy
c) Sensorineural hearing loss in MD is typically asymmetrical and in younger patients
d) Stroke-like syndromes in MD are associated with abnormalities in a particular vascular territory on neuro-imaging and a poor clinical recovery

4. Which TWO statements are correct?
a) Stroke-like syndromes in MD tend to be preceded by a typical clinical prodrome
b) Sodium valproate is the anticonvulsant of choice for the seizures of MD
c) The retinal pigmentary changes seen in MD are usually sight-threatening
d) The ptosis of MD is asymmetrical and slowly progressive, with little diurnal variation

5. Which TWO statements are correct?
a) The diabetes of MD is associated with insulin insensitivity
b) The diabetes of MD is associated with early onset, severe retinopathy and peripheral neuropathy
c) Metformin is appropriate for the control of the diabetes of MD
d) The diabetes of MD is easily controlled with oral hypoglycaemic agents

6. Which TWO statements are correct?
a) The pathological hallmark of MD is the 'ragged-red fibre' seen on muscle biopsy tissue, reflecting mitochondrial proliferation in abnormally functioning muscle fibres
b) In individuals with mutant mtDNA the percentage of mutant mtDNA in any cell may vary between zero and 100%
c) The degree of clinical severity is not proportional to the amount of abnormal mtDNA in a tissue or organ
d) White blood cells are the ideal tissue for mtDNA analysis

7. Which THREE statements are correct?
a) Muscle is the preferred tissue for mtDNA genetic analysis
b) If muscle tissue is not available, hair follicles and urine are alternative tissues for precise mtDNA analysis
c) Stroke-like episodes in MD can be associated with metabolic stressors (eg, sleep deprivation, infections, emotional stress, constipation)
d) Prophylactic L-arginine may reduce the frequency of stroke-like episodes and may also be useful in acute attacks

8. Which TWO statements are correct?
a) Blepharoplasty is the preferred surgical treatment for the ptosis of MD
b) Diplopia from the external ophthalmoplegia of MD rarely occurs
c) Diplopia may be corrected by fixation and alignment of the extraocular muscles
d) Retinal pigmentary changes may be associated with loss of dark/light adaptation

9. Which THREE statements are correct?
a) Patients with MD and palpitations are at risk of life-threatening arrhythmias
b) Patients with MD may develop hypertrophic or dilated cardiomyopathy
c) Pseudo-obstruction of the bowel in patients with MD is best treated surgically
d) Tailored use of aerobic exercise may improve muscle performance in people with myopathy

10. Which TWO statements are correct?
a) Avoidance of occupational or excessive recreational noise exposure is recommended in people with MD
b) Prenatal genetic diagnosis for MD is crucial for family planning
c) Prenatal diagnosis of the type of inheritance of mtDNA mutations is straightforward and predictable
d) In prenatal genetic diagnosis, determining the amount of mtDNA is highly predictive of clinical disease in the offspring

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2011-13 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

HOW TO TREAT Editor: **Dr Giovanna Zingarelli**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Giovanna Zingarelli**

NEXT WEEK The next How to Treat is the first part of a two-part series on lymphoproliferative disorders, in particular aggressive non-Hodgkin lymphoma and Hodgkin lymphoma. The authors are **Dr Piers A Blombery**, advanced trainee in clinical and laboratory haematology, division of cancer medicine, Peter MacCallum Cancer Centre, East Melbourne; **Associate Professor Andrew Wirth**, radiation oncologist, division of radiation oncology, Peter MacCallum Cancer Centre; and **Professor H Miles Prince**, consultant haematologist, division of cancer medicine, Peter MacCallum Cancer Centre, and Cabrini Hospital, Malvern, Victoria.