

## Information for Patients with Maternally Inherited Diabetes & Deafness (MIDD)

### Background

The key identifying features of maternally inherited diabetes and deafness (MIDD), as the name suggests, are the presence of diabetes and/or deafness that are inherited by the children of an affected mother but not by the children of an affected father.

Maternally Inherited Diabetes and Deafness (MIDD) is caused by a disease-causing variant in the mitochondrial DNA (the most common variant is known as m.3243A>G) and was first identified in 1992. As all the mitochondria we inherit are inherited from our mothers the genetic variant is passed down from an affected mother to all her children. However with these particular genetic variants there is considerable variation in how much people inheriting these variants are affected. This means some children will only have deafness or only have diabetes or may have no problems at all. Fathers who have MIDD can be reassured that they will not pass the condition on to their children as all mitochondria are inherited from the mother. This means that although children of both sexes will inherit the affected mitochondria only women will pass the condition on to the next generation.

It is important to make a definite genetic diagnosis of MIDD as this helps diagnose the cause of the deafness and diabetes, helps with the treatment, guides which additional tests are recommended and helps advise other members of the family.

### Why are mitochondria important?

The main purpose of mitochondria is to generate energy within the cells by producing a substance called ATP this allows the cell to perform their functions correctly. MIDD tends to affect the organs where cells are most active such as the pancreas and the cochlea (in the ear) and in some cases the retina (the back of the eye), the muscles, kidneys and brain.

### What about the diabetes?

MIDD affects up to 1% of all diabetes but often goes unrecognised and is misdiagnosed as either Type 1 or Type 2 diabetes. The average age at which diabetes develops is 37 years but it ranges 11 years to 68 years of age and often needs insulin treatment. Those with MIDD are usually of normal body weight. MIDD leads to diabetes because it reduces the amount of insulin made by the beta cells in the pancreas.

The majority of people with MIDD can, at the start, be treated with dietary changes or tablets. However insulin therapy is usually needed within 2 years of diagnosis reflecting the reduced insulin secretion. Metformin, a commonly used treatment in diabetes is probably best avoided as Metformin is known to interfere with mitochondrial function and the risk of lactic acidosis may be increased although this has not been reported to date.

### What about the deafness?

The deafness is a result of the nerve to the ear being affected in both ears and develops in around 75% of people with MIDD who also have diabetes. The hearing loss typically develops in young adulthood (although may develop as children or later in life) and usually is present before the diabetes. The deafness is more common in men than women and men have more severe and rapidly progressive hearing loss. Half of those with hearing loss suffer a rapid decline in their hearing while the remainder have slowly progressive hearing loss over many years. Hearing loss is variable, but can require bilateral hearing aids; although it seldom leads to total deafness. Typically the impaired hearing relates to the inability to hear high frequencies. Early detection of deafness by periodic audiograms in children is important and prompt antibiotic treatment of any ear infections is also logical. Cochlear implants have been successful in cases of severe hearing loss in MIDD.

### Other features that can occur in MIDD

In keeping with other mitochondrial disorders, MIDD can, in some patients, result in other medical problems apart from diabetes and deafness. As with the diabetes and deafness there is considerable variation in the extent to which these occur. Even within one family individuals may have varying numbers and varying severity of clinical features with some having diabetes alone and others having many organs affected.

### Other features sometimes associated with MIDD:

- Short stature is common and MIDD patients are frequently thin (body mass index less than 20).
- Heart problems: It is important to screen all MIDD patients in case they have heart involvement which can cause serious problems with the rhythm of the heart. This would include an ECG (and usually an echocardiogram) at age of 35 years, or earlier if there are any clinical features or history of problems in any family members. In high risk individuals this should be conducted annually. Statin medications should be used in those with cardiovascular risk factors.
- Myopathy (Muscle weakness): muscle problems of either weakness or cramps may be present in around 40% of cases of MIDD. This generally involves proximal muscles (shoulders, buttocks and thighs) which are used when climbing stairs and presents as exercise induced muscle cramps or weakness.
- Renal (kidney) disease: Protein is commonly found in the urine of MIDD patients, particularly in women. Renal disease sometimes presents before the diabetes or deafness. The most common renal problem is called focal segmental glomerular sclerosis and some patients develop end stage renal failure. Renal function should be monitored annually as part of the routine diabetes check up. Tablets called ACE inhibitors should be started early due to the high degree of renal complications and good blood pressure control is also important.

- Retina (back of the eyes): Problems can include macular dystrophy including pigmented lesions and thinning of the epithelium. Visual symptoms are rare but can include visual loss, night blindness, blind spots and dislike of bright lights. Most patients with this macular disease have had diabetes for more than 40 years and are aged over 40 years. Eye screening is important and should be carried out annually.
- Strokes: In young adults less than 45 years of age stroke may occur in around 1% of patients.
- Gastrointestinal disease: Gastrointestinal complaints may be quite common in MIDD, particularly constipation.

### Genetic testing

Genetic testing should be conducted to confirm the diagnosis and should be performed using the first pass of an early morning urine sample.

### Family follow up

Maternal adult relatives of patients with MIDD are at risk of developing diabetes, hearing loss, renal failure or heart problems so long term follow up of relatives is advisable.