Newcastle Mitochondrial Disease Guidelines

Diabetes Mellitus in Adult Mitochondrial Disease:

Screening and Initial Management

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Introduction

Diabetes mellitus is a common endocrine feature of patients with mitochondrial disease, predominantly due to its association with the m.3243A>G mutation, the most common heteroplasmic mtDNA mutation associated with human disease. The m.3243A>G mutation can result in the phenotype of maternally inherited diabetes and deafness (MIDD), mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) or chronic progressive external ophthalmoplegia (CPEO) but there is often considerable overlap between phenotypes and diabetes can occur in all three. Diabetes forms part of the established phenotype in a number of much rarer mtDNA mutations (eg m.14709T>C), but can occur in most mitochondrial disorders.

Clinical presentation varies considerably, ranging from ketone positive, insulin dependent diabetes through to classical non-insulin dependent diabetes. There is an increased risk of gestational diabetes (GDM). In patients with the m.3243A>G mutation, diabetes usually develops in the early adult years peaking in the late 30s. It is most common for the clinical presentation to mimic type 2 diabetes, but patients are rarely obese and in fact usually have a low body mass index (BMI). Most patients progress rapidly to insulin dependency over a period of 2 to 4 years, as a result of pancreatic islet cell dysfunction. Autoimmune markers of type 1 diabetes (GAD and islet cell antibodies) are generally absent.

We recommend annual screening for the development of diabetes mellitus in any patient known to have mitochondrial disease, or in patients at risk of developing mitochondrial disease by virtue of pedigree analysis or known carrier status. Attendance at a specialist mitochondrial centre is recommended to oversee the management of multisystem disease and to provide guidance to the local diabetes services.

Patient-centred Care

This guideline offers expert consensus advice on the care of patients with mitochondrial disease. The care of these patients and their treatment should take into account patients' needs and preferences. People with mitochondrial disease should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines –'Reference guide to

consent for examination or treatment' (2001), available from www.dh.gov.uk. Healthcare professionals should also follow the code of practice accompanying the Mental Capacity Act (a summary of this code is available from www.dca.gov.uk/menincap/bill-summary.htm).

Good communication between healthcare professionals and patients is essential. It should be supported by the best available information tailored to the patients' needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English. If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care. Families and carers should also be given the information and support they need.

Key Priorities for Implementation

In view of the diverse phenotypes of mitochondrial disease, we recommend that all patients diagnosed with mitochondrial disease should have annual screening for diabetes mellitus. This guidance also applies to those asymptomatic carriers deemed to be at significant risk of developing disease. Following diagnosis, all patients should be referred to the local diabetes service for diabetes education, support, and to start glucose monitoring. Attendance at a specialist mitochondrial centre is recommended to oversee the management of multisystem disease and to provide guidance to the local diabetes services. This document is intended for guidance only, and should not replace patient-specific management plans influenced by other factors such as patient preference and pragmatism.
The guidance is informed by the National Institute of Health and Clinical Excellence (NICE): www.nice.org.uk/diabetes

1. Screening for Diabetes in Patients with Mitochondrial Disease

1.1. Asymptomatic patients: HbA1c is recommended for patients as follows:

1.1.1. All patients, at the time of diagnosis.

1.1.2. All patients, at an interval of 12-months

1.2. Symptomatic patients: symptoms of polydipsia and/or polyuria should prompt a random glucose and HbA1c measurement.

1.3. Pregnancy: mitochondrial disease increases the risks of gestational diabetes (GDM). This is particularly true of genotypes associated with a diabetic phenotype (e.g. m.3243A>G mutation). Because of this increased risk we recommend an oral glucose tolerance test (OGTT) as follows:

1.3.1. Previous GDM: in accordance with NICE guidelines we recommend OGTT at 16 weeks and again at 24-28 weeks if the 16 week OGTT was normal (www.nice.org.uk/guidelines CG63).

1.3.2. High risk genotypes: women carrying mitochondrial mutations associated with a diabetic phenotype (e.g. m.3243A>G, m.14709T>C) should be screened by OGTT at 20 weeks gestation. This should also be offered to women who have a strong family history of diabetes associated with inherited mitochondrial disease.

1.3.3. Other risk factors: women not falling into the two categories above should be offered OGTT at 24-28 weeks gestation if they have additional risk factors for GDM (e.g. BMI > 30kg/m^2, ethnic background etc) as per NICE guidelines (www.nice.org.uk/guidelines CG63).

1.3.4. Increasingly metformin is being used in gestational diabetes however in patients with mitochondrial disease metformin risks worsening or precipitating lactic acidosis so is best avoided. We recommend the use of insulin therapy if required.

1.4. Patients/carers should be educated as to the risk of diabetes and warning symptoms that might require further investigation.

2. **Diagnosis of Diabetes in Patients with Mitochondrial Disease**

2.1. Diagnosis of diabetes is based on WHO recommendations and does not differ in mitochondrial disease.

2.1.1. Asymptomatic patients: an HbA1c > 42 mmol/mol (6.0%) should prompt a confirmatory diagnostic test. This can be either a fasting plasma glucose or an oral glucose tolerance test (OGTT). A fasting plasma glucose ≥ 7 mmol/l and/or a 2 hour OGTT plasma glucose ≥11.1 mmol/l are diagnostic of diabetes. Impaired glucose tolerance (7.8mmol - 11.0 mmol) is monitored using annual HbA1c measurements.

2.1.2. Symptomatic patients: for patients presenting with polydipsia and/or polyuria, a random plasma glucose ≥11.1 mmol/l is diagnostic of diabetes. A raised HbA1c should be investigated as in 2.1.1. above if the random glucose measurement is not diagnostic.

2.2. Assessing insulin dependence:

2.2.1. Urinary ketones: a positive ketone test points to insulin deficiency and the need for insulin therapy. Patients with mitochondrial diabetes have a high risk of insulin dependence. Recent

vomiting/starvation can result in falsely raised ketones. Under these circumstances it is wise to stabilize the patient on insulin and check C-peptide later (see 2.2.2)

2.2.2. C-peptide: a random C-peptide level helps to gauge pancreatic reserve.

2.2.3. Anti-GAD antibody: a positive anti-GAD titre raises the possibility of coincidental autoimmune Type 1 diabetes.

3. Glycaemic Management in Mitochondrial Diabetes

Following diagnosis, the patient needs to be referred to the local diabetes service for diabetes education, support, and to start glucose monitoring. The purpose of treatment is to relieve symptoms, ensure safety and prevent complications. The target HbA1c needs to be agreed based upon personal circumstances, but as a general rule we aim for an HbA1c between 48 and 57 mmol/mol (6.5- 7.5%).

3.1. Insulin dependence: features that point to insulin dependence include:

- Short history (weeks) of osmotic symptoms (polydipsia and/or polyuria) and weight loss
- Ketone positive
- C-peptide below the normal range

3.1.1 Insulin therapy: the presence of one or more of these features point to the need for immediate insulin therapy. The choice of insulin regimen should be guided by the patient's capabilities and needs in relation to lifestyle, occupation and daily living.

3.1.2 Low BMI: patients with a low BMI generally need to start with lower dosages and titrate upwards.

3.2 Non-insulin dependence: features that point to non-insulin dependence include:

- Asymptomatic, only identified through screening
- Longer history (months) of osmotic symptoms with no clear weight loss
- Ketone negative
- C-peptide in the normal range or above

These patients can be treated using an adaptation of the Type 2 diabetes guidelines (www.nice.org.uk/guidelines_CG87):

3.2.1 Lifestyle: Most patients are not obese but education regarding lifestyle change including healthy eating and regular exercise where possible should be provided.

3.2.2 Metformin: as a general rule, it is best to avoid metformin because of the enhanced risk of lactic acidosis. In most cases alternative agents are available (see below). Metformin may be used with caution under specialist supervision, but lactate levels should be monitored throughout treatment and patients (and GPs) educated as to scenarios where they should contact their specialist (or GP) to consider stopping the drug (eg acute infection).

3.2.3 Sulphonylureas: as most patients are not obese, the 1st line agent of choice is a sulphonylurea. There is clinical evidence to suggest that patients with mitochondrial disease can show sulphonylurea sensitivity (unpublished clinical observation) with the associated

increased risk of hypoglycaemia. For this reason we recommend prescribing a sulphonylurea with a short half-life (eg tolbutamide, glipizide or gliclazide) and starting at a low dose and titrating upwards. Because of the risk of hypoglycaemia, we recommend patients be offered home blood glucose monitoring.

3.2.4 Second-line agents: failure to achieve the glycaemic target leads to the addition of a second agent. This can be a DDP4 inhibitor (eg sitagliptin or saxagliptin) or pioglitazone. However, the latter is only generally used in patients were there is evidence of fatty infiltration of liver, and is best avoided particularly in view of the increased risk of cardiac dysfunction in patients with mitochondrial disease.

3.2.5 GLP-1 analogues: the GLP-1 analogues (eg exenatide or liraglutide) are particularly useful in those patients with obesity +/- fatty infiltration of the liver, and should be used according to current prescribing guidelines. In particular, they should not be used if there is a personal and/or family history of pancreatitis.

3.2.6 Insulin therapy: failure to achieve the glycaemic target despite combination therapy points to insulin therapy using the principles described above.

3.2.7 Ubiquinone: despite reports of benefit in mitochondrial diabetes there is currently insufficient evidence to recommend routine use in this context.

4. Screening for Complications of Mitochondrial Diabetes

As the diabetes can present relatively early in the patient's life and progress rapidly to insulin therapy, there is a need to offer standard systematic diabetes care and screening for complications. Annual screening should include:

4.1. Retinal screening for diabetic eye disease

4.2. Podiatry assessment (peripheral pulses and sensation) for diabetic foot disease

4.3. eGFR and urinary albumin creatinine ratio (ACR) for diabetic kidney disease

4.4. Blood lipid profile, blood pressure and LFTs (screening for raised ALT consistent with fatty liver).

5. Management of Cardiovascular Disease (CVD) Risk Factors

CVD risk factors need to be managed actively as in other diabetic patients. Cerebral, cardiac and renal function may be affected by mitochondrial diseases itself so it is important to keep additional vascular insults to a minimum.

5.1. Lipid lowering: patients with a raised non-HDL cholesterol (>4mmol/l) need a lipid lowering agent. The 1st line agent should be a statin. As patients with mitochondrial disease have a high likelihood of a pre-existing myopathy, a baseline creatine kinase (CK) is recommended before starting treatment and a low dose prescribed with a view to titrating up. Patients should have their CK repeated on treatment after 3 weeks and if patients report new weakness or myalgia. For those patients that cannot tolerate a statin, other possible treatments include ezetimibe and fibrates such as fenofibrate. However, these too carry the risk of low grade myopathy. In most cases we feel the benefits of lipid lowering agents (where indicated) outweight the potential risks, with the possible exception of patients who have previously suffered episodes of rhabdomyolysis.

5.2. Blood pressure needs active management because of the high risk of renal disease and cardiac disease. The target BP is < 140/80 but should be lower (<130/70) in patients with evidence of renal/cardiac dysfunction. ACE inhibitors are the 1st line agents, but other agents can be added as required according to BP management guidance.

5.3. Patients should be advised to stop smoking.

6. Additional considerations

6.1. Additional support: diabetic education and monitoring needs to be tailored to the individual. Some patients with mitochondrial disease may have learning difficulties or dementia. Others may be blind or deaf. In others, myoclonus or ataxia may necessitate help with blood glucose monitoring or insulin administration.

6.2. Feeding and nutrition: It is important to consider the effects of reduced oral intake in some patients, both in general but also during transient illness. Some patients may have a relatively low calorific intake or have to eat small but frequent meals due to gastrointestinal dysmotility or dysphagia. Others may have PEG feeding. Occasionally paralytic ileus or encephalopathy may limit oral intake until the event has resolved.

6.3. Kidney/pancreas transplant: progression to renal failure and dialysis is a real and challenging risk in mitochondrial diabetes. For those patients deemed suitable for kidney transplantation, consideration should be given to the possibility of simultaneous kidney/pancreas or pancreas after kidney transplantation. This is because the removal of the diabetes improves the survival of the kidney grafts, and also the grafts should survive longer than those given to patients with Type 1 diabetes who are at risk of graft damage due to the on-going autoimmune process.

6.4. Multisystem disease: neuropathy, nephropathy and cardiomyopathy may occur due to mitochondrial disease alone, but it is important that this is not assumed to be the case and those treatable causes such as poor glycaemic control are addressed. Where possible it is helpful to try to ascertain the cause of end organ disease, whether diabetic, mitochondrial, or a combination of the two.

6.5. Pregnancy: Women with diabetes who are planning to become pregnant should be advised to take folic acid (5 mg/day) until 12 weeks of gestation to reduce the risk of having a baby with a neural tube defect. This is in accordance with NICE guidelines (CG63).

7. Notes on the scope of this guidance

The guideline was developed by experts in mitochondrial disease and diabetes based at the Newcastle Mitochondrial Centre and the Newcastle upon Tyne Hospitals NHS Foundation Trust. This group specified which aspects of the screening, diagnosis and management of diabetes in patients with mitochondrial disease was to be included and excluded.

7.1 Audience

These guidelines are intended for use by the following people or organisations:

- all healthcare professionals
- people with mitochondrial disease and their carers
- patient support groups
- commissioning organisations
- service providers

7.2 Guideline Limitations

Limitations of these guidelines include:

- Lack of a firm evidence base for reference. Guidelines in mitochondrial disease are currently unable to adopt the evidence-based approach used by organisations such as NICE, and at present are predominantly based on consensus expert opinion.
- Overall, the evidence review identified no randomized controlled trials or high quality case-control or cohort studies.
- Further studies are needed (see research recommendations below).
- Specialist Mitochondrial Centres are located in Newcastle, London, and Oxford. The development of these centres represents an important advance in the care of patients with mitochondrial disease.

8. Implementation

Integral to this guideline is publication of the benefits of access to a specialist clinic with experience in mitochondrial disease.

- Specialist mitochondrial clinics are provided by selected centres with the support of the NHS Highly Specialised Services. The accumulation of experience within these centres, and access to focussed multi-disciplinary team input is designed to offer the best available care for patients with mitochondrial disease.
- Centres are currently located in Newcastle, London and Oxford.
- Patient education is an important aspect of the initial consultation, but also as a vital component of future care. We aim to provide an understanding of the role of diabetic screening, and the potential impact of screening and early intervention on prognosis.
- Access to specialist clinics allows relevant genetic counselling and family tracing to facilitate the identification of those at risk of developing disease.
- Close liaison is required both with diabetic services at the specialist centre itself, but also local diabetic services who may be closely involved with future follow up and management of patients where frequent central review is impractical.

9. Research recommendations

9.1 Natural history studies

Many studies exist offering varying estimates of the prevalence of mitochondrial diabetes, or the proportion of diabetes attributable to mitochondrial DNA mutations. Further studies are required to clarify the progression, end organ involvement, response to treatment and overall morbidity/mortality attributable to mitochondrial diabetes.

9.2 Pancreatic/renal transplant outcomes

Pancreatic transplant is usually performed at the same time, or following renal transplant for end stage diabetic nephropathy. Pancreatic transplants in mitochondrial disease should in theory last longer than those in patients with autoimmune forms of type 1 diabetes where autoimmune damage to the graft may occur. Outcomes of pancreatic (and renal) transplants should be assessed.

10. Updating the guideline

The Newcastle Mitochondrial Guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence every 2 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may update the guidance prior to any scheduled changes.

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Appendix A: The Guideline Development Group

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