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Review

Endocrine disorders in mitochondrial disease

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ABSTRACT

Endocrine dysfunction in mitochondrial disease is commonplace, but predominantly restricted to disease of the endocrine pancreas resulting in diabetes mellitus. Other endocrine manifestations occur, but are relatively rare by comparison. In mitochondrial disease, neuromuscular symptoms often dominate the clinical phenotype, but it is of paramount importance to appreciate the multi-system nature of the disease, of which endocrine dysfunction may be a part. The numerous phenotypes attributable to pathogenic mutations in both the mitochondrial (mtDNA) and nuclear DNA creates a complex and heterogeneous catalogue of disease which can be difficult to navigate for novices and experts alike. In this article we provide an overview of the endocrine disorders associated with mitochondrial disease, the way in which the underlying mitochondrial disorder influences the clinical presentation, and how these factors influence subsequent management.

Contents

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1. Introduction

The term mitochondrial disease refers to a heterogeneous group of multi-system disorders characterised by mitochondrial respiratory chain deficiency in which neurological involvement is often prominent (McFarland et al., 2010; Ylikallio and Suomalainen, 2012). Numerous distinct genotypes give rise to varied and overlapping phenotypes. Endocrine dysfunction is a frequent feature, predominantly due to the prevalence of diabetes mellitus associated with the m.3243A > G mutation, the most common heteroplasmic mtDNA mutation associated with human disease (Schaefer et al., 2008). Other forms of endocrine disease are described less frequently, occurring in numerous mitochondrial disorders due to either mutations within mtDNA or associated with nuclear-driven disorders of mtDNA maintenance. For many mutations, reports of endocrine disease are so rare as to challenge the hypothesis that they are mediated by defects of oxidative phosphorylation at all, and merely represent the background prevalence of endocrine disease in a well studied population. There is a danger that associations based on single case reports (sometimes dating back 20 years and beyond) are repeatedly cited in reviews such as this, perpetuating an unproven connection with mitochondrial disease. Analysis of large patient cohorts are likely to be key, and while this dilemma may not be readily resolved for rare mutations, it should be feasible to answer the question in more prevalent disorders. As ever, further studies are needed in this area.

This review summarises the range of endocrine involvement in mitochondrial disease and the genotypes and phenotypes in which these occur. We offer insights from a specialist mitochondrial clinic as to the use of pattern recognition and pedigree analysis in the diagnosis and subsequent management of these complex patients and their families.

2. Mitochondrial biochemistry and genetics

Mitochondria are essential organelles, present in all nucleated mammalian cells, whose main role is to produce ATP by the process of oxidative phosphorylation (OXPHOS). The OXPHOS machinery is made up of ~90 different polypeptides, organised into five transmembrane complexes. The oxidation of foodstuffs generates electrons which are shuttled to oxygen along the first four respiratory chain complexes whilst protons are pumped across the inner mitochondrial membrane from the matrix to the intermembrane space forming an electrochemical gradient which is harnessed by ATP synthase, to phosphorylate ADP to form ATP. Mitochondrial function and biosynthesis is under the dual genetic control of both the mitochondrial genome – encoding just 13 proteins and 37 gene products in total and the nuclear genome, which encodes for some 1400–1500 mitochondrial proteins. Whilst mutations within either DNA molecule can cause a respiratory chain defect, the unique genetic rules which govern the behaviour of the mitochondrial genome provide some insight into the phenotypic heterogeneity which particularly characterise mtDNA disorders.

Several recent reviews have detailed the importance of mtDNA mutations in human disease (Greaves et al., 2012; Schon et al., 2012). The mitochondrial genome is a highly-organised, 16.6 kb circular genome whose complete sequence was published over 30 years ago (Anderson et al., 1981), prompting the discovery of the first pathogenic mutations in 1988 involving either mtDNA rearrangements or deletions (Holt et al., 1988) or point mutations (Wallace et al., 1988). Strictly inherited through the maternal lineage, it is present within cells in multiple copies, reflecting the demand for OXPHOS-derived energy of that particular tissue. When all mtDNA molecules within a cell are identical, a situation known as homoplasmy prevails. The presence of two or more mitochondrial genotypes, as typified in many pathogenic mtDNA mutations, results in a situation known as heteroplasmy in which the ratio of wild-type to mutated mtDNA determines the onset of clinical symptoms. A minimum critical proportion of mutated mtDNA molecules are required before biochemical deficiency manifests as a clinical phenotype, with this threshold level varying for different mutations and tissues. Functional consequences are most commonly seen in post-mitotic tissues with high energy requirements (e.g. muscle, brain, and heart) but almost any tissue can be involved, including the endocrine organs. Individual mtDNA mutations often dictate the pattern of involvement, with some more strongly associated with endocrine disease than others.

The exact prevalence of mtDNA disease has proven difficult to define but estimates from our cohort in the North East of England suggest that mtDNA mutations of all types cause a point prevalence of disease in adults of 9.2/100,000 population, with a further 16.5/100,000 at risk of developing disease due to carrier status at any one time (Schaefer et al., 2008). Birth prevalence studies have reported mutation frequencies of 0.14% for some common mtDNA mutations such as the m.3243A > G mutation (Elliott et al., 2008), although most individuals will not manifest clinical disease as the majority of mutations are present at subthreshold levels.

Several other factors are important in understanding the behaviour of pathogenic, heteroplasmic mtDNA mutations in relation to clinical disease. During mitotic cell division, mitochondria are randomly segregated to daughter cells and as such the proportion of mutated mtDNA can shift in the presence of heteroplasmy. The observation of a rapid segregation in mammalian heteroplasmic mtDNA genotypes between generations is evidence for the existence of a mtDNA developmental genetic bottleneck; this involves a marked reduction in mtDNA copy number in the germline followed by the replication of a subgroup of mtDNA molecules during oogenesis although the precise mechanism remains to be fully determined (Cao et al., 2007; Cree et al., 2008; Wai et al., 2008).

In addition to primary mtDNA mutations, mutations in nuclear genes involved in mtDNA replication or repair (often termed mtDNA maintenance) can give rise to secondary qualitative or quantitative mtDNA abnormalities. Mutations in nuclear genes implicated in many other mitochondrial processes including structural respiratory chain components, mitochondrial nucleotide salvage and synthesis and mitochondrial translation are increasingly being described with the advent of next-generation screening and mito-exome sequencing (Ylikallio and Suomalainen, 2012; Calvo et al., 2012) highlighting that mitochondrial disease may be inherited as Mendelian traits, with autosomal dominant (ad-), autosomal recessive (ar-), and even X-linked forms.

3. Investigation of mitochondrial disease

The complex interplay between mtDNA heteroplasmy and phenotypic expression, and the potential contribution from both nuclear and mitochondrial genomes, makes mitochondrial disease one of the most difficult inherited disorders to diagnose. The lack of curative treatments for these conditions places greater emphasis on accurate genetic advice and counselling, which should be undertaken by a specialist with experience in this area.

Our own algorithms for the laboratory investigation of mitochondrial disease have been published extensively (Taylor et al., 2004; Tuppen et al., 2010; McFarland et al., 2010) and rely on information from the clinical phenotype and functional data (histochemistry and biochemistry) to guide genetic studies of both mtDNA and nuclear genes. Some common mtDNA mutations can be reliably detected and screened in blood, but there is a potential for false-negative results in some mutations. This possibility should be highlighted in the case of the m.3243A > G mutation,

particularly as it is the most frequently requested analysis for presumed mitochondrial disease and is associated with numerous clinical syndromes including mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), maternally-inherited diabetes and deafness (MIDD), and, less commonly, myoclonic epilepsy with ragged red fibres (MERRF). Levels of this mutation within leucocytes have been shown to decrease by ~1.4% per year (Rahman et al., 2001) and we have several patients within our own cohort in whom the m.3243A > G mutation would not have been detected from blood alone. The risk of false negative results may be decreased by screening alternative mtDNA sources including urinary epithelial cells (McDonnell et al., 2004; Blackwood et al., 2010). For some mutations, notably m.3243A > G, the level in this tissue correlates well with clinical severity (Whittaker et al., 2009). Muscle biopsy remains the gold standard, yet in a minority of patients a complete biochemical analysis of muscle tissue can be normal, whilst the demonstration of histological and histochemical hallmarks of mitochondrial disease still require additional genetic testing. A pragmatic strategy for genetic testing is often best derived from liaison with a specialist mitochondrial centre. Pattern recognition is key and specific phenotypes may raise an otherwise rare mutation to the forefront of the process (e.g. Alper syndrome due to recessively-inherited *POLG* gene mutations). Pathogenic mtDNA mutations and mtDNA rearrangements are now relatively easy to exclude where a muscle biopsy has already been performed, and in many cases should be screened in both adults and children prior to nuclear genetic testing, a process which may require investigating numerous candidate genes. This once laborious process is being revolutionised by the next-generation sequencing revolution leading to the identification of many new mitochondrial disease genes over the last 2–3 years.

4. Diabetes mellitus

Diabetes mellitus is well recognised within mitochondrial phenotypes and is the most common endocrine manifestation of disease. This is mainly because of its association with the MIDD phenotype which is common in patients carrying the m.3243A > G *MTTL1* mutation (van den Ouweland et al., 1992; Whittaker et al., 2007). Diabetes is also a common condition in its own right, estimated to affect 4.45% of the UK population. It is not surprising, therefore, that it is common for mitochondrial diabetes to be misdiagnosed, even in the presence of other features that may provide clues as to the underlying genetic disease. The importance of pattern recognition in diagnosis is discussed subsequently, but for the m.3243A > G mutation, the cardinal features are of maternal inheritance and pre-senile sensorineural hearing loss. Prevalence of the m.3243A > G mutation in unselected diabetic populations varies between 0% and 2.8% from the larger studies (Vionnet et al., 1993; Katagiri et al., 1994; Otabe et al., 1994; t'Hart et al., 1994; Kishimoto et al., 1995; Odawara et al., 1995; Uchigata et al., 1996; Abad et al., 1997; Saker et al., 1997; Tsukuda et al., 1997; Holmes-Walker et al., 1998; Lehto et al., 1999; Matsuura et al., 1999; Malecki et al., 2001; Ohkubo et al., 2001; Suzuki et al., 2003; Maassen et al., 2004; Murphy et al., 2008). Deafness, neuromuscular disease, end stage renal disease, and a maternal family history all increase the likelihood of mitochondrial disease (t'Hart et al., 1994; Majamaa et al., 1997; Newkirk et al., 1997; Smith et al., 1999; Ng et al, 2000; Iwasaki et al., 2001; Klemm et al., 2001; Suzuki et al., 2003; Murphy et al., 2008). There are several other mtDNA mutations recognised to consistently express a phenotype which includes diabetes. These include the m.14709T > C mutation (Hanna et al., 1995; Vialettes et al., 1997; Choo-Kang et al., 2002) which has been reported to be homoplasmic in some patients (McFarland et al., 2004) and may cause up to 13% of mitochondrial diabetes in the North East of England (Whittaker et al., 2007). The m.8296A > G *MTTK* gene mutation was identified in 0.9% unrelated Japanese patients with diabetes, and 2.3% with diabetes and deafness (Kameoka et al., 1998). The m.14577T > C *MTND6* mutation, associated with isolated complex I deficiency, was found in 0.79% unrelated Japanese patients with diabetes (Tawata et al., 2000).

Other mtDNA point mutations have been described but appear much rarer. The m.12258T > C *MTTS2* gene mutation has been associated with diabetes (Lynn et al., 1998) but in other maternally-related kindreds, diabetes has been notably absent (Mansergh et al., 1999). The m.3271T > C *MTTL1* mutation has been associated with the MIDD, MELAS and MERRF phenotypes (Goto et al., 1991; Suzuki et al., 1996; Tsukuda et al., 1997), whilst the m.3264T > C *MTTL1* mutation was observed with MIDD, the proband having chronic progressive external ophthalmoplegia (CPEO) and cervical lipomata in addition (Suzuki et al., 1997).

In a number of mtDNA mutations, diabetes is not considered part of the established phenotype, despite rare reports. This group includes the m.8344A > G mutation causing myoclonic epilepsy and ragged-red fibres (MERRF) (Austin et al., 1998; Whittaker et al., 2007), the m.8993T > C mutation which is associated with the maternally-inherited Leigh syndrome (MILS) phenotype (Nagashima et al., 1999) and mtDNA mutations causing Leber hereditary optic atrophy (LHON) (Newman et al., 1991; Du Bois and Feldon, 1992; Pilz et al., 1994; Cole and Dutton, 2000).

Single, large-scale mtDNA deletions have been reported to cause diabetes in 11% (6 of 55 patients) of well-defined, clinical cohorts of patients with CPEO and Kearns Sayre Syndrome (KSS) (Whittaker et al., 2007). An earlier paper reviewing existing case reports of KSS reported the prevalence of diabetes to be 13% (29 of 226) but not all cases had genetic confirmation of a deleted mitochondrial genome (Harvey and Barnett, 1992). A single report documents a child who presented with insulin dependent diabetes mellitus (IDDM) and adrenal insufficiency prior to the development of ophthalmoplegia and a diagnosis of KSS (Mohri et al., 1998). Rarely, mtDNA deletions have been reported to cause IDDM in Pearson's Syndrome, but on the whole pancreatic failure is usually exocrine (Superti-Furga et al., 1993; Williams et al., 2012). Other mtDNA rearrangements, notably maternally-transmitted duplications of the mitochondrial genome, have been reported in association with diabetes (Rötig et al., 1992; Ballinger et al., 1994).

The recognised spectrum of disease due to mutations within nuclear maintenance genes is still expanding, but diabetes has been reported in 11% of adult CPEO phenotypes with ar-*POLG* mutations (Horvath et al., 2006). In adult-onset PEO due to *RRM2B* mutations, only 4.5% (1 of 22 in this cohort) had diabetes (Pitceathly et al., 2012). Late-onset type-2 diabetes is rare (3 of 83) in *OPA1* pedigrees (Yu-Wai-Man et al., 2010) and is not a feature of ar-*PEO1* (Twinkle) gene mutations (Lönnqvist et al., 2009).

There are other documented mutations associated with diabetes, most of which are sufficiently rare as an individual entity as to not warrant lengthy discussion in this review. The role of the 16,189 variant in causing diabetes remains unclear (Poulton et al., 2002; Das et al., 2007) but the numerous reports of pathogenic mtDNA mutations associated with a diabetic phenotype does highlight that the endocrine pancreas is particularly susceptible to mitochondrial dysfunction. Combined with involvement of other tissues this is a useful pointer towards mitochondrial disease as a diagnosis.

5. Mitochondrial diabetes

5.1. Pattern recognition

Faced with the fact that mitochondrial diabetes is relatively scarce in the general diabetes clinic, it is helpful to have a

structured approach to help decide which patients should be considered for mtDNA mutation screening.

The text book description of the short, deaf patient with diabetes is in reality a rare occurrence and probably represents the tip of the iceberg in terms of mitochondrial diabetes. Historically these descriptions referred to patients with severe disease due to either m.3243A > G or KSS. These 'textbook' patients are usually younger and with low Body Mass Index (BMI) as well as height. This probably reflects more extensive multisystem involvement with higher levels of heteroplasmy in most tissues, and rarely will the diabetic clinic be the first medical encounter for these patients. The same is true of recessive forms of mitochondrial disease, where clear multisystem disease is likely to have raised the question of mitochondrial disease already.

There are differences between mitochondrial diabetes and type-2 diabetes, and these will be discussed in the subsequent paragraphs. Within the real world however, of busy clinics filled with common disorders, a physician who diagnoses mitochondrial diabetes without additional clues should consider themselves particularly astute. A maternal family history or sensorineural deafness should raise suspicion. While deafness in old age or a family history of type-2 diabetes is not uncommon, pre-senile sensorineural deafness is unusual, and especially so if combined with diabetes and a maternal history of either disorder, and/or other conditions such as cardiomyopathy, epilepsy, ptosis or unusual sounding strokes. Each additional feature adds weight to the growing suspicion of a mitochondrial disorder. Asymptomatic individuals and apparently 'skipped' generations within a pedigree should not lessen the suspicion as this is a common observation in mtDNA mutations due to carriers with low levels of heteroplasmy. In our mitochondrial cohort in the North East of England, 82/138 (59%) individuals within m.3243A > G pedigrees showed no signs of disease at the time of assessment, despite being at risk by virtue of maternal inheritance patterns; 82% of relatives opting for predictive testing subsequently test positive (Schaefer et al., 2008). This frequency remains constant whether testing 1st, 2nd or 3rd degree relatives. 30% of these patients go on to develop typical features associated with the m.3243A > G mutation over the next 5 years (Schaefer et al., 2008) and this figure continues to rise with subsequent follow up (Schaefer and colleagues, unpublished data).

There is conflicting evidence regarding the predictive value of a maternal family history alone (Ng et al., 2000; Choo-Kang et al., 2002). As pure diabetic phenotypes are extremely rare in mtDNA disease, it is probably true that a family history of diabetes alone is unlikely to suggest mitochondrial disease (Choo-Kang et al., 2002). The detail of the pedigree analysis is all important, however, as often enquiry is restricted to the scope of the clinic being attended, whether diabetic or neurological; and important associations may be easily overlooked. Most mitochondrial patients in the diabetic clinic will have a more subtle presentation, but deafness is usually present when diabetes is diagnosed (Suzuki et al., 1994; Guillausseau et al., 2001; Uimonen et al., 2001). An audiogram can confirm its presence if it has not been formally assessed. A variable number of additional features (such as ptosis, proximal myopathy, cerebellar ataxia, axonal sensorimotor neuropathy, gastrointestinal dysmotility and pigmentary retinopathy) are commonly present, but are often subtle and may be missed if not looked for specifically. Regular ophthalmologic assessments in diabetic patients afford an opportunity to identify pigmentary retinopathies, but the pick-up rate is increased if the ophthalmologist is aware of the clinical suspicion.

5.2. Age-at-onset

Mitochondrial diabetes usually presents insidiously, much like type-2 diabetes. When due to the m.3243A > G mutation it can present at virtually any age, but typically develops in mid-life with an average age-at-onset of 37 or 38 years (Guillausseau et al., 2004; Whittaker et al., 2007). Only rarely does the diabetes present in childhood (Guillausseau et al., 2004).

5.3. Insulin requirements

Mitochondrial diabetes is felt to occur as a result of insulin deficiency (Reardon et al., 1992; Oka et al., 1993; Kadowaki et al., 1993; Kadowaki et al., 1994; Katagiri et al., 1994; Walker et al., 1995a) rather than insulin resistance (Walker et al., 1995b; Velho et al., 1996), but in some patients both mechanisms may play a part (Szendroedi et al., 2009). Approximately 20% of cases of mitochondrial diabetes may present acutely, with 8% suffering from ketoacidosis (Guillausseau et al., 2001; Guillausseau et al., 2004; Maassen et al., 2004), but only 13% of diabetic patients carrying the m.3243A > G mutation require insulin at diagnosis (Whittaker et al., 2007). Of the remaining 87% of patients, mitochondrial diabetes develops insidiously but usually progresses rapidly to insulin requirement, another observation unusual in type-2 diabetes; 45.2% of such patients made this transition (Whittaker et al., 2007). Average transition rates to insulin requirement range between 2 and 4.2 years (Guillausseau et al., 2001; Guillausseau et al., 2004; Maassen et al., 2004; Whittaker et al., 2007). Those patients assessed by Whittaker and colleagues were under stringent review in a specialist mitochondrial clinic, and early diagnosis of diabetes through screening programmes may explain the longer transition times as compared to other studies.

5.4. Body Mass Index (BMI)

One of the clues that appears consistent in mitochondrial diabetes is the tendency for patients to have a lower than average BMI (Guillausseau et al., 2004; Whittaker et al., 2007), an unusual observation in typical type-2 diabetes. Lower BMI tends to correlate with earlier onset of diabetes, earlier insulin requirements, and higher HbA1C measurements (Guillausseau et al., 2004). This probably reflects a higher overall disease burden as lower BMI tends to be associated with an earlier onset of disease and a more severe phenotype in general (Schaefer and colleagues, unpublished data).

5.5. End organ disease

Although neuropathy and renal disease can occur independently of diabetes in the m.3243A > G mutation, each complication has been reported to be significantly more prevalent in those patients with diabetes. In addition, patients with diabetic retinopathy or renal impairment demonstrated higher HbA_{1C} levels than those who did not (Whittaker et al., 2007). This suggests that poor glycaemic control plays a major role in their pathogenesis. The risk of neuropathy and renal disease in the same diabetic m.3243A > G cohort was reported to be higher than in other forms of either type-1 or type-2 diabetes, which implies that pre-existent mitochondrial dysfunction within these end organs predisposes to the microvascular complications of diabetes (Whittaker et al., 2007). Prevalence rates for these complications exceed those reported in the United Kingdom Prospective Diabetes Study in type-2 diabetes or the DCCT in type-1 diabetes (The Diabetes Control and Complications Trial Research Group, 1993; Adler et al., 2003). Interestingly, several studies have reported lower rates of diabetic retinopathy in MIDD (Holmes-Walker et al., 1998; Massin et al., 1999; Smith et al., 1999; Latvala et al., 2002) than would normally be expected in type-1 or type-2 diabetes (Misra et al., 2009; Thomas et al., 2012). The same appears true of cataracts. This has been proposed to be due to reduced glucose metabolism by the

polyol pathway (Holmes-Walker et al., 1998). Abnormal glucose tolerance also appears to increase the clinical expression of the pigmentary retinopathy typically seen in patients with the m.3243A > G mutation. 15 of 23 patients from MIDD kindreds had evidence of a pigmentary retinopathy, 13 of which had evidence of glucose intolerance (Holmes-Walker et al., 1998).

m.3243A > G heteroplasmy levels from muscle-derived mtDNA did not correlate with the age of onset of diabetes, whilst heteroplasmy levels from blood or muscle did not correlate with the time taken to progress to insulin requirement, or the risk of diabetic complications; an inverse correlation between age of diabetic onset and heteroplasmy level in blood derived mtDNA was reported (Whittaker et al., 2007), but the true significance of this was difficult to predict as heteroplasmy levels in blood are known to decrease year by year in patients carrying the m.3243A > G mutation due to replicative disadvantage (Rahman et al., 2001). A subsequent multicentre study found that correcting for age negated the significance of a similar finding in their cohort, but did note a correlation between age-adjusted blood heteroplasmy levels and both $HbA_{1C,}$ levels and low BMI (Laloi-Michelin et al., 2009).

5.6. Pancreatic pathology

Mitochondrial dysfunction within the metabolically active pancreatic B-cells is presumed to account for reduced function and ultimately loss of B-cell mass (Kobayashi et al., 1997; Lynn et al., 2003). It has been difficult to demonstrate apoptosis (Kobayashi et al., 1997) which is the presumed explanation for the surprisingly low levels of heteroplasmy found in remaining B-cell tissue at autopsy (Togashi et al., 2000; Lynn et al., 2003). HLA polymorphisms associated with type-1 susceptibility have not been found in mitochondrial diabetes (van Essen et al., 2000). Our own m.3243A > G cohort do not, in general, carry islet cell or GAD antibodies (unpublished data) but these have been found in a minority of patients by other groups (Oka et al., 1993; Murphy et al., 2008). These cases may represent coincidental autoimmune type-1 diabetes but it has also been hypothesised that antibodies might be produced in direct response to pancreatic B-cell destruction as a result of mitochondrial mechanisms (Oka et al., 1993). Acute or chronic pancreatitis is rarely described (Kishnani et al., 1996; Schleiffer et al., 2000; Verny et al., 2008; Ishiyama et al., 2012).

5.7. Diabetes management

The majority of patients present with non-insulin dependent diabetes. A sulphonylurea is the first agent of choice. Care must be taken because some patients appear to be particularly sensitive to sulphonylurea induced hypoglycaemia. For this reason, we favour sulphonylureas with a short half-life, and always start with the very lowest dose and titrate up. Metformin is best avoided because of the risk of exacerbating lactic acidosis. Having said this, we have used metformin in patients with accompanying obesity and have not experienced any clinical problems. The emergence of newer agents such as DDP4 inhibitors and GLP-1 analogues offer alternative therapeutic opportunities, and we are using them as second line treatment in preference to metformin depending upon the clinical indications. As detailed above, a minority of patients require insulin from the time of diagnosis, and those with initial non-insulin dependent diabetes often progress rapidly to insulin therapy. We tailor the insulin regimen to patient's individual lifestyle and daily needs.

As described above, progression to end stage renal failure and kidney transplantation is a recognised outcome. This opens up the possibility of pancreas transplantation, either as a simultaneous kidney and pancreas procedure or as a pancreas after kidney transplant. A key attraction is that there is no on-going autoimmune process in mitochondrial diabetes (unlike patients with type 1 diabetes undergoing transplantation), and so the transplanted organs in theory should last longer.

While discussing management it is worth clarifying the role of statins in mitochondrial diabetes. Statins are often recommended for diabetic patients to help lessen the risks of atherosclerotic complications. Understandably, use of a drug with the potential to induce a myositis often causes concern in relation to pre-existing mitochondrial myopathy. In the majority of cases we do not believe the risks outweigh the benefits, but do advise caution. As many patients with mitochondrial disease often have a mildly elevated creatine kinase (CK < 1000IU) at baseline, we recommend documentation of pre-treatment CK levels with repeat CK measurements while on statin therapy and advise to report new myalgia or weakness.

It is evident that mitochondrial diabetes is complicated. The disease pattern with a high risk of rapid progression to insulin and the high prevalence of complications means that patients need access to a specialist diabetes service offering regular review. The situation is further complicated by the multisystem nature of mitochondrial disease. As a consequence, we have just recently established a combined mitochondrial/diabetes clinic run jointly by the neurologists and diabetologists that provides an integrated, one-stop service for patients with mitochondrial diabetes. We have also developed Best Practice Guidelines for mitochondrial diabetes which are available online (http://www.newcastle-mitochondria.com/service/patient-care-guidelines/).

6. Hypoparathyroidism

Hypoparathyroidism is best described in KSS which occurs as a result of a sporadic, single large-scale mtDNA rearrangement. Although reports are relatively rare, they seem consistent (Quade et al., 1992; Isotani et al., 1996; Katsanos et al., 2001; Cassandrini et al., 2006; Wilichowski et al., 1997). In each case children have multisystem disease, often with renal disease or other endocrinopathies in addition to the classic KSS phenotype. There does not appear to be an autoimmune basis to the hypoparathyroidoism (Isotani et al., 1996). Autopsy studies suggest absent or atrophic hypoparathyroid glands (Horwitz and Roessmann, 1978; Bordarier et al., 1990). Although some patients with basal ganglia calcification on CT have been found to have hypoparathyroidism (Seigel et al., 1979; Cassandrini et al., 2006) the majority have no abnormalities of calcium homeostasis. The genetic basis of KSS was first confirmed in 1988 (Holt et al., 1988) and reports of hypoparathyroidism (and other endocrinopathies) in KSS prior to that period are unsupported by genetic studies ((Horwitz and Roessmann, 1978; Seigel et al., 1979; Dewhurst et al., 1986). It is possible that some of these cases may have harboured mtDNA point mutations (e.g. m.3243A > G) or multiple mtDNA deletions of a nuclear cause. Harvey and Barnett's (1992) review found 14 of 226 patients with KSS and CPEO to have hypoparathyroidism, but the relevant message from this study is probably more pertinent to endocrine disease associated with the phenotype than the genotype, as not all cases had been genetically confirmed (Harvey and Barnett, 1992). Hypoparathyroidism has been described in patients with ar-*RRM2B* mutations, for example, and historically would have been included in this group on the basis of the clinical features (Pitceathly et al., 2012).

In our experience, hypoparathyroidism is extremely rare in adult forms of mitochondrial disease. The paucity of case reports in the literature suggests likewise (Tanaka et al., 2000). It seems most likely to occur in very severely affected patients who present in childhood with multisystem disease. This may suggest that clinically significant levels of heteroplasmy within the parathyroid

glands, or alternatively the heteroplasmic threshold for dysfunction of the parathyroid glands, is only reached in cases where very high levels of heteroplasmy are present in most tissues.

7. Hypothalamo-pituitary axis

The most consistent descriptions of endocrine dysfunction due to impairment of the hypothalamopituitary axis appear to be in severe mitochondrial phenotypes presenting in childhood. MELAS and KSS appear the most common phenotypes. The endocrine disorder may precede the neurological features and lactic acidosis is often the clue to a mitochondrial cause. Short stature is usually present and more classical phenotypic expression develops later if the patient survives. Reports in adults are much rarer.

8. Growth hormone deficiency

Growth hormone (GH) deficiency has been described in KSS, both before and after genetic testing became available (Harvey and Barnett, 1992; Quade et al., 1992; Mohri et al., 1998; Berio and Piazzi, 2000; Cassandrini et al., 2006; Berio and Piazzi, 2007). It has also been reported in MELAS due to the m.3243A > G mutation in children (Yorifuji et al., 1996; Robeck et al., 1996; Balestri and Grosso, 2000; Matsuzaki et al., 2002) and in very rare adult cases with the MELAS (Ishii et al., 1991) and MIDD phenotypes (Joko et al., 1997). GH deficiency is often declared to be the cause of short stature in the mitochondrial myopathies, but the causes are more likely to be complex and multi-factorial for most patients (Wolny et al., 2009). Publication bias is probably to blame for the lack of reports documenting short stature and normal GH, but these probably form the majority of cases.

9. Hypogonadism

Mutations in the *POLG* gene have been associated with primary testicular failure (Filosto et al., 2003), primary ovarian failure (Luoma et al., 2004; Hakonen et al., 2005), and ovarian dysgenesis (Bekheirnia et al., 2012). ar-*PEO1* mutations are reported to cause female hypergonadotrophic hypogonadism by teen age (Lönnqvist et al., 2009). Hypogonadism has been reported in association with mtDNA depletion due to ar-*RRM2B* mutations whilst cases of both hypergonadotropic and hypogonadotropic hypogonadism have been described in reports of mitochondrial neurogastrointestinal encephalopathy (MNGIE) (Carod-Artal et al., 2007; Kalkan et al., 2012). It has been suggested from review of the early literature that up to 20% of patients with KSS develop gonadal dysfunction, either before or after puberty (Harvey and Barnett, 1992; Quade et al., 1992). Both sexes were affected equally. It is possible however that some of the patients diagnosed on clinical and histological grounds alone may have carried other mtDNA mutations or AR forms of disease rather than single deletions of the mtDNA. Genetically-confirmed case reports exist but are rare (Barrientos et al., 1997). Low levels of follicle stimulating hormone (FSH) and luteinizing hormaone (LH) have both been reported in MELAS (Ishii et al., 1991; Robeck et al., 1996; Ohkoshi et al., 1998; Balestri and Grosso, 2000) but are also rare. In both KSS and MELAS it is possible that hypogonadism is underdiagnosed where other forms of multisystem disease dominate the clinical picture.

10. Hypothyroidism

Thyroid disease is not a recognised complication of mitochondrial disease. Observations from our own mitochondrial cohort are that it occurs in similar frequency to the background population, and is often associated with thyroid antibodies as might be expected. Reports in KSS are rare and usually associated with autoimmunity (Berio and Piazzi, 2006; Sanaker et al., 2007); only rare reports exist for patients with the m.3243A > G mutation (Balestri and Grosso, 2000; Lau et al., 2007). Hypothyroidism was documented in 2/18 adult *RRM2B* patients, but antibody status was not reported (Pitceathly et al., 2012).

11. Hypoadrenalism

This is rarely described in mitochondrial disease but importantly has been reported in children prior to the development of typical features of KSS. Patients are often neurologically normal at presentation but have short stature and may exhibit a lactic acidosis. Adrenocorticotropic hormone (ACTH) is elevated but antibodies negative (Nicolino et al., 1997; Boles et al., 1998). We have recently identified an adult harbouring a single, large-scale mtDNA deletion and a mild KSS phenotype who developed non-autoimmune adrenal insufficiency at 51 years of age (personal observation).

12. SIADH

The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) is probably under recognised as an endocrine disorder in mitochondrial disease. Hyponatraemia may also occur as a result of unrecognised renal disease, adrenal insufficiency, or gastrointestinal losses related to pseudoileus, while in other cases the cause may not be identified (Kubota et al., 2005; Gurrieri et al., 2001). In our experience, hyponatraemia is relatively common in patients carrying the m.3243A > G mutation, but not always due to SIADH. When this occurs it is usually transient and associated with stroke-like episodes and more specifically ongoing seizure activity (Patel et al., 2007). In this respect SIADH can sometimes be an indication of active cerebral dysfunction. MELAS patients appear prone to SIADH, or exacerbation of pre-existing SIADH, with certain anticonvulsants such as carbamazepine. In most cases this is not severe enough to prevent the use of clinically useful drugs in the acute setting, but may affect subsequent treatment choices.

13. Adipose tissue as an endocrine organ

There has been very little work looking at adipose tissue function in mitochondrial diabetes. A recent study compared adipose tissue and liver fat metabolism between patients with the m.3243A > G mutation and healthy control subjects. They found that patients with the mutation showed evidence of adipose tissue insulin resistance and a tendency to increased liver fat. However, as there were no diabetes controls, it was not clear to what extent the metabolic changes reflect the diabetic state rather than specific changes related to the mitochondrial disease (Lindroos et al., 2011). Further work is needed to determine whether there are adipose tissue abnormalities that are specific to mitochondrial disease.

One such scenario occurs in Ekbom's Syndrome. Originally described as 'hereditary ataxia, photomyoclonus, skeletal deformities and lipoma' (Ekbom, 1975), it was subsequently confirmed to occur as a result of the m.8344A > G *MTTK* mutation associated with the MERRF phenotype (Träff et al., 1995). Many MERRF patients develop unusual lipomata around the neck and shoulder region corresponding to the distribution of brown fat tissue; these lesions may be painful, restrict movement, and account for major aesthetic

and psychological morbidity, although the mechanisms underlying this phenomenon are currently undetermined.

14. Autoimmune endocrinopathy

Autoimmune endocrine disease has been reported in several forms of mitochondrial disease. Despite this, overall there is a lack of firm evidence to suggest autoimmune disorders are any more prevalent in mitochondrial cohorts than in the general population. Most cases of MIDD do not have anti-GAD or islet cell antibodies but these have been reported in small numbers (Oka et al., 1993; Murphy et al., 2008) and more frequently in some cohorts (Kobayashi et al., 1996). It has been hypothesised that mitochondrial dysfunction may play some role in the development of autoimmunity but this remains unproven. In diabetes, pancreatic B-cell destruction has been proposed as the catalyst for antibody production (Oka et al., 1993).

Autoimmune hypothyroidism is described rarely in patients with KSS, one such report also having Addison's disease with adrenal antibodies (Berio and Piazzi, 2006; Sanaker et al., 2007).

Autoimmune polyglandular syndrome type II has been reported once in a mild KSS/CPEO phenotype. The endocrine features were Addison's disease, IDDM, autoimmune thyroiditis and primary ovarian failure. Interestingly this patient carried both a 2,532-bp deletion of her mtDNA, consistent with KSS, but also a heteroplasmic m.3243A > G mutation which was also present in her mother's mtDNA. Whether mitochondrial disease played a role in this is unclear (Ohno et al., 1996).

15. Conclusion

Endocrine dysfunction in mitochondrial disease is common, but predominantly due to the prevalence of the m.3243A > G mutation and its association with diabetes mellitus. Other mtDNA mutations reliably expressing a diabetic phenotype are rare, and other forms of endocrine dysfunction are unusual when considering the mitochondrial diseases as a whole. Pattern recognition and detailed pedigee analysis are key when evaluating the likelihood of a mitochondrial disorder, and the presence of endocrine disease may contribute to the diagnostic process. Furthermore, appreciation of the endocrine organs at risk in a specified genotype/phenotype allows an appropriate level of screening to be initiated as part of the patient's multidisciplinary care strategy. KSS patients are at risk of hypoparathyroidism, and patients with advanced multi-system disease presenting in childhood, whether due to mtDNA mutations or nuclear mtDNA maintenance genes, appear at risk of hypothalamopituitary dysfunction. Most patients with mitochondrial disease, but most notably those carrying the m.3243A > G mutation, should have access to annual screening for diabetes. The tendency to multisystem disease in these complex families can make management difficult, even in asymptomatic carriers. For this reason we recommend referral to a specialist mitochondrial centre for disease specific advice and management plans.

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