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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,