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Progress Report

Unexplained gastrointestinal symptoms: Think mitochondrial disease

Thomas P. Chapman[a], Gina Hadley[a], Carl Fratter[b], Sue N. Cullen[c], Bridget E. Bax[d], Murray D. Bain[d], Robert A. Sapsford[e], Joanna Poulton[f], Simon P. Travis[a,*]

[a] Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford, UK
[b] Oxford Medical Genetics Laboratories, Churchill Hospital, Oxford, UK
[c] Buckinghamshire Hospitals NHS Trust, Department of Gastroenterology, Level 6, Queen Alexandra Road, High Wycombe, UK
[d] Division of Clinical Sciences, St. George's University of London, London, UK
[e] Rectory Meadow Surgery, School Lane, Amersham, Bucks, UK
[f] Nuffield Dept Obstetrics and Gynaecology, University of Oxford, The Women's Centre, Oxford, UK

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ABSTRACT

Defects in mitochondrial function are increasingly recognised as central to the pathogenesis of many diseases, both inherited and acquired. Many of these mitochondrial defects arise from abnormalities in mitochondrial DNA and can result in multisystem disease, with gastrointestinal involvement common. Moreover, mitochondrial disease may present with a range of non-specific symptoms, and thus can be easily misdiagnosed, or even considered to be non-organic.

We describe the clinical, histopathological and genetic findings of six patients from three families with gastrointestinal manifestations of mitochondrial disease. In two of the patients, anorexia nervosa was considered as an initial diagnosis. These cases illustrate the challenges of both diagnosing and managing mitochondrial disease and highlight two important but poorly understood aspects, the clinical and the genetic.

The pathophysiology of gastrointestinal involvement in mitochondrial disease is discussed and emerging treatments are described. Finally, we provide a checklist of investigations for the gastroenterologist when mitochondrial disease is suspected.

1. Introduction

Defects in mitochondrial function are increasingly recognised as central to the pathogenesis of many diseases, both inherited and acquired [1]. Mitochondria are dynamic organelles present in every nucleated cell and play an essential role in cellular energy production. Consequently mitochondrial defects can result in dysfunction of almost any organ, particularly those with high energy demand.

Many of these mitochondrial defects result from abnormalities in mitochondrial DNA (mtDNA). While mtDNA disease may result from sporadic mutations, when transmission does occur it is classically through the maternal line, as either point mutations or complex mtDNA rearrangements [2–4]. However, as mtDNA relies upon the cell nucleus for replication and maintenance, nuclear gene defects can result in secondary mtDNA abnormalities. This is seen in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), which is inherited as an autosomal recessive disorder [5]. In addition, there are many other genes involved in mitochondrial biogenesis and dynamics; an example is the *OPA1* gene which plays a key role in mitochondrial dynamics, with mutations leading to optic atrophy syndromes [6]. Fig. 1 provides an overview of the common abnormalities in the mitochondrial genome, and the associated diseases. The diverse group of disorders that result from mitochondrial disease are described in greater detail in the following articles [7,8].

Mitochondrial disease is more common than previously thought, with an estimated prevalence of 1 in 500 [9]. Greater awareness of mitochondrial disease and improvements in analytical technique have led to improved detection of simple mtDNA defects, such as the single deletion commonly seen in Chronic Progressive External Ophthalmoplegia [10]. However, more complex mtDNA rearrangements which classically result in multisystem disease are still greatly under-diagnosed. This is partly because multisystem mitochondrial disease may present to many medical specialties without being diagnosed.

The prevalence of medically unexplained symptoms (MUS) in outpatients is common and ranges between 25% and 75% [11]. Comorbid psychiatric disorders are frequent in such patients, who present major challenges to conventional medical management, are commonly frequent attenders and may have misattributed

* Corresponding author at: Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, UK. Tel.: +44 1865 228753; fax: +44 1865 228763.
E-mail address: simon.travis@ndm.ox.ac.uk (S.P. Travis).

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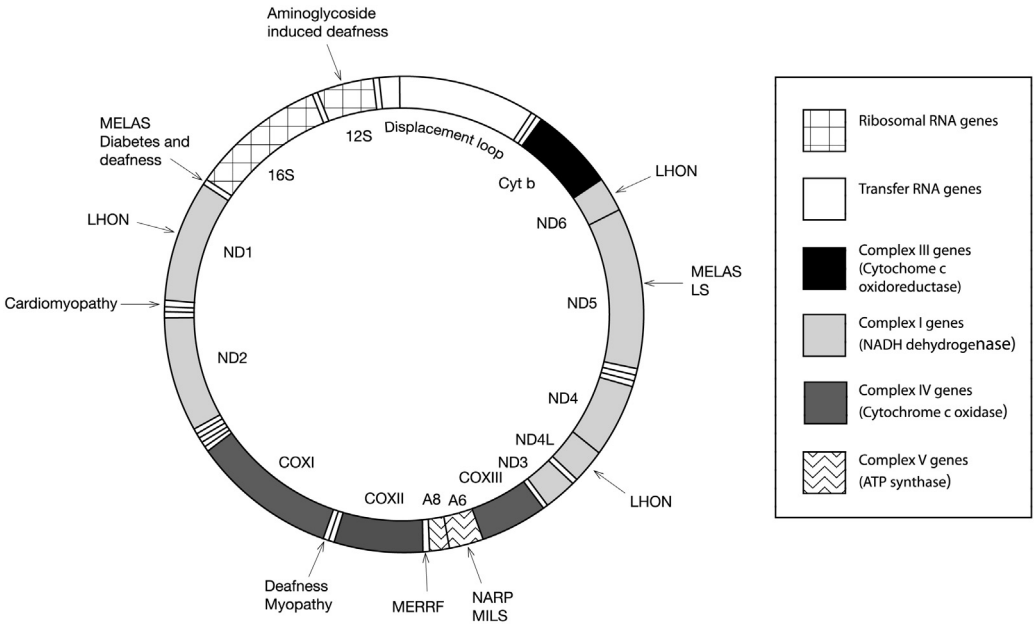

Fig. 1. Diagram of the human mitochondrial genome and sites of mutations leading to important clinical phenotypes. Adapted from "Seminars in medicine of the Beth Israel Hospital, Boston. Mitochondrial DNA and disease" by Johns [7]. The 16,569 np mtDNA map demonstrates the genes for the subunits of NADH dehydrogenase (ND), cytochrome c oxidase (COX), cytochrome b (cyt b), ribosomal RNA (12S and 16S) and ATPase (A6 and A8). LHON, Leber's hereditary optic neuropathy; MELAS, syndrome of mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes; LS, Leigh's syndrome; NARP, neuropathy, ataxia and retinitis pigmentosa; MILS, maternally inherited Leigh's syndrome; MERRF, myoclonic epilepsy with ragged-red fibres.

psychiatric conditions. MUS can, however, only be diagnosed when organic disease has been excluded [11]. Gastrointestinal involvement is common in patients with mtDNA disease, affecting up to 15%, yet symptoms are frequently overlooked as they may be non-specific such as abdominal pain, chronic constipation or vomiting [12]. Other manifestations include severe gut dysmotility and profound weight loss, which may be among the principal presentations of mitochondrial disease, as in MNGIE [13]. Importantly, mitochondrial disease can be easily mistaken for anorexia nervosa. Indeed the misdiagnosis of organic disease as 'anorexia nervosa' is well recognised in the literature [14–17].

In addition to the often non-specific presentation of mitochondrial disease, the genetics present further challenges to diagnosis. Firstly, even when sought, underlying complex mtDNA rearrangements are often missed by routine analytical techniques or are indistinguishable from simple, single deletions, consistent with low overall rates of detection [5,18,19]. Accurately defining the genetics has important implications both for the transmission and clinical presentation of mitochondrial disease. Complex mtDNA rearrangements including duplications are frequently maternally inherited and multi-systemic, whereas simple deletions are generally sporadic and myopathic. Secondly, there is marked variability in clinical presentation of mtDNA disorders, even within the same family and with apparently similar genotypes. Two unique features of mitochondrial genetics play an important role in determining phenotypic differences: these are heteroplasmy (the existence of two or more mitochondrial genotypes within the same cell, the proportion of which may vary both between and within individuals) and the threshold effect (the level of mutant mtDNA load necessary for clinical expression), but there is still much to explain [1]. A better understanding of complex mtDNA mutations is essential to provide further insight; it is likely that incomplete mapping of complex mtDNA rearrangements may account for some of the unexplained phenotypic variation seen with mtDNA disorders.

2. Case series

2.1. Family A

Three siblings from a consanguineous family (mother and father were first cousins), who initially presented with medically unexplained gastrointestinal and neurological symptoms are described, in whom the diagnosis of a mitochondrial disease due to MNGIE was subsequently established. The genetic pedigree is shown in Fig. 2. A psychiatric disorder (anorexia nervosa) was considered in two of the family members.

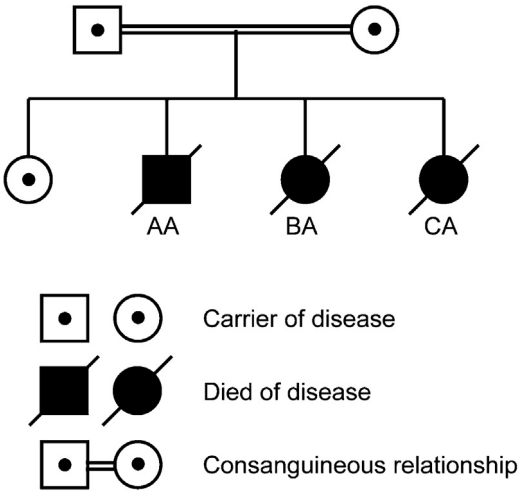

Fig. 2. The genetic pedigree of family A.