SHORT REPORT

The UK MRC Mitochondrial Disease Patient Cohort Study: clinical phenotypes associated with the m.3243A>G mutation—implications for diagnosis and management

Victoria Nesbitt,[1] Robert D S Pitceathly,[2] Doug M Turnbull,[1] Robert W Taylor,[1] Mary G Sweeney,[3] Ese E Mudanohwo,[3] Shamima Rahman,[2] Michael G Hanna,[2] Robert McFarland[1]

VN and RDSP contributed equally to the manuscript.

[1]Wellcome Trust Centre for Mitochondrial Research Group, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK
[2]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK
[3]Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, London, UK

Correspondence to
Dr Robert McFarland, Wellcome Trust Centre for Mitochondrial Research Group, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne NE2 4HH, UK; robert.mcfarland@ncl.ac.uk

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ABSTRACT

Background Population-based studies suggest the m.3243A>G mutation in *MTTL1* is the most common disease-causing mtDNA mutation, with a carrier rate of 1 in 400 people. The m.3243A>G mutation is associated with several clinical syndromes including mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS), maternally inherited deafness and diabetes (MIDD) and progressive external ophthalmoplegia (PEO). Many patients affected by this mutation exhibit a clinical phenotype that does not fall within accepted criteria for the currently recognised classical mitochondrial syndromes.

Methods We have defined the phenotypic spectrum associated with the m.3243A>G mtDNA mutation in 129 patients, from 83 unrelated families, recruited to the Mitochondrial Disease Patient Cohort Study UK.

Results 10% of patients exhibited a classical MELAS phenotype, 30% had MIDD, 6% MELAS/MIDD, 2% MELAS/chronic PEO (CPEO) and 5% MIDD/CPEO overlap syndromes. 6% had PEO and other features of mitochondrial disease not consistent with another recognised syndrome. Isolated sensorineural hearing loss occurred in 3%. 28% of patients demonstrated a panoply of clinical features, which were not consistent with any of the classical syndromes associated with the m.3243A>G mutation. 9% of individuals harbouring the mutation were clinically asymptomatic.

Conclusion Following this study we propose guidelines for screening and for the management of confirmed cases.

INTRODUCTION

As clinically heterogeneous disorders, mitochondrial diseases pose particular challenges to clinicians for both diagnosis and management. There are over 250 known pathogenic mutations in mitochondrial DNA (mtDNA)[1] but the diverse phenotypic spectrum associated with many of these mutations renders correlation between genotype and phenotype difficult.[2 3] Within the same cell, mitochondria house multiple copies of mtDNA, and it is thought that the proportion of mutated to wild-type mtDNA strongly influences both the disease severity and the phenotypic spectrum observed with particular mtDNA mutations.[2]

In 1975, a syndrome associated with stroke-like episodes, lactic acidaemia and ragged red fibres was reported[4] and subsequently termed 'mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS)' syndrome.[5] Following numerous case reports, a set of diagnostic criteria for the diagnosis of MELAS was established,[6] and there are now currently over 30 mtDNA gene mutations reported to be associated with this syndrome (http://www.ncbi.nlm.nih.gov/omim/540000). By far the most common pathogenic variant is the m.3243A>G transition in *MTTL1*, accounting for approximately 80% of cases.[7] This mutation leads to impaired translation of all mitochondrial encoded respiratory chain subunits with a resultant decrease in ATP synthesis.[2 3 7] Population-based studies suggest the m.3243A>G mutation is the most common disease-causing mtDNA mutation, with a carrier rate of 1 in 400 people.[8 9]

m.3243A>G is responsible for several other reported clinical syndromes aside from MELAS including: maternally inherited deafness and diabetes (MIDD); progressive external ophthalmoplegia (PEO); and Leigh syndrome (OMIM 540000). Other reported features include isolated myopathy, cardiomyopathy, seizures, migraine, ataxia, cognitive impairment, bowel dysmotility and short stature.[2 3 10] Although usually maternally inherited, sporadic cases have also been recognised.

The Mitochondrial Diseases Patient Cohort Study UK is the largest cohort of living patients with biochemically and/or genetically confirmed mitochondrial disease globally. Funded by the Medical Research Council (MRC) Centre for Translational Research in Neuromuscular Diseases, the cohort comprises symptomatic adults and children, as well as asymptomatic individuals who have requested genotyping due to a family history and have proved positive. Phenotypes in all individuals are characterised in out-patient clinics on the basis of clinical history, examination and detailed investigation. The Newcastle Mitochondrial Diseases Assessment Scale is also performed providing prospective data on the disease progression of symptomatic and asymptomatic individuals. All patients included in the cohort have given informed consent to be part of the data registry. The invaluable

wealth of data in the cohort permits focused natural history studies on large numbers of patients with confirmed disease, allowing the transmission and progression of mitochondrial disease to be studied in more detail. In doing so the ability to develop drugs and novel treatment strategies also becomes possible and large-scale interventional trials can be facilitated.

AIMS

This report aims to define the phenotypic spectrum associated with the m.3243A>G mtDNA mutation in patients recruited to the MRC Mitochondrial Disease Patient Cohort Study UK.

METHODS

Patients were identified from the MRC Centre for Neuromuscular Diseases Mitochondrial Disease Patient Cohort Study UK. This study details the clinical phenotype of all patients with confirmed biochemical and/or genetic disease. Patients for this study had a confirmed m.3243A>G mutation in urine ± blood ± muscle and were under active clinical follow-up at the time of enrolment to the study. The phenotype was ascertained by clinicians with expertise in mitochondrial disorders in two specialist centres and reviewed by independent clinicians. Selection bias was minimised by including symptomatic and asymptomatic carriers of all ages and gender. Standard clinical evaluations were performed on all patients included in the study, at least once, as were 12-lead ECG and transthoracic echocardiogram. All evaluations took place between 2009 and 2011.

RESULTS

We reviewed the records of 129 patients (50 male, 79 female) from 83 unrelated families (table 1). Current patient age ranged from 11 months to 74 years (119 adults and 10 children). A total of 68 patients (53%) were considered to have a mitochondrial phenotype that should prompt screening for the m.3243A>G mutation: 13 patients (10%) exhibited a classical MELAS phenotype, 39 (30%) had MIDD, 8 (6%) MELAS/MIDD, 2 (2%) MELAS/chronic PEO (CPEO) and 6 (5%) MIDD/CPEO overlap syndromes. In all, 8 (6%) had PEO and other features of mitochondrial disease not consistent with another recognised syndrome. Isolated PEO was not observed in our cohort. One patient demonstrated myoclonic epilepsy with ragged red fibres phenotype.

Sensorineural hearing loss was evident in 66 patients (51%), confirmed by audiological testing; in 4 (3%), this was the only feature of the disease. Diabetes (type I or II), diagnosed on the basis of elevated HbA1C and serum glucose and confirmed by oral glucose tolerance testing, was present in 54 patients (42%).

Overall, 36 patients (28%) did not conform to any of the classical syndromes associated with the m.3243A>G mutation. The phenotypic spectrum seen in this group was diverse with central nervous system and muscle involvement being most common (proximal myopathy (27%), ataxia (24%), migraine (23%) and seizures (18%)). A total of 12 individuals (9%) harbouring the mutation were clinically asymptomatic, having undergone screening because of affected maternal relatives. There was no difference in age or gender compared with the symptomatic group.

All patients had echocardiography performed. Cardiomyopathy, in addition to other clinical features of mitochondrial disease, was confirmed in 24 patients (19%), of whom 6 (25%) demonstrated dilated and 18 (75%) hypertrophic morphology. There were no cases of isolated cardiomyopathy. Patients were either conservatively managed or treated with β-blockers ± ACE inhibitors;

Table 1 Summary of clinical features seen in 129 patients with the m.3243A>G mutation from 'The UK MRC Mitochondrial Disease Patient Cohort Study'

Clinical phenotype	Number of patients (M : F) (n=129)	Non-syndromic clinical features																
		CPEO	Retinopathy	SNHL	DM	CVA-like episodes	Encephalopathy	Proximal myopathy	Ataxia	Migraine	Seizures	Dystonia	DD or cognitive decline	GI	SS	CM	
																D	H
MELAS	13 (7:6)	0	1	3	2	13	13	2	4	5	7	1	3	1	1	1	4
MIDD	39 (15:24)	0	11	39	39	1	0	8	7	8	3	0	0	4	2	3	6
MELAS/MIDD	8 (4:4)	0	0	8	8	8	8	4	5	2	5	0	0	0	0	0	3
CPEO	0 (0:0)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
MELAS/CPEO	2 (0:2)	2	1	1	1	2	2	1	2	1	1	0	0	0	0	0	0
MIDD/CPEO	6 (4:2)	6	2	6	6	0	1	1	2	1	1	0	0	0	0	1	0
CPEO+	8 (4:4)	8	0	2	1	1	1	4	3	5	1	0	0	0	0	0	1
MERRF	1 (1:0)	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
Isolated SNHL	4 (2:2)	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0
Asymptomatic	12 (3:9)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Atypical	36 (10:26)	0	1	13	0	2	4	17	7	14	9	2	3	6	1	1	4

CM, cardiomyopathy; CPEO, chronic progressive external ophthalmoplegia; CVA, cerebrovascular accident; D, dilated; DD, developmental delay; DM, diabetes mellitus; F, female; GI, gastrointestinal; H, hypertrophic; M, male; MELAS, mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibres; MIDD, maternally inherited deafness and diabetes; MRC, Medical Research Council; SNHL, sensorineural hearing loss; SS, short stature.

no patients were listed for cardiac transplantation in the defined study period.

Heteroplasmy levels were measured in only 87 individuals (67%) in this study and in a variety of tissue types (ie, muscle, blood and/or urinary epithelial cells) at varying stages of the disease and therefore correlation with phenotypic features was not attempted. The measurement of blood lactate levels for diagnosis is inconsistent: spurious results resulting in relative tissue hypoxia and a falsely elevated lactate level can be misleading; similarly a normal blood lactate does not exclude an underlying mitochondrial disease. Blood lactate levels are notoriously vulnerable to errors in sampling technique, for example, application of tourniquet, and were not routinely measured in this cohort.

DISCUSSION

This is the largest cohort study to date reviewing the clinical phenotypes of patients harbouring the m.3243A>G mutation, and represents 23% of all patients currently recruited to the MRC Mitochondrial Diseases Patient Cohort Study UK. These data confirm the considerable clinical variability among individuals with this mutation. Just over half of patients exhibited a recognised classical phenotype, confirming the diagnosis could be missed if clinicians considered the diagnosis only in terms of a 'complete syndrome'. In all, 10% of our cohort met diagnostic criteria for MELAS, significantly fewer than in previous reports.[7 10] There is also major overlap between the classical phenotypes contributing to the spectrum of the disease. Central nervous system involvement predominates in adults but usually in combination with at least one other system. Based on the findings in our cohort, and the high frequency of this mutation within the general population[8 9] we suggest patients should be considered for screening for m.3243A>G when any of the following criteria are present: (1) MELAS, MIDD or an overlap syndrome; (2) a maternal family history of m.3243A>G; (3) three or more clinical features, with no other causative unifying diagnosis, found to commonly occur in the miscellaneous group: cardiomyopathy, deafness, developmental delay or cognitive decline, diabetes mellitus, epilepsy, gastrointestinal disturbance (constipation and/or irritable bowel syndrome), migraine, PEO and retinopathy. Using these criteria, all of the patients in our cohort would have been diagnosed with the m.3243A>G mutation.

The clinical information gained from the analysis of this cohort indicates clear implications for the management of patients harbouring the m.3243A>G mutation who require comprehensive multi-system clinical review, including cardiac, audiological and ophthalmological assessment. Continuing health surveillance, for the development and complications of diabetes, and particularly for cardiomyopathy, may be prevented by early intervention.

CONCLUSIONS

While the m.3243A>G mtDNA mutation in *MTTL1* results in an eclectic range of clinical features, many patients affected by this mutation exhibit a clinical phenotype that does not fall within accepted criteria for the currently recognised classical mitochondrial syndromes. Failure to diagnose these individuals will prevent their access to important health surveillance and may allow clinically significant health sequelae, such as unrecognised cardiomyopathy, to arise. We propose criteria for initiating testing of the m.3243A>G mutation to ensure these patients are not overlooked. A comprehensive description of clinical phenotype is essential when documenting the natural history of m.3243A>G-related disease and to promote development of outcome measures for future clinical trials of disease-modifying therapies.

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Contributors All authors have made a contribution to the work. The authors take full responsibility for the data, analyses and interpretation, and agree with the contents of the manuscript. VN and RDSP contributed to the design, analysis and interpretation of the study in addition to drafting the manuscript, and contributed to the ascertainment of the clinical phenotype of the patients. DMT and RMF contributed to the conceptualisation of the study in addition to revising the manuscript, and contributed to the ascertainment of the clinical phenotype of the patients. RWT contributed to the collation of molecular genetic data and curation of the mitochondrial disease cohort database. MGS and EEM contributed to the collation of molecular genetic data. SR and MGH contributed to revising the manuscript and to the ascertainment of the clinical phenotype of the patients.

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Competing interests VN is a Clinical Research Associate for the MRC Mitochondrial Disease Patient Cohort Study UK. RDSP is a Clinical Research Associate for the MRC Mitochondrial Diseases Patient Cohort Study UK. SR is supported by Great Ormond Street Hospital Children's Charity, and a Principal Investigator for the MRC Mitochondrial Disease Patient Cohort Study UK. RWT is Professor of Mitochondrial Pathology and a Principal Investigator for the MRC Mitochondrial Disease Patient Cohort Study UK. DMT is the Chief Investigator for the MRC Mitochondrial Disease Patient Cohort Study UK. MGH is a Principal Investigator for the MRC Mitochondrial Disease Patient Cohort Study UK. RMF is a Principal Investigator, and Data Custodian, for the MRC Mitochondrial Disease Patient Cohort Study UK.

Ethics approval Approval for the MRC Centre for Translational Research in Neuromuscular Diseases Mitochondrial Disease Patient Cohort Study UK was granted by Trent Research Ethics Committee UK (REC reference number 08/H0405/72).

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