Canadian Journal of Cardiology 31 (2015) 1360–1376

Review

Mitochondrial Diseases and Cardiomyopathies

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ABSTRACT

Mitochondrial cardiomyopathies are clinically and genetically heterogeneous. An integrative approach encompassing clinical, biochemical, and molecular investigations is required to reach a specific diagnosis. In this review we summarize the clinical and genetic aspects of mitochondrial disorders associated with cardiomyopathy, including disorders of oxidative phosphorylation. It also describes groups of disorders that, although not usually classified as mitochondrial disorders, stem from defects in mitochondrial function (eg, disorders of β-oxidation and the carnitine cycle), are associated with secondary mitochondrial impairment (eg, organic acidurias), and are important diagnostically because they are treatable. Current biochemical and molecular techniques for the diagnosis of mitochondrial cardiomyopathies are described, and a diagnostic algorithm is proposed, to help clinicians in their approach to cardiomyopathies in the context of mitochondrial diseases.

RÉSUMÉ

Les cardiomyopathies mitochondriales sont cliniquement et génétiquement hétérogènes. Une approche intégrée englobant les examens cliniques, et les analyses biochimiques et moléculaires est requise pour poser un diagnostic précis. Dans cette revue, nous résumons les aspects cliniques et génétiques des maladies mitochondriales associées à la cardiomyopathie, dont les désordres de la phosphorylation oxydative. La revue décrit également les groupes de maladies qui, bien qu'inhabituellement classifiées comme des maladies mitochondriales qui découlent des anomalies du fonctionnement des mitochondries (p. ex. les troubles de la β-oxydation et du cycle de la carnitine), sont associées à des altérations mitochondriales secondaires (p. ex. les aciduries organiques) et sont importantes sur le plan diagnostique puisqu'elles sont traitables. Les techniques biochimiques et moléculaires actuelles pour le diagnostic des cardiomyopathies mitochondriales sont décrites, et un algorithme diagnostique est proposé pour aider les cliniciens dans leur approche des cardiomyopathies dans le contexte des maladies mitochondriales.

Although metabolic disorders account for a minority of cases of cardiomyopathy, the finding of an inborn error of metabolism as the underlying cause might have profound prognostic, therapeutic, and counselling implications.[1-3] Major groups of metabolic disorders associated with cardiomyopathy include lysosomal diseases (eg, Fabry disease), glycogenoses and related disorders (eg, Pompe disease, Danon disease), organic acidurias, congenital disorders of glycosylation, disorders of mitochondrial fatty acyl-coenzyme A (CoA) β-oxidation and the carnitine cycle, disorders of mitochondrial oxidative phosphorylation (OXPHOS), and others.[1,2,4] In this review we focus on disorders of mitochondrial OXPHOS associated with cardiomyopathy. Disorders of other mitochondrial functions (eg, disorders of mitochondrial fatty acid β-oxidation and the 3-methylglutaconic acidurias) are also addressed, and disorders that cause secondary mitochondrial dysfunction, such as organic acidurias and Friedreich ataxia.

Mitochondrial Disease

Mitochondrial diseases are the largest subgroup of inborn errors of metabolism, resulting from deficiencies in the OXPHOS system. Various studies on prevalence have been published with recent estimates of up to 1 in 4000 affected individuals.[5-10] These diseases are clinically, biochemically, and genetically heterogeneous and might present at any age, or even in utero.[11] Because mitochondrial OXPHOS is a ubiquitous and essential cellular function, mitochondrial diseases might present with single or multiorgan involvement (with impairment of seemingly unrelated tissues), and nonspecific but often progressive or severe symptoms. Lactic acidosis might be present, but might also be intermittent or absent.[2] Defects of different components of the OXPHOS system and different underlying gene defects might result in the same phenotype, and a given gene defect might lead to various clinical presentations, thus complicating the establishment of a diagnosis.

The OXPHOS system comprises 5 multisubunit enzyme complexes: complexes I-IV, which make up the respiratory chain, and complex V, the adenosine triphosphate (ATP)

Received for publication July 3, 2015. Accepted August 21, 2015.

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See page 1371 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.08.017

synthase. The respiratory chain couples electron transfer to acceptors of increasingly higher electron affinity with the generation of a proton gradient across the inner mitochondrial membrane. The energy stored in this electrochemical gradient drives the production of ATP from adenosine diphosphate by complex V. All 5 OXPHOS complexes are embedded in the inner mitochondrial membrane. The OXPHOS chain also comprises 2 electron transporters: coenzyme Q_{10} (CoQ_{10}) and cytochrome c. CoQ_{10} shuttles the electrons between complexes I and III and between complexes II and III, and cytochrome c between complexes III and IV. The genes encoding the subunits of the 5 enzymatic OXPHOS complexes are distributed among the mitochondrial DNA (mtDNA) and the nuclear DNA. Approximately 1500 proteins are required to build and ensure the functioning of the OXPHOS chain.[12] Ninety-nine percent of these are encoded by nuclear DNA and approximately 1% is encoded by mtDNA. The mtDNA is circular and 16.5 kilobase pairs in length, and is maternally inherited.[13,14] It contains 37 genes encoding the 13 subunits of the 5 OXPHOS complexes (7 complex I subunits, 1 complex III subunit, 3 complex IV subunits, and 2 complex V subunits), 2 ribosomal RNAs (rRNAs), and 22 transfer RNAs (tRNAs) that are involved in mitochondrial translation. Each cell contains hundreds of mitochondria and there are hundreds to thousands of copies of mtDNA within each mitochondrion, with a positive correlation between the mtDNA copy number of a cell and its respiratory demand.[15]

Within the mtDNA population of a cell, a mutation is said to be homoplasmic when all mtDNA molecules of that cell carry it. Maternally inherited homoplasmic pathogenic mtDNA mutations have been associated with mitochondrial cardiomyopathy; penetrance might be incomplete.[16-18] These pathogenic homoplasmic mutations might cause a restriction of the biochemical defect to a single affected tissue (eg, the heart) with normal activity in skeletal muscle and fibroblasts; this differential phenotypic expression might be the effect of additional factors, such as tissue-specific nuclear modifier genes.[18,19]

A mutation might also only be found in a subpopulation of the mtDNA molecules, which creates a mixed population of wild type and mutant mtDNA within a single cell, a condition known as heteroplasmy. The tissue-specific level of heteroplasmy has been shown to mirror the tissue expression of disease and the clinical phenotype in a number of patients.[20] A minimum threshold of mutated mtDNA is necessary before biochemical defects and clinical symptoms become apparent. This threshold is different between tissues and for each mutation. A threshold of 60% mutant load or more is usually associated with disease, but a lower threshold of 20%-25% has also been associated with clinical symptoms.[15,21] Maternal homoplasmic mtDNA mutations are transmitted to all offspring, often with incomplete penetrance, whereas the heteroplasmic mtDNA mutations are distributed randomly to offspring; this makes the phenotype of children of affected mothers difficult to predict.

Approximately 15% of mitochondrial diseases are caused by a mutation in mtDNA[6]; thus, most mitochondrial diseases are caused by mutations in nuclear genes. Hundreds of different nuclear encoded proteins are required for the biosynthesis of the OXPHOS machinery (assembly factors, mitochondrial translation factors, proteins involved in mitochondrial fission and fusion processes, and in mtDNA maintenance, substrate transporters, etc). Mutations in 250 nuclear genes and >1000 potential disease candidate genes account for defects in the mitochondrial energy-generating system by causing isolated or combined deficiencies of the OXPHOS enzyme complexes. A list of these genes and their variants is regularly updated at MitoMap (http://www.mitomap.org/MITOMAP). With improved methods and lower costs for gene mutation screening, the spectrum of mitochondrial diseases might be expected to expand.

Mitochondrial Cardiomyopathies

The frequency of cardiomyopathy in patients with mitochondrial disease has been estimated to be approximately 20%-25%, and up to 40% in some series.[22-25] Screening for cardiomyopathy is therefore a standard part of the management of children and adults with known or suspected mitochondrial disease.[26] In reported series, mortality in children with mitochondrial disease was significantly higher in those with cardiomyopathy (71%) than in those without (26%).[23]

Mitochondrial cardiomyopathy must also be considered in the absence of known mitochondrial disease, of which it might be the first, or even the sole, clinical manifestation.[17,18,27-30] Hypertrophic cardiomyopathy is the most common form, occurring in 40% of patients,[24,26,31] but mitochondrial cardiomyopathies might also present as left ventricular noncompaction or as dilated, histiocytoid, or restrictive cardiomyopathies, or might be associated with endocardial fibroelastosis.[23,25,26,32]

A summary of the main mitochondrial disorders reported in association with cardiomyopathy is shown in Table 1.

Mitochondrial "syndromes"

Mitochondrial "syndromes"—constellations of signs and symptoms typically associated with specific abnormalities of mtDNA—might be accompanied by cardiomyopathy, conduction abnormalities, or both. Kearns-Sayre syndrome is part of a spectrum of disease phenotypes caused by mtDNA deletions. Cardiac conduction block is one of its cardinal manifestations (the others include pigmentary retinopathy, progressive external ophthalmoplegia, increased cerebrospinal fluid protein concentration, cerebellar ataxia, and onset before the age of 20 years),[33] but cardiomyopathy might also be observed.[34,35] Cardiomyopathy and/or conduction abnormalities might also accompany mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS),[36] myoclonic epilepsy with ragged red fibres (MERRF),[37] and mtDNA-associated Leigh syndrome/neuropathy, ataxia, and retinitis pigmentosa syndromes[38] (Table 1); hypertrophic cardiomyopathy is most common, but dilated cardiomyopathy and left ventricular noncompaction have been reported, as have rare instances of histiocytoid and restrictive cardiomyopathy (the latter with the common m.3243A>G MELAS mutation[32]). It is worth noting that symptom severity and the number of organs affected might vary greatly both in time and from one individual to another, even within the same kindred; a patient whose cardiomyopathy is due to a mitochondrial syndrome-associated mutation might not, therefore, present an overall clinical picture suggestive of this syndrome. For