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Review

Mitochondrial respiratory chain disorders in childhood: Insights into diagnosis and management in the new era of genomic medicine ☆

Minal J. Menezes [a,b], Lisa G. Riley [b], John Christodoulou [a,b,c,*]

[a] Disciplines of Paediatrics and Child Health, Sydney Medical School, University of Sydney, New South Wales, Australia
[b] Genetic Metabolic Disorders Research Unit, Kids Research Institute, Children's Hospital at Westmead, Sydney, NSW, Australia
[c] Genetic Medicine, Sydney Medical School, University of Sydney, New South Wales, Australia

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ABSTRACT

Background: Mitochondrial respiratory chain disorders (MRCDs) are some of the most common metabolic disorders presenting in childhood, however because of it clinical heterogeneity, diagnosis is often challenging. Being a multisystemic disorder with variable and non-specific presentations, definitive diagnosis requires a combination of investigative approaches, and is often a laborious process.
Scope of review: In this review we provide a broad overview of the clinical presentations of MRCDs in childhood, evaluating the different diagnostic approaches and treatment options, and highlighting the recent research advances in this area.
Major conclusions: Extensive research over the years has significantly increased the frequency with which accurate diagnosis is being made, including the identification of new biomarkers and next generation sequencing (NGS) technologies. NGS has provided a breakthrough in unravelling the genetic basis of MRCDs, especially considering the complexity of mitochondrial genetics with its dual genetic contributions.
General significance: With an increased understanding of the pathophysiology of this group of disorders, clinical trials are now being established using a number of different therapeutic approaches, with the hope of changing the focus of treatment from being largely supportive to potentially having a positive effect on the natural history of the disorder.
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1. Introduction

The most important carrier of chemical energy in almost all living organisms is adenosine triphosphate (ATP). The useful energy in ATP is bound in highly energetic phosphor-anhydride bonds, which release free energy when hydrolyzed. This energy is used for diverse cellular functions such as synthesis of macromolecules, contraction of muscle cells, movement of individual cells from one location to another and the transport of molecules against a concentration gradient [1].

This range of fundamental cell functions is dependent on energy, and so it should not be surprising that impaired cellular energy production can affect any organ or tissue [2]. The vast majority of ATP is produced within mitochondria, intracellular organelles present in virtually all eukaryotic cells. The most important pathway for the synthesis of most cellular ATP is the mitochondrial respiratory chain (MRC), through a process of oxidative phosphorylation (OXPHOS) [3]. The MRC, which is composed of five enzyme complexes (complexes I–V) (refer to Fig. 1), and consists of approximately 90 subunits, is located in the inner mitochondrial membrane. Mitochondrial proteins are encoded by two distinct genetic systems, mitochondrial DNA (mtDNA) and nuclear DNA (nDNA). Of the 90 subunits of the RC only 13 are encoded by mtDNA, which is a small 16.6 kb circle of double stranded DNA [4].

Complex I [NADH-coenzyme Q (CoQ) reductase] consists of 47 polypeptides, seven of which are encoded by mtDNA. Complex I carries reducing equivalents from NADH to CoQ. Complex II (succinate-CoQ reductase), which includes FAD-dependent succinate dehydrogenase and iron–sulphur proteins, is the only complex for which all four of its subunits are nuclear encoded, and carries reducing equivalents from $FADH_2$ to CoQ [4]. Complex III (reduced CoQ-cytochrome *c* reductase) consists of 11 subunits, of which only one is encoded by the mitochondrial genome. Complex III forms a homodimer and transfers electrons from CoQ to cytochrome *c* [5]. Complex IV [cytochrome *c* oxidase (COX)] consists of 13 protein subunits (three of which are encoded by mtDNA), two cytochromes (cytochromes *a* and *a*3) and two copper atoms. It is the terminal oxidase of the MRC, and catalyses the transfer of reducing equivalents from cytochrome *c* to molecular oxygen [4]. Complex V is composed of a membrane-bound subcomplex (F_0), a large extra membranous complex (F_1) that resides in the matrix

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* Corresponding author at: Western Sydney Genetics Program, Children's Hospital at Westmead, Locked Bag 4001, Westmead, New South Wales 2145, Australia. Tel.: +61 2 9845 3452; fax: +61 2 9845 1864.
E-mail address: john.christodoulou@health.nsw.gov.au (J. Christodoulou).

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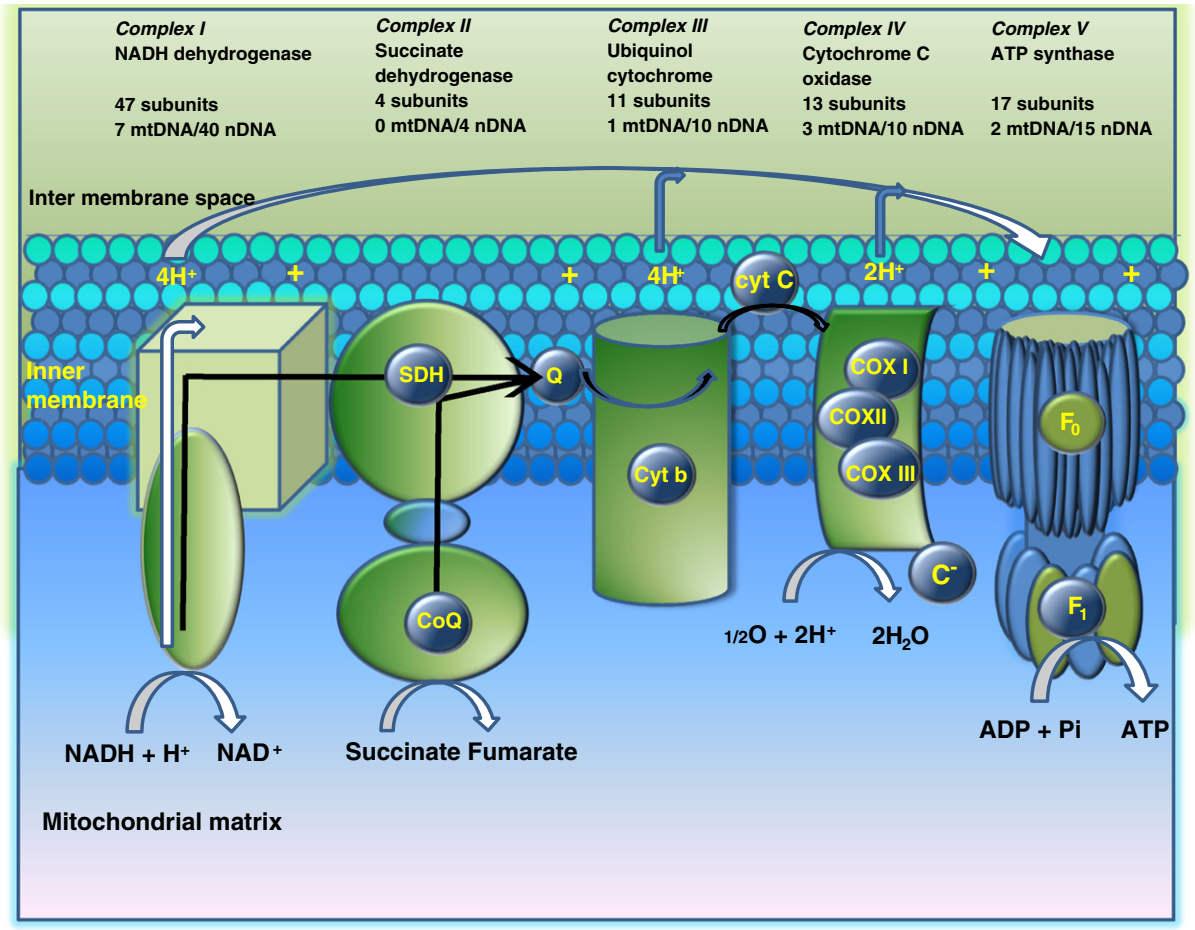

Fig. 1. The mitochondrial respiratory chain. The respiratory chain consists of five enzyme complexes (complexes I–V) and two intermediary substrates (coenzyme Q and cytochrome *c*). Complexes I and II are the two main entry points of reducing equivalents in the MRC. The NADH + H^+ and $FADH_2$ produced by intermediary metabolism are oxidised further by the MRC to establish an electrochemical proton gradient. Complex III forms a homodimer and transfers electrons from CoQ to cytochrome *c*. Electron transfer is then coupled to complex V, which uses the proton motive force created to generate ATP.

space, and a stalk connecting the two complexes. Protons from the intermembrane space are allowed to enter complex V through the (F_0) complex, leading to subunit rotation within the enzyme complex. The energy from this rotation is then used to generate ATP, which takes place in the (F_1) complex [6].

The oxidation process is fuelled by pyruvate generated from the glycolysis of carbohydrates and fatty acids released from triglycerides. They are imported into the mitochondrial matrix, allowing pyruvate to be metabolised by the pyruvate dehydrogenase complex, and fatty acids to be catabolised by the β-oxidation pathway, both leading to the generation of acetyl CoA. The citric acid cycle then utilises these acetyl groups to produce substrates like NADH and $FADH_2$ for OXPHOS. In addition, acetyl CoA may be used to generate ketone bodies, which can be utilised as an alternate energy source by the brain and striated muscle. The electrons released from NADH and $FADH_2$ are then shuttled through the various complexes of the MRC, resulting in the production of ATP and water. The metabolism of one molecule of glucose in the mitochondria produces 36 molecules of ATP, whereas glycolysis in the cytoplasm produces only 2 molecules of ATP. This means that organs with a high-energy demand are vulnerable if mitochondrial energy production is compromised. Indeed, disorders affecting energy metabolism are often multisystemic, particularly affecting high energy-demanding tissues like skeletal muscle and brain, and together are collectively often referred to as the mitochondrial encephalomyopathies [7,8].

1.1. Prevalence of mitochondrial respiratory chain disorders

The first reported mitochondrial respiratory chain disorder (MRCD) was in a woman with severe hypermetabolism in 1962 [8], and subsequently the range of clinical conditions attributed to this group of disorders has expanded greatly. This group of disorders is now reported to be one of the most common groups of inborn errors of metabolism, with an estimated frequency of one in 5000 live births [9], and in paediatric neurology they are regarded as the most frequent cause of metabolic abnormality [10]. This is most likely an underestimate of the actual prevalence of these disorders as the symptoms are nonspecific and can be mistaken for other diseases [10]. Most MRCDs presenting in childhood have an autosomal recessive pattern of inheritance and therefore have a higher incidence in ethnic groups where consanguinity is seen [11], although all forms of inheritance have been reported. On the other hand, most diagnosed MRCDs first presenting in adulthood are due to an underlying primary mtDNA defect [11,12].

2. Clinical and molecular features of MRCDs

2.1. Clinical presentation in childhood

A defective OXPHOS system should be suspected in a patient who presents with a combination of unexplained neuromuscular and non-neuromuscular symptoms [2]. Childhood manifestations of MRCDs are

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