Applications of magnetic resonance spectroscopy to diagnosis and monitoring of mitochondrial disease

Matthews P.M., Taivassalo T.

Clinical Magnetic Resonance Spectroscopy Laboratory, Dept. of Neurology and Neurosurgery, Montreal Neurological Institute, 3801 University St., Montreal, Canada

Magnetic resonance spectroscopy (MRS) can now be performed on routine high-field clinical magnetic resonance imaging systems. Over the last decade it has provided several useful insights into the pathophysiology of mitochondrial disorders. More recently, the feasibility of applications to clinical diagnosis and monitoring have been demonstrated. Exciting new work suggests that carefully supervised physical conditioning in conjunction with sodium dichloroacetate administration can markedly enhance both biochemical measures of aerobic metabolism and functional performance of patients with mitochondrial myopathies.

Key words: Magnetic resonance spectroscopy — MRI — Mitochondrial disease — Myopathy — Therapy

Introduction

The explosion of interest in mitochondrial diseases over the last decade reflects two important technological advances in their evaluation. First is the application of biochemical methods developed in animal studies to analysis of mitochondrial enzyme activities and respiratory function in small human muscle biopsy samples, allowing definition of abnormalities of oxidative metabolism in the affected tissue. Second is the identification of disease-associated mutations in mitochondrial DNA.

Magnetic resonance spectroscopy was applied very early to the diagnosis and monitoring of mitochondrial disease as an extension of the first, biochemical approach to disease characterization. Initially, it offered dramatic, direct demonstration that mitochondrial function could be impaired in intact tissue to a similar extent to the reduction of activity observed in vitro [19]. Later, it was proposed as a useful adjunct to other non-invasive approaches to characterization of muscle pathology, potentially with an important role in selection of patients for more invasive, specific, and costly biochemical or genetic studies [9]. More recently, MRS has found a useful role as an objective marker of treatment response in clinical trials of therapies for mitochondrial disorders [1, 3, 4, 14, 18]. There is particular importance for such a marker of potentially high sensitivity because of the necessarily limited number of patients with these rather rare disorders that can be studied with any given protocol.

In this review we will briefly remind readers of fundamental principles of mitochondrial disease and MRS. Information available from MRS examinations will be outlined and its potential role for evaluation of mitochondrial disorders in a clinical setting will be outlined. Applications to the study of mitochondrial disease will be illustrated by results of studies of experimental therapies for this challenging range of disorders.

Mitochondrial disease

The brain relies primarily on oxidative energy metabolism. Although muscle can use glycolysis alone for energy production during brief periods, sustained work is primarily aerobic, relying on mitochondrial oxidative phosphorylation. It is therefore not surprising that symptoms referable to brain and muscle are prominent in mitochondrial disorders [8]. Mitochondrial oxidative metabolism occurs primarily with production of reducing equivalents by matrix enzymes and the terminal reduction of molecular oxygen with coupling of the energy released to ATP production by the membrane-bound enzyme complexes of the electron-transport chain. Clinically important disorders of mitochondrial metabolism can result from a broad range of different defects: (i) defective substrate catabolism (e.g., pyruvate dehydrogenase deficiency); (ii) deficiencies of tricarboxylic acid cycle enzymes (e.g., fumarase deficiency); (ii) defects of the electron transport chain complexes (e.g., in mitochondrial DNA [mtDNA] deletion syndromes); (iv) “futile cycling” of ions across the mitochondrial inner membrane (e.g., the calcium leak of Luft’s syndrome); and (v) defective ATP synthase function (e.g., the ATPase 6 mtDNA mutation associated with NARP).

The clinical spectrum of mitochondrial disorders is large.
In part this reflects the biochemical heterogeneity alluded to above. Other factors also may play major roles. First, the most common disorders result from mtDNA mutations, which are heteroplasmic and can show varying proportions of mutant and wild-type mitochondrial genomes in different tissues and even in different cells within the same tissue, affecting expression of the biochemical phenotype [17]. Second, there are interactions between polymorphisms of mtDNA (and potentially also nuclear DNA) that affect presentation. Third, environmental factors and patterns of tissue activity also most likely influence the degree of expression of the underlying defects. In consequence, clinical diagnosis of mitochondrial disease is difficult and a good diagnostic sensitivity of detection in a population necessarily demands intensive evaluation of a large proportion of patients who do not have primary mitochondrial disease. Development of tools such as MRS that can be used for screening of patients prior to more invasive and expensive procedures therefore is important.

MRS has the additional advantage of offering quantitative indices of in vivo mitochondrial function. This affords the opportunity to follow the characteristically fluctuating course of the diseases with an endpoint that can be correlated usefully with (less reliable) clinical measures of impairment. It also allows the difficult problem of primary vs secondary mitochondrial disease to be addressed. Secondary mitochondrial disorders may arise from impairment of blood flow (e.g., claudication) or oxygen delivery (e.g., hypoxia) or release of mitochondrial toxins (e.g., AZT myopathy). They may be recognized by association with another (underlying) pathology and correlation of severity of mitochondrial dysfunction with severity of the primary pathology or of the toxin (e.g., AZT).

MRS: principles

Magnetic resonance spectroscopy (MRS) allows for direct, continuous and noninvasive assessment of muscle or brain metabolites. MRS techniques have advanced considerably in the past 15 years, allowing examinations to be conducted within a routine clinical imaging schedule using standard high-field imaging systems. The basic technique of MRS involves the delivery of a radiofrequency pulse to the tissue when the subject is positioned in a strong magnetic field. Atomic nuclei with a magnetic moment or spin (such as naturally occurring isotopes of phosphorus or hydrogen) will align themselves with the applied magnetic field. With application of an appropriate radiofrequency pulse, nuclei will absorb energy and be displaced from thermal equilibrium. After the brief radiofrequency pulse, as the nuclei relax back to thermal equilibrium, radiofrequency energy is emitted. This can be detected as a sinusoidal signal called free induction decay. The Fourier transformation of the free induction decay generates a spectrum conventionally represented as a plot of resonance frequency of excited nuclei in the sample as function of signal intensity.

Fig. 1. 1.5 T phosphorus MRS of gastrocnemius muscle from a normal subject. Relative metabolite concentrations are reflected in relative resonance intensities. Resonances are labeled as follows: 1. phosphomonoesters; 2. inorganic phosphate; 3. phosphodiesters; 4. phosphocreatine; 5. ATP-phosphate; 6. ATP-phosphate and NADH; 7. ATP-phosphate. The abscissa is a parts per million (ppm) chemical shift scale (reproduced with permission from reference [12]).