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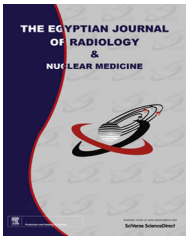

ORIGINAL ARTICLE

Role of brain magnetic resonance spectroscopy in the evaluation of suspected mitochondrial diseases in children: Experience in 30 pediatric cases

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KEYWORDS

Magnetic resonance spectroscopy;
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Abstract *Introduction:* Mitochondrial diseases are a group of inherited disorders caused by derangement of mitochondrial respiration. MR spectroscopy (MRS) has been shown to detect abnormal accumulation of lactate in brain parenchyma and CSF in patients with mitochondrial disorders, but the frequency of detection is largely unknown.
Aim of the work: To evaluate the role of brain MR spectroscopy in the assessment of suspected mitochondrial diseases in the pediatric age group.
Patients and methods: Thirty children with suspected mitochondrial diseases were examined by MRS. Examination was done using multisection technique and multiple echo times mainly short (35 ms) and intermediate (144 ms). Mitochondrial disease criteria scoring system was used to confirm the suspected diagnosis.
Results: All patients showed elevated lactate peak with the CSF being the most sensitive (100%). Among the 30 patients, 26 (86.7%) had elevated levels of blood lactate/pyruvate ratio. Conventional MRI showed highly suggestive features in 15 patients while non specific findings were detected in 11 patients and 4 showed normal appearing brain.
Conclusions: MRS provides a noninvasive tool for the diagnosis of mitochondrial diseases, especially in children with non specific findings on MRI, normal appearing MRI or a normal blood lactate/pyruvate ratio.

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1. Introduction

Mitochondrial disorders (MDs) are no longer regarded as rare disorders, and approximately one-third of inherited metabolic disorders in children are attributable to mitochondrial defects (1). Mitochondrial disorders (MDs) are a family of genetically and clinically heterogeneous diseases characterized by defective energy production. Their heterogeneity is due in part to the biochemical complexity of mitochondrial respiration and the fact that two genomes, one mitochondrial and the other nuclear, encode the subunits of the respiratory chain complexes (2).

Mitochondrial disorders (MDs) manifest in tissues and organs with high-energy demands, with the central nervous system (CNS) being the second most frequently affected system after the muscular system because of its strong dependence on oxidative phosphorylation (3). CNS manifestations are found in both syndromic and non-syndromic mitochondrial disorders with the most common known mitochondrial syndromes include Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes (MELAS), Kearns–Sayre syndrome (KSS), and Alpers disease (4).

Clinical manifestations of MDs in the pediatric age group are often nonspecific because symptoms may arise from any organ or system. Although recent advances in genetics have led to the development of diagnostic tools for many MDs, still most of the patients present with challenging diagnostic dilemmas. Therefore, diagnostic confirmation of a MD is based on a combination of modalities including clinical features, metabolic survey, neuroradiologic findings, histopathologic analysis of muscle specimens, and molecular genetic studies (4).

Apart from the clinical, biochemical and morphological investigations, neuroimaging is of great importance when diagnosing mitochondrial disorders with CNS involvement. Since the study by Barkovich et al. (5), claims that the combination of deep gray matter and peripheral white matter involvement in children should suggest a mitochondrial disorder, the field of neuroimaging has witnessed a marked progress. Both structural MRI and functional brain imaging methods, including magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI) and perfusion MRI, have helped greatly to increase our knowledge of mitochondrial disorders by allowing a non-invasive pathological assessment of the anatomic lesions, metabolism and hemodynamics of the brain (6).

MRI signal abnormalities, can reveal specific or 'signature' disease features (as in MELAS syndrome), non-specific features or leukodystrophic-like features suggesting a mitochondrial disorder, while a structurally normal brain on MRI may also be found (7,8).

The most common known radiological features of mitochondrial syndromes include bilateral symmetrical signal abnormalities, most frequently in the lentiform (putamen more often than globus pallidus) and caudate nuclei, as well as periaqueductal gray matter, red nuclei and dentate nuclei in Leigh syndrome, stroke-like lesions which are often transient with the lesions predominantly affecting the occipital gray matter, yet not confined to vascular territories in MELAS; and the involvement of the subcortical U fibers with sparing of the periventricular white matter in Kearns–Sayre syndrome (KSS) which differentiates it from most lysosomal and peroxisomal disorders where subcortical regions are only affected late in the disease (9).

MRS is an MR-based, non-invasive method to get chemical information from the brain. The development of proton MRS (H-MRS) has made it possible to study both normal and abnormal metabolite concentrations in the pediatric brain at different developmental stages. These include N-acetyl aspartate (NAA), creatine (Cr), choline (Cho), myoinositol (myo-I), glutamate, glutamine, and lactate (10).

When oxidative phosphorylation is impaired as in mitochondrial diseases, energy metabolism follows the alternative route of anaerobic glycolysis and produces lactic acid. Lactate has a chemical shift of 1.33 ppm and presents as a doublet peak on in vivo H-MRS due to coupling effects (10). Lactate elevation has been found as the most prominent MRS signal abnormality in mitochondrial diseases (6).

A consensus mitochondrial disease criteria scoring system (MDC) has been recently established to facilitate the diagnostic work-up of patients with suspected mitochondrial disorders (11). MDC is based on a multidisciplinary approach that includes clinical signs and symptoms, metabolic/imaging studies and muscle histology. Among these criteria brain magnetic resonance imaging (MRI) and brain magnetic resonance spectroscopy (MRS) examinations play an important role, especially in children, since MR findings may influence the decision to precede with additional specific tests such as molecular analysis (which is not available at every center) or muscle biopsy (which is an invasive procedure) (8,11).

The aim of this study was to evaluate the role of brain MRS in the assessment of suspected mitochondrial diseases in the pediatric age group.

2. Materials and methods

Thirty children with clinically suspected diagnosis of mitochondrial disease were referred for MR imaging and MR spectroscopy between October 2011 and May 2013. Detailed neuro logical examination and basic laboratory tests were performed on all patients. The laboratory tests consisted of analysis of arterial blood gas, blood lactate level (normal 3–12 mg/dl), lactate/pyruvate ratio (normal less than 18) and metabolic surveys including assays of blood amino acids and urinary organic acids, with lactate/pyruvate ratio being the main laboratory test which we depended upon in our analysis.

2.1. MRI imaging

All patients in our study population required sedation or anesthesia. Pre-scanning preparation included 3–6 h fasting. MR imaging and MR spectroscopy examinations were performed in a single session in most cases with a 1.5-T MR unit (Signa Horizon 1.5; GE Medical Systems, Milwaukee, WI). T1-weighted images [echo time (TE)/repetition time (TR) 11 ms/550 ms], T2-weighted images (TE/TR 93 ms/4000 ms), fluid-attenuated inversion recovery (FLAIR) (TE/TR/inversion time 110 ms/10000 ms/2250 ms) and diffusion weighted images (DWI) (TE/TR: 105 ms/5200 ms) were performed.

Axial and sagittal T1-weighted images were assessed in particular for the presence of cortical atrophy, agenesis/hypoplasia of the corpus callosum, enlargement/dilatation of the ventricles and/or subarachnoid spaces. Axial and coronal T2-weighted images, including fluid attenuated inversion recovery (FLAIR) images, were studied to identify signal intensity