



Electrocardiography as an early cardiac screening test in children with mitochondrial disease

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Received: 14 September 2009, Revised: 25 September 2009
Accepted: 20 October 2009

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Introduction

Mitochondria are the main energy producing cellular organelles¹⁾. Mitochondrial disease (MD) is an inherited metabolic disorder which generally affects the cellular energy metabolism of tissues due to defects in the mitochondrial respiratory chain complex (MRC)²⁾. These MRC defects affect cellular function in several of ways³⁾. The most commonly recognized clinical manifestations of MRC defects are related to the neuromuscular system. However, MRC defects can affect any organ system in the

Purpose: To evaluate myocardial conductivity to understand cardiac involvement in patients with mitochondrial disease.

Methods: We performed retrospective study on fifty-seven nonspecific mitochondrial encephalopathy patients with no clinical cardiac manifestations. The patients were diagnosed with mitochondrial respiratory chain complex defects through biochemical enzyme assays of muscle tissue. We performed standard 12-lead electrocardiography (ECG) on all patients.

Results: ECG abnormalities were observed in 30 patients (52.6%). Prolongation of the QTc interval (>440 ms) was seen in 19 patients (33.3%), widening of the corrected QRS interval in 15 (26.3%), and bundle branch block in four (7.0%). Atrioventricular block, premature atrial contraction and premature ventricular contraction were seen in two patients each (3.5%) and Wolff-Parkinson-White syndrome in one patient (1.8%).

Conclusion: Given this finding, we recommend active screening with ECG in patients with mitochondrial disease even in patients without obvious cardiac manifestation.

Key words: Electrocardiography, Mitochondria, Respiratory chain, Heart, Conductivity, Child

human body, and the clinical symptoms vary greatly depending on the organs affected^{4, 5)}.

Cardiovascular involvement has been studied as an important prognostic factor in many diseases⁶⁻¹⁰⁾. It follows that cardiovascular involvement could also be an important prognostic factor in MD^{11, 12)}. A previous study reported that the prevalence of cardiovascular involvement ranked second behind visceral involvement in patients with MD¹³⁾. Also, Finsterer¹⁴⁾ followed 113 MRC defect patients over a ten-year period and found that 40% of the patients developed heart disease including cardiomyopathy and heart

failure. But unfortunately, most of the studies have been made on cardiovascular involvement or cardiomyopathy in children with specific classic mitochondrial syndrome such as mitochondrial encephalopathy, lactic acidosis, and stroke like syndrome (MELAS) or Kearns-sayre syndrome or with specific mitochondrial DNA mutation. Little reports were made concerning cardiac conduction in patients with diverse mitochondrial diseases not to mention in Korean patients.

In this study, we analyzed characteristics of cardiac conductivity using ECG in patients with nonspecific MD who take higher percentage than those with specific types among mitochondrial disease population.

Materials and methods

1. Patients group

We performed a retrospective study on 57 MD patients with MRC defect and nonspecific encephalopathy who did not have clinical cardiovascular disease manifestations. The patients had been previously treated in the Department of Pediatrics of Gangnam Severance Hospital from March 2006 to February 2008. All MRC defect patients were confirmed by biochemical enzyme assays of muscle tissue. We excluded the specific mitochondrial syndrome and only included patients with MRC defect I, the most common type of MRC defect, to increase the homogeneity of the study.

We evaluated mitochondrial enzyme function of isolated mitochondria collected from muscle tissue using the spectrophotometric assay previously described by Rustin et al¹⁵. The activities of nicotinamide adenine dinucleotide (NADH), coenzyme Q (CoQ) reductase (complex I), succinate-CoQ reductase (complex II), succinate-cytochrome c reductase (complex II-III), cytochrome c reductase (complex III), cytochrome c oxidase (complex IV), oligomycin-sensitive ATPase (complex V) and citrate synthase were evaluated and we defined MRC defects as residual enzyme activity of less than 20% compared to that of the age-matched controls.

2. Electrocardiography

We performed standard 12-lead ECG on all patients and recorded amplitude by 1 mV/10 mm and speed by 25 mm/sec. All patients were in the supine position during the ECGs. Cardiologists analyzed all ECGs retrospectively from paper printouts. We measured RR and QT intervals in lead II and then corrected QT (QTc) by Bazett's formula, $QTc = QT / \sqrt{RR}^{16}$.

The abnormalities on the ECGs were compared with the normal

reference ranges^{7, 17, 18} (Normal PR interval: 90 to 170 ms for 7-15 years old and 120 to 200 ms for ≥ 16 years old; Normal QRS duration: 40 to 90 ms for 7-15 years and 50 to 100 ms for ≥ 16 years old; Normal QTc: ≤ 440 ms; Abnormal T wave: QRS-T angle $> 60^\circ$ in limb lead, T wave $< 10\%$ of QRS height or negative T wave in leads V4-6).

Results

1. Patient characteristics

The mean age of MRC defect patients was 4.8 ± 2.6 (mean \pm SD, years) and the gender ratio was 1:19 (Male:Female). Regarding clinical manifestations, all 57 patients (100%) showed neuromuscular system involvement, all showed delayed development and 50 (87.7%) suffered from epilepsy. Cardiovascular involvement was detected in 30 patients (52.6%) by ECG results. There were five patients (8.8%) with renal system involvement, of which four (7.0%) had decreased glomerular filtration rate and one (1.8%) had hypercalciuria (random urine Calcium/Creatinine ratio > 0.2). Hepatobiliary involvement was seen in six patients (10.5%). Five (8.8%) patients had abnormal liver echogenicity on sonography and four (7.0%) had chronic elevation of amino transferase. Ophthalmologic involvement was seen in 16 patients (28.1%). Decreased visual acuity was noted in nine (15.8%) children and abnormal visual evoked potential in 12 (21.1%). Auditory involvement in four (7.0%), and endocrine

Table 1. Demographic Characteristics of Mitochondrial Disease Patients

Characteristics	
Age (mean \pm SD, years)	4.8 \pm 2.6
Sex (M:F)	26:31
Organ involvement (No, %)	
Neuromuscular	57 (100)
Developmental delay	57 (100)
Epilepsy	50 (87.7)
Cardiovascular	30 (52.6)
ECG abnormalities	30 (52.6)
Renal	5 (8.8)
Decreased glomerular filtration rate	4 (7.0)
Hypercalciuria	1 (1.8)
Hepatobiliary	6 (10.5)
Abnormal liver echogenicity on sonography	5 (8.8)
Chronic elevation of aminotransferase	4 (7.0)
Ocular	16 (28.1)
Decreased visual acuity	9 (15.8)
Abnormal finding in visual evoked potential	12 (21.1)
Auditory	4 (7.0)
Abnormal finding in auditory evoked potential	4 (7.0)
Endocrinology	1 (1.8)
Hypoparathyroidism	1 (1.8)

Abbreviation: ECG, Electrocardiography

Table 2. The Abnormalities Detected by Electrocardiography in Mitochondrial Disease Patients

Abnormalities	
QTc prolongation (ms)	19 (33.3)
QRS widening (ms)	15 (26.3)
Bundle branch block	4 (7.0)
Atrioventricular block	2 (3.5)
Premature atrial contraction	2 (3.5)
Premature ventricular contraction	2 (3.5)
Wolff-Parkinson-White syndrome	1 (1.8)

Abbreviation: ECG, Electrocardiography

involvement in one (1.8%) with hypoparathyroidism (Table 1).

2. ECG findings

ECG abnormalities were observed in 30 patients (52.6%). Prolongation of the QTc interval (>440 ms) was seen in 19 patients (33.3%), widening of the corrected QRS interval in 15 (26.3%), and bundle branch block in four (7.0%). Atrioventricular block, premature atrial contraction and premature ventricular contraction were seen in two patients each (3.5%). Wolff-Parkinson-White syndrome was noted in one patient (1.8%) (Table 2).

Discussion

In this study, prolongation of QTc was the most frequent pathologic finding on ECG. The QT interval reflects the total duration of ventricular repolarization and depolarization, and the QTc is a known predictor of cardiovascular mortality in patients with and without known cardiac disease^{18, 19}. Prolongation of QTc can cause fatal ventricular arrhythmia as a consequence of early development of depolarization. Many studies have focused on the relationship between QTc prolongation and mortality in a variety of diseases. Salles et al²⁰ studied the relationship between QTc prolongation and mortality risk in patients with type 2 diabetes mellitus and found that the hazard ratio increased among patients with QTc prolongation. Okin et al²¹ also found that diabetic patients with QTc prolongation had an increased risk of death and a five-year mortality of 25.3% compared with 13.9% in individuals without QTc prolongation. Based on studies that have shown that QTc prolongation is associated with increased mortality, we think that it could be used as an indicator for decreased cardiac function and possible sudden cardiac death in patients with MD.

Previous studies of cardiac involvement in MD patients have mostly focused on cardiomyopathy^{11-13, 22, 23}, and the studies that do focus on conduction abnormalities have been restricted to Kerns-Sayre syndrome, which is associated with long QT syndrome^{24, 25}.

In this study, we could observe a variety of ECG abnormalities in our patients. Up until now, the pathophysiology of cardiovascular involvement in MD has been explained by a decrease in adenosine triphosphate (ATP) synthesis and damage by reactive oxygen species. Defects in ATP synthesis seem to affect both cardiac conduction and contraction^{12, 22}.

Our study of nonspecific mitochondrial encephalopathy patients again demonstrated that the heart is the second most frequently involved organ behind the neuromuscular system. Since the heart is heavily dependent on energy metabolism, it is one of the first organs to be affected when there is a defect in MRC¹¹. There have been similar findings in other metabolic disorders. Bonnet et al²⁶ recently found 24 cases of arrhythmias in 107 patients with defects in fatty acid oxidation. In those 24 patients, they also detected accumulations of long-chain acylcarnitine in fibroblasts. These accumulations occurred because the long-chain fatty acid transporters could not cross the mitochondrial inner membrane. Furthermore, Koisumi et al²⁷ found that patients with abnormally low levels of serum free carnitine had a higher risk of ventricular hypertrophy and provided evidence that low carnitine levels could induce electromyocardial changes. More extensive studies on mitochondrial metabolism are needed as seems to be intimately related to those results.

There are some limitations in this study. Since MD is rare we could not perform a prospective study. We did, however, evaluate cardiac function in patients with nonspecific mitochondrial encephalopathy and not just with a specific mitochondrial syndrome, an evaluation which had not yet been done. We found that their cardiac conductivity was affected. Because of this finding, we strongly recommend active screening and regular follow-up of patients with MD using ECG even in patients who do not exhibit typical cardiac manifestations. In addition, we think that not only screening test on conductivity but also contractility using echocardiography would be useful as well. These screening techniques will allow for early detection of any abnormalities in conductivity or contractility that could potentially lead to cardiomyopathy and sudden cardiac death. That being said, further study of cardiac involvement in patients with MD is needed to explore methods for reducing the risks of cardiomyopathy and sudden cardiac death.

Acknowledgment

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MEST) (No. KRF-2008-331-E00154).

References

- 1) McFarland R, Taylor RW, Turnbull DM. Mitochondrial diseases-its impact, etiology, and pathology. *Curr Top Dev Biol* 2007;77:113-55.
- 2) Finsterer J. Mitochondriopathies. *Eur J Neurol* 2004;11:163-86.
- 3) Munnich A, Rötig A, Chretien D, Cormire V, Bourgeron T, Bonnefont JP, et al. Clinical presentation of mitochondrial disorders in childhood. *J Inherited Metab Dis* 1996;19:521-7.
- 4) Gillis L, Kaye E. Diagnosis and management of mitochondrial diseases. *Pediatr Clin North Am* 2002;49:203-19.
- 5) Haas RH, Parikh S, Falk MJ, Saneto RP, Wolf NI, Darin N, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics* 2007;120:1326-33.
- 6) Bettinelli A, Tosoletto C, Colussi G, Tommasini G, Edefonti A, Bianchetti MG. Electrocardiogram with prolonged QT interval in Gitelman disease. *Kidney Int* 2002;62:580-4.
- 7) Bondy CA, Ceniceros I, Van PL, Bakalov VK, Rosing DR. Prolonged rate-corrected QT interval and other electrocardiogram abnormalities in girls with Turner syndrome. *Pediatrics* 2006;118:e1220-5.
- 8) Baumgartner D, Scholl-Bürgi S, Sass JO, Sperl W, Schweigmann U, Stein JI, et al. Prolonged QTc intervals and decreased left ventricular contractility in patients with propionic acidemia. *J Pediatr* 2007;150:192-7.
- 9) Giunti S, Bruno G, Lillaz E, Gruden G, Lolli V, Chaturvedi N, et al. Incidence and risk factors of prolonged QTc interval in type 1 diabetes: the EURODIAB Prospective Complications Study. *Diabetes Care* 2007;30:2057-63.
- 10) Soliman OI, van der Beek NA, van Doorn PA, Vletter WB, Nemes A, Van Dalen BM, et al. Cardiac involvement in adults with Pompe disease. *J Intern Med* 2008;264:333-9.
- 11) Lev D, Nissenkorn A, Leshinsky-Silver E, Sadeh M, Zeharia A, Garty BZ, et al. Clinical presentations of mitochondrial cardiomyopathies. *Pediatr Cardiol* 2004;25:443-50.
- 12) Holmgren D, Wählander H, Eriksson BO, Oldfors A, Holme E, Tulinius M. Cardiomyopathy in children with mitochondrial disease; clinical course and cardiological findings. *Eur Heart J* 2003;24:280-8.
- 13) Finsterer J, Stöllberger C, Blazek G, Kunafer M, Prager E. Cardiac involvement over 10 years in myotonic and Becker muscular dystrophy and mitochondrial disorder. *Int J Cardiol* 2007;119:176-84.
- 14) Finsterer J. Overview on visceral manifestations of mitochondrial disorders. *Neth J Med* 2006;64:61-71.
- 15) Rustin P, Chretien D, Bourgeron T, Gérard B, Rötig A, Saudubray JM, et al. Biochemical and molecular investigations in respiratory chain deficiencies. *Clin Chim Acta* 1994;228:35-51.
- 16) Desai M, Li L, Desta Z, Malik M, Flockhart D. Variability of heart rate correction methods for the QT interval. *Br J Clin Pharmacol* 2003;55:511-7.
- 17) Piccirillo G, Magri D, Matera S, Magnanti M, Torrini A, Pasquazzi E, et al. QT variability strongly predicts sudden cardiac death in asymptomatic subjects with mild or moderate left ventricular systolic dysfunction: a prospective study. *Eur Heart J* 2007;28:1344-50.
- 18) Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation* 1991;84:1516-23.
- 19) van Noord C, Straus SM, Sturkenboom MC, Hofman A, Aarnoudse AJ, Bagnardi V, et al. Psychotropic drugs associated with corrected QT interval prolongation. *J Clin Psychopharmacol* 2009;29:9-15.
- 20) Salles GF, Bloch KV, Cardoso CR. Mortality and predictors of mortality in a cohort of Brazilian type 2 diabetic patients. *Diabetes Care* 2004;27:1299-305.
- 21) Okin PM, Devereux RB, Lee ET, Galloway JM, Howard BV. Electrocardiographic repolarization complexity and abnormality predict all-cause and cardiovascular mortality in diabetes: the strong heart study. *Diabetes* 2004;53:434-40.
- 22) Ishikawa K, Kimura S, Kobayashi A, Sato T, Matsumoto H, Ujiie Y, et al. Increased reactive oxygen species and anti-oxidative response in mitochondrial cardiomyopathy. *Circ J* 2005;69:617-20.
- 23) Bonnet D, de Lonlay P, Gautier I, Rustin P, Rötig A, Kachaner J, et al. Efficiency of metabolic screening in childhood cardiomyopathies. *Eur Heart J* 1998;19:790-3.
- 24) Skinner JR, Yang T, Purvis D, Chung SK, Roden DM, Rees MI. Coinheritance of long QT syndrome and Kearns-Sayre syndrome. *Heart Rhythm* 2007;4:1568-72.
- 25) Barrera-Ramírez CF, Barragán-Campos HM, Ilarraza H, Iturralde P, Avila-Casado MC, Oseguera J. Cardiac involvement in Kearns-Sayre syndrome. *Rev Esp Cardiol* 2005;58:443-6.
- 26) Bonnet D, Martin D, De Lonlay P, Villain E, Jouvet P, Rabier D, et al. Arrhythmias and conduction defects as presenting symptoms of fatty acid oxidation disorders in children. *Circulation* 1999;100:2248-53.
- 27) Koizumi A, Nozaki J, Ohura T, Kayo T, Wada Y, Nezu J, et al. Genetic epidemiology of the carnitine transporter OCTN2 gene in a Japanese population and phenotypic characterization in Japanese pedigrees with primary systemic carnitine deficiency. *Hum Mol Genet* 1999;8:2247-54.
- 28) Kim JT, Lee YJ, Lee YM, Kang HC, Lee JS, Kim HD. Clinical characteristics of patients with non-specific and non-categorized mitochondrial diseases. *Acta Paediatr* 2009;98:1825-9.
- 29) Lee SM, Kim JH, Lee YM, Lee JS, Kim HD. Evaluation of renal function in children with mitochondrial respiratory chain complex defect: usefulness of cystatin C. *Acta Paediatr* 2009;98:1014-8.
- 30) Lee YM, Kang HC, Lee JS, Kim SH, Kim EY, Lee SK, et al. Mitochondrial respiratory chain defects: underlying etiology in various epileptic conditions. *Epilepsia* 2008;49:685-90.