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Respiratory Chain Defect in a Patient with Cerebral palsy; First Identification in Korea

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Defects of mitochondrial respiratory chain are important causes of human disease. The great clinical diversity of these disease with respiratory chain dysfunction means that accurate biochemical definition is essential and measurement of individual respiratory chain complexes is an important component of the investigations for these disorders. We developed assays which measure complexes I to IV in mitochondria and in addition, optimized these assays to provide sensitive and reliable diagnostic technique for the first time in Korea. We identified respiratory chain defect in complex I+III in a patient with cerebral palsy presenting severe developmental delay and seizure disorder. Our study supports that respiratory chain defects should be considered in a patient with cerebral palsy or seizure disorder of unexplained, as an etiology

INTRODUCTION

Defect of mitochondrial respiratory chain are increasingly being recognized as important causes of human disease. In the past, respiratory chain defect was regarded only as neuromuscular diseases. However, oxidative phosphorylation is not restricted to the neuromuscular system but proceeds in all cells that contain mitochondria. Therefore, a respiratory chain defect can theoretically give rise to any symptom in any organ or tissue at any age. The clinical symptoms range from isolated organ involvement, such as muscle disease or blindness, to multisystem disease, often associated with severe lactic acidosis. In addition, defects of the respiratory chain have been implicated in the etiology of several neurodegenerative diseases including Parkinson's disease and may be a factor in ageing. The great clinical diversity of conditions now linked with respiratory chain dysfunction means that accurate biochemical definition is essential and measurement of individual respiratory chain complexes is an important component of the investigation for disease due to mitochondrial dysfunction. However, due to difficulty and unavailability of enzyme assays, no single case has been reported in Korea yet until we identified the first case presenting here. We established assays which measure complex I to IV in mitochondria for the first time in Korea, and detected respiratory chain defect in a patient with cerebral palsy, delayed development and infantile spasm. After treatment with decaquinone, his overall general condition improved significantly.

CASE REPORT

A 6 month-old male infant was referred for the evaluation of delayed development and hypotonia. The patient have no history of perinatal asphyxia and hypoxic encephalopathy. He was treated for patent ductus arteriosus on the second day of the birth and at that time neurosonography revealed

increased echogenicity of deep periventricular white matter, suggestive of periventricular leukomalacia of unexplained. The measurement of lactate and pyruvate was 4.1 mmol/L and 0.055 mmol/L respectively, showing lactic acidosis. Amino acid analysis in plasma/urine and organic acid analysis in urine were nonspecific. The brain Magnetic Resonance Imaging (MRI) scan taken at 3 month of age showed diffuse atrophy of brain cortex, irregular contour of lateral ventricular wall and loss of deep white matter. Visual evoked potential (VEP) was normal but brain auditory evoked potential (BAEP) showed bilateral prechiasmal or retrochiasmal lesion. He was diagnosed as having cerebral palsy and started rehabilitation program. L-carn, folic acid, thiamin, and riboflavin were used empirically but he did not show any symptomatic improvement. Two months later, he showed brief symmetric contractions of the neck, trunk, and extremities and diagnosed as infantile spasm, subsequently treated with vigabatrin and clonazepam. At 17 months of age further investigations was performed in our laboratory in order to exclude the possibility of metabolic disorder. Pyruvate dehydrogenase complex and pyruvate carboxylase assay were normal. In the assay of respiratory chain complexes, mitochondria I+III complex showed decreased activity in contrast with normal controls. After diagnosis, he was put on decaquinone and showed marked improvement in activities and cognition.

Table 1. Respiratory Chain Enzyme Activities

	Citrate synthase (nmol/mg/min)	Complex I+III (nmol/mg/min)	% (I+III:CS)
Patient	32.5	16	49.2
Normal A	28	36	128.6
Normal B	27	41.2	152.6
Normal C	29.8	44.4	149.0
Normal D	29.3	37.6	128.3

DISCUSSION

It is well known that mitochondria carry out oxidative energy metabolism as their primary function. Since all work in the cell utilizes ATP, which is hydrolyzed to ADP and inorganic phosphate with concomitant release of energy, most mammalian cells rely on the ATP produced by oxidative phosphorylation for survival and function. The enzymatic machinary necessary to carry out aerobic metabolism of sugars and fats is located in the inner mitochondrial membrane. Functionally the system is composed of five enzyme complexes : NADH CoQ reductase (I), succinate CoQ reductase (II), ubiquinol cytochrome c oxydase (III), cytochrome c oxidase (COX) (IV), and ATP synthase (V). complexs I-IV make up the respiratory chain; coenzyme Q and cytochrome c act as shuttle molecules for electrons between the complexes. Electrons donated from NADH or FADH2 enter the chain at complex I or II, are passed to carriers of progressively greater electron affinity, and are ultimately accepted by molecular oxygen. At three stages energy is conserved as ATP in the ATP synthase reaction (complex V), functionally coupling electron transport along the respiratory chain to oxidative phosphorylation.

Defects in the function of this system result in various diseases, many of which are multisystem disorders, prominently involving highly aerobic postmitotic tissues because all the cell depend on the mitochondria for energy metabolism. For this reason, the investigation of patients at risk includes the systematic screening of all target organ, by contrast, the diagnosis of a respiratory chain deficiency is difficult to consider initially when only one abnormal symptom is present.

Recently many cases with respiratory chain defect have been reported as a new etiolgoy for various disease, which vary from fatal lactic aci-

dosis in infancy to neurodegenerative disease such as Alzheimer's disease in adults. Willis TA et al reported cytochrome oxidase deficiency presenting as birth asphyxia. They showed respiratory chain defect in a patient with Hypoxic-ischemic encephalopathy (HIE), presenting abnormal neuroimaging and lactic acidosis, and recommanded that inborn disorders of the respiratory chain should be considered in the differential diagnosis of HIE.

Until now, respiratory chain defect have been questioned by immunoblotting study without enzyme assay in Korea. When considering its low sensitivity and specificity, many cases must haven been missed. We suggest that respiratory chain defect should be considered for a patient with lactic acidosis, cerebral palsy or seizure disorder with unexplained etiology, and the enzyme assay needs to be followed.