

## A Case of Early Onset MELAS Patient with Wolff-Parkinson-White Syndrome

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### = Abstract =

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is one of the classic mitochondrial diseases characterized by symptoms of repeated episodes of hemiparesis with mitochondrial DNA mutation. We report a rare case of early onset MELAS patient confirmed by genetic analysis with Wolff-Parkinson-White syndrome.

**Key Words :** Mitochondrial Myopathies, MELAS syndrome, Wolff-Parkinson-White syndrome

### Introduction

Mitochondria, a cell organelle containing a DNA of its own, plays an important role in cellular energy production by synthesizing adenosine triphosphate (ATP). When a defect happens in its oxidative phosphorylation system (OXPHOS) pathway, we call it mitochondrial disease<sup>1)</sup>. The clinical symptoms or the onset age presented of mitochondrial disease tend to be quite variable. Though it shows multiple system involvement, brain and skeletal muscle are affected most of the time along with the heart<sup>2, 3)</sup>.

The mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

syndrome was first described in 1984<sup>4)</sup>. It is characterized by symptoms of repeated episodes of hemiparesis, hemianopsia, migraine, nausea, or vomiting. The point mutation (A3243G) of tRNA gene in mitochondria has been reported in 80% of the cases<sup>5)</sup>. Cardiac involvement is also reported, it is but rarely known to be combined with Wolff-Parkinson-White (WPW) syndrome<sup>6)</sup>. WPW syndrome is defined as the presence of an accessory pathway (AP) and has a predisposition to the development of supra-ventricular tachydysrhythmias. Conduction over an AP circumvents conduction delay occurring within the atrioventricular node, which leads to early eccentric activation of ventricles and fusion complex<sup>7)</sup>.

Here we present a rare case of early onset MELAS patient with WPW syndrome.

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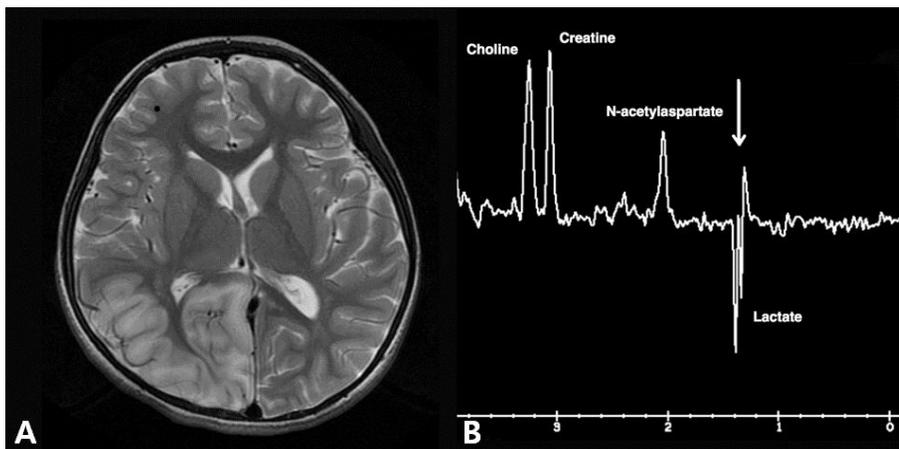
## Case Report

A Six years and 2 months old female was transferred to Gangnam Severance Hospital for her left side weakness and gait disturbance. She had a birth history of prematurity and hyaline membrane disease which led her to have ventilator care then. She could control her head at 4 month, walk holding on to furniture at 12 month, she produce meaningful words at 13 month. Though she had a mild developmental delay, she was capable of independent walking, running, and had no problem in verbal communication. She had no serious disability in her daily life and no specific neurological complication before the onset of the symptoms mentioned above. Her mental status was alert, vital sign was normal. She could walk alone, and she didn't show muscle weakness and other signs of neurologic deficit. There was no specific finding in her family history, including arrhythmia, heart disease, stroke, either.

The brain MRI preformed after the admission

revealed diffuse cerebral atrophy and high signal in her right temporal, parietal, and occipital area on T2 weighted image that were suspected as infarction while the MR spectroscopy showed a lactate peak (Fig. 1).

Laboratory tests, including those for muscle enzymes, lactate, pyruvate, and amino acid and organic acid assays were performed. The results were normal except an increased plasma lactate level 8.2 mmol/L (normal, 0.5–1.6 mmol/L). CK, CK-MB level was 96 U/L, 3.6 mcg/L, liver enzyme (AST/ALT) was 28/14 U/L, hemoglobin was 11.9 g/dL. As for muscle biopsy, ragged red fiber was observed with Gomori trichrome stain, but no specific aberration was found with other immunohistochemical stain and electron microscopy. In the biochemical respiratory chain complex enzyme assay using muscle tissue, the enzyme activity was all decreased in the whole complex. More specifically, complex I enzyme activity was as low as less than 10% of the normal control. Direct sequencing of mitochondrial DNA (mtDNA) in the blood and muscle specimens of the patient revealed mtDNA A3243G



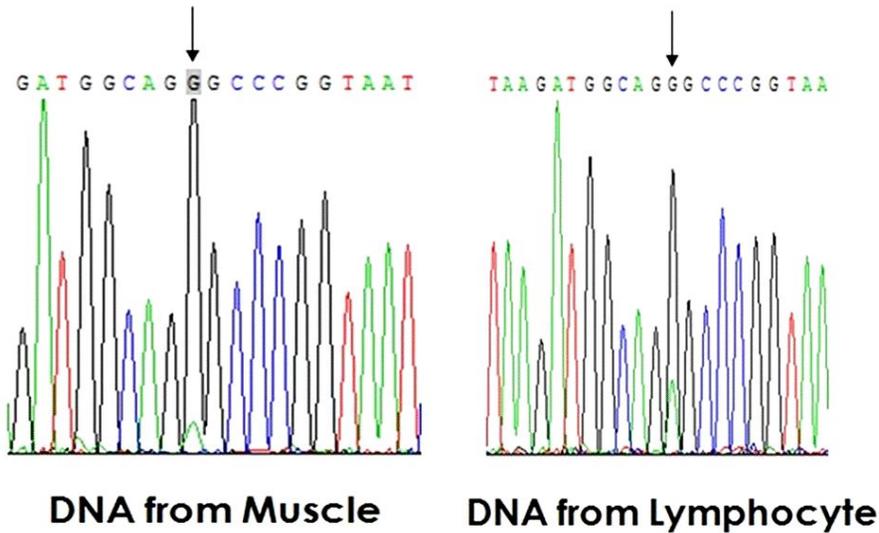
**Fig. 1.** Brain MRI and MR spectroscopy of the patient. Brain MRI shows diffuse cerebral atrophy and high signal in right temporal, parietal and occipital area on T2 weighted image (A). MR spectroscopy shows lactate peak (B).

mutation confirming that she had MELAS, a specific type of mitochondrial disease (Fig. 2).

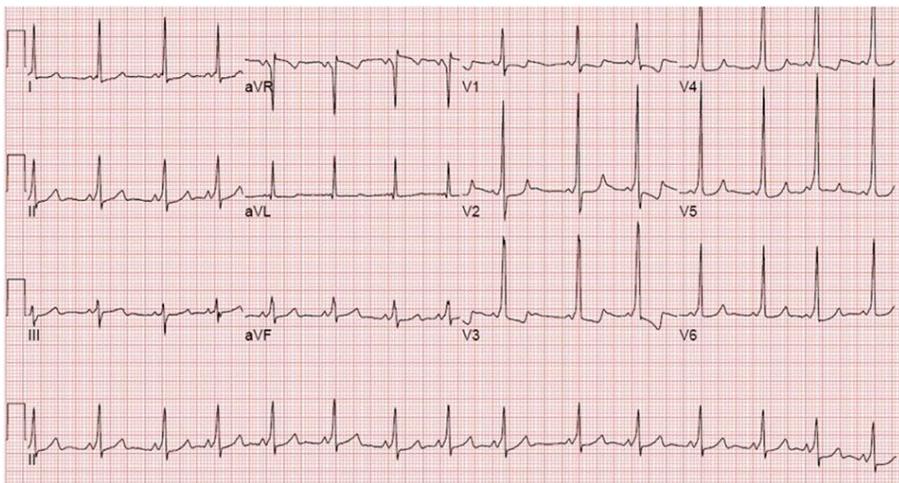
WPW syndrome was diagnosed by delta wave, short PR interval, and QRS widening on an electrocardiogram (Fig. 3). Echocardiography showed no anatomical abnormality with normal left ventricle contractility, either. The left ventricular

ejection fraction was checked as 73%.

Mitochondrial cocktail (Coenzyme Q10, thiamine, carnitine and multivitamin) were prescribed for the patient after the diagnosis of mitochondrial disease was made. Propranolol was also given to treat WPW syndrome. Left side weakness is still remaining and a mild decline of cog-



**Fig. 2.** mtDNA sequencing of the patient. Direct sequencing of mtDNA in blood and muscle specimens revealed mtDNA A3243G mutation.



**Fig. 3.** Electrocardiogram of the patient. Electrocardiogram shows delta wave, short PR interval and QRS widening compatible to Wolff-Parkinson-White syndrome.

nitive function is observed, but no new stroke-like episode has been broken yet for about 2 years. Also, though WPW syndrome is still observed in the series of follow-up electrocardiogram, there had been no change of heart contractility.

## Discussion

MELAS tend to show normal development at its early stage. That is up to about 90% of its patients. The onset usually occurs before the age of 40 and can be seen even at childhood, followed by gradual deterioration. Clinical symptoms are highly variable though. Episodic headaches with vomiting are the most common symptoms in MELAS, observed in almost all the patients. Also, seizures are noted in the majority<sup>8-10</sup>. Our patient had a first neurological manifestation at the age of 6 mainly consisting of unilateral weakness. No headache or vomiting which are the common symptoms of MELAS was observed. This could be due to the fact that the patient was too young to express her symptoms more precisely, but it is also possible that an early onset type of MELAS present with somewhat different clinical features. Though the girl had birth history of prematurity and hyaline membrane disease, there has been no specific proof that they are related with mitochondrial disease or MELAS.

Cardiac involvement including preexcitation, atrioventricular heart block, rhythm abnormalities and dilated or hypertrophic cardiomyopathy is reported in up to half of the patients with MELAS, though not as a predominant symptom<sup>8, 9, 11, 12</sup>. Whether those abnormalities tend to progress to major cardiac abnormalities or not are still needed to be studied. WPW syndrome is even

harder to find among MELAS patients. Peter NS et al. reported abnormal mitochondria found in surgically resected pathways in WPW syndrome. Mutation in the PRKAG2 gene, which encodes the r2 regulatory subunit of AMP-activated protein kinase, and the mutation may result in defects during cardiac morphogenesis, resulting development of accessory pathway<sup>7</sup>. An abnormality in heart conduction was found, but cardiac contractility was normal in our patient as well. This could mean that the severity, disease duration, or mutant burden of MELAS can affect the variability of symptom within the same organ system.

The studies concerning WPW Syndrome in patients with MELAS have been very limited and in children even more. There was a report by Hirano et al. that noted 6 patients with WPW syndrome out of 43 with MELAS, and another 3 patients with cardiac conduction block out of 47 with MELAS<sup>13, 14</sup>. Okajima et al. reported 3 cases with WPW syndrome among 11 pediatric patients with MELAS syndrome<sup>11</sup>. Sproule et al. reported 4 of 30 patients (13%) with MELAS who had a clinical history of, or electrocardiographic findings that matches with WPW syndrome<sup>6</sup>. In their reports, WPW syndrome preceded MELAS syndrome by 15 and 21 years in 2 of their patients. However, those studies were done based on adult patients who showed their symptoms mostly after adolescent period which makes us hard to figure out the precise prevalence in the pediatric aged group. We also have difficulty in identifying which came first that is between electrocardiogram abnormality of WPW syndrome and neurological manifestation in our patient. Since the onset of symptom vary greatly in MELAS, studies on WPW syndrome of patients diagnosed with MELAS during childhood

would be needed.

In this case, the patient have taken propranolol as chronic maintain therapy. And haven't developed any tachyarrhythmias. Individualized chronic maintenance therapy must be established based in the severity of the presentation. And other factors such as proximity of hospital, medication side effect, and doctor's experience. We don't consider cardiac surgery or electrophysiologic intervention not yet<sup>15)</sup>.

The prevalence of WPW syndrome appears much higher in patients with MELAS and the A3243G mutation than in the general population. Because there is a possibility that cardiac involvement may manifest earlier than neurologic symptoms and the dysfunction may have important therapeutic and prognostic consequences, we'd like to recommend that all patients with MELAS receive cardiac evaluations in order to detect abnormalities including cardiomyopathy and WPW syndrome.

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### 한글 요약

#### **Wolff-Parkinson-White 증후군을 동반한 MELAS 증후군 환자 1례**

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) 증후

군은 반복되는 편측 마비가 특징적으로, 대표적인 미토콘드리아 질환이다. 저자들은 초기에 신경학적 이상이 발현된 MELAS 증후군 환자 중 심장 전도 이상과 관련하여 드물게 발견되는 Wolff-Parkinson-White (WPW) 증후군을 동반한 1례를 경험하였기에 보고하는 바이다.

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