

## Neonatal Mitochondrial Respiratory Chain Defect and Vaginal Embryonal Rhabdomyosarcoma: Possibility of Oncogenesis?

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Mitochondrial disorders are rare metabolic diseases. They often present during neonatal period but with nonspecific clinical features such as feeding difficulties, failure to thrive, and seizures. Mitochondrial defects have also known to be associated with neurological disorders, as well as cancers. We report the first case of neonatal mitochondrial respiratory chain defect with sarcoma botryoides confirmed by pathologic diagnosis, suggesting another possible link between mitochondrial dysfunction and cancer.

**Key words:** Mitochondria, Respiratory chain defect, Neonate, Embryonal rhabdomyosarcoma, Oncogenesis

### Introduction

Mitochondrial disorders are uncommon energy metabolic diseases<sup>1-4</sup>. Since mitochondrial dysfunction induces lower energy production of cellular bases in affected organs, a great variety of symptomatology and progressive course are resulted in most cases. Furthermore, neonatal presentation is relatively common because of the high energy requirements of the growing newborn. Clinical unspecific features such as hypotonia, feeding difficulties, failure to thrive, and seizures are seen frequently as early-onset manifestation<sup>5</sup>.

A rapid and fatal course is generally expected in neonatal patients, because the age of onset is the strongest predictor of mortality in mitochondrial disorders<sup>6, 7</sup>.

Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood, categorized as a clinically and biologically heterogeneous disease<sup>8</sup>. Sarcoma botryoides is a form of embryonal rhabdomyosarcoma that tends to be less invasive than other forms and known to show favorable prognosis<sup>8, 9</sup>.

There has been no case reported yet about mitochondrial respiratory chain enzyme complex (MRC) defect with rhabdomyosarcoma. To our knowledge, this is the first case of mitochondrial cytopathy concurrent with sarcoma botryoides diagnosed in pediatric population.

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### Case Report

A 1-month-old female neonate was admitted to our hospital with failure to thrive. She had normal birth history, but feeding difficulty and seizure like movement were noticed after then. She also

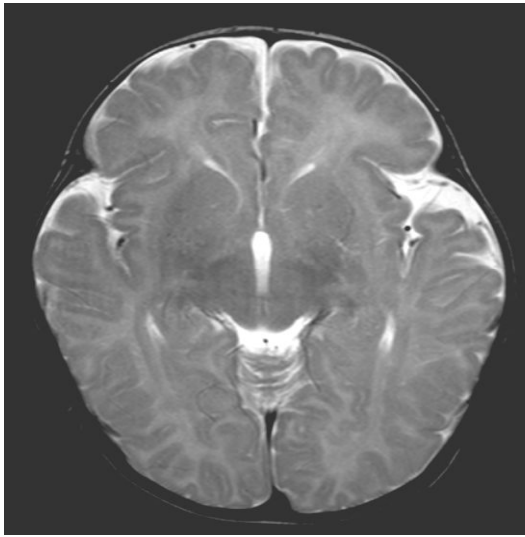


Fig. 1. Axial T2-weighted MRI showed nonspecific finding considering the patient's age.

gradually developed hypotonicity. Her parents were not consanguineous, and no family member including two elder brothers had shown abnormal neurological symptoms. On physical examination, she showed chronic ill looking appearance and had a head circumference 40 cm (50–75 percentile) with no dysmorphic morphology. No organomegaly was observed. During neurological examination, hypotonia and not increased deep tendon reflexes were seen. Asymptomatic premature atrial contraction, premature ventricular contraction, and atrial tachycardia without cardiac murmur were observed in electrocardiogram. But no cardiac anomaly was observed in echocardiography. Lactate level was elevated in blood and cerebrospinal fluid. Brain magnetic resonance imaging demonstrated no abnormal findings while proton magnetic resonance spectroscopy revealed small but definite lactate peak at right frontal lobe and right basal ganglia (Fig. 1, 2). Elevated alanine and lysine were observed on plasma amino acid assay, and nonspecific mild organic aciduria was noted on urine organic acid assay. Muscle biopsy was per-

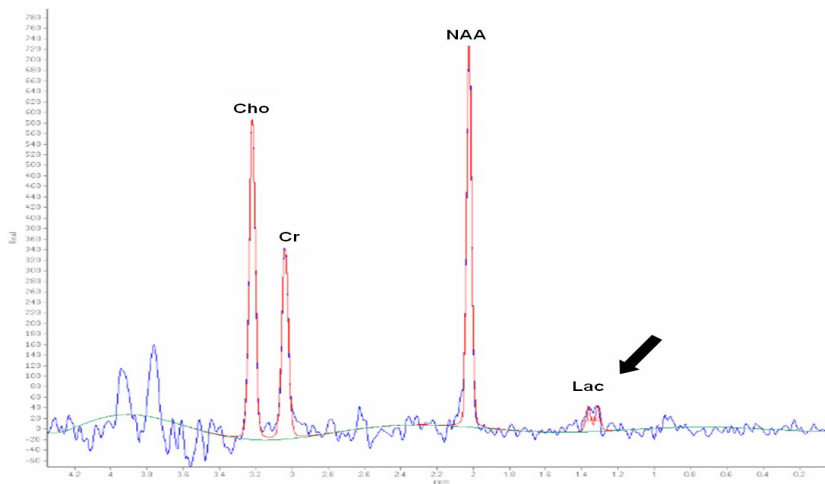
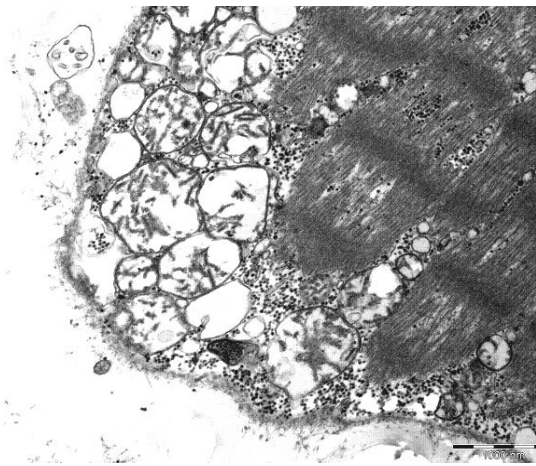


Fig. 2. Proton MR spectroscopy showed small but definite lactate peak(arrow) at right frontal lobe and right basal ganglia (Cho: choline; Cr: creatine; NAA: N-acetyl-aspartate; Lac: lactate).

formed, and abnormal features of multiple megaconia were identified under electron microscopy (Fig. 3). On biochemical enzyme assay for mitochondrial respiratory chain using spectrophotometric method in muscle tissue, MRC II defect was confirmed finally defined as lower than 10% of that in controls<sup>10</sup>). We started cocktail therapy including coenzyme Q10, L-carnitine and multi-vitamin after diagnosis of mitochondrial cytopathy.



**Fig. 3.** Electron microscopy showed multiple megaconia between subsarcolemmal area and intermyofibrillar area.

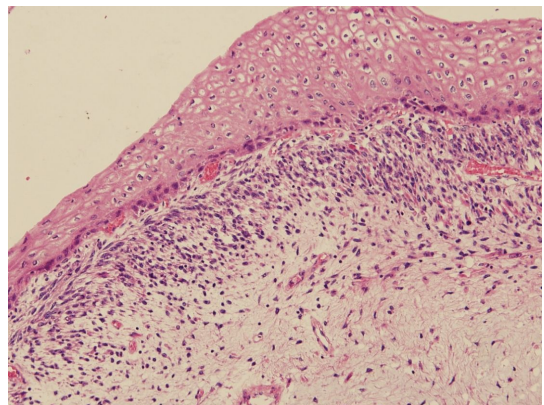


**Fig. 4.** Pelvic MRI showed lobulated heterogeneous mass in perineum (arrow). It contained both solid and cystic features.

Her development was improved after mitochondrial cocktail therapy. A vaginal mass was detected at the age of 6 months. The mass had characteristic polypoid appearance resembling a bunch of grapes. It was gradually increased in size of an adult fist. Pelvic MRI showed lobulated heterogeneous mass in perineum and it contained both solid and cystic features (Fig. 4). Excision was made. The specimen was of a typical polypoid



**Fig. 5.** Characteristic grape-like polypoid mass of sarcoma botryoides measuring 5.2×11.5 cm was observed.



**Fig. 6.** Cambium layer, a subepithelial condensation of tumor cells separated from an intact surface epithelium zone, was seen under light microscopy (H&E staining, ×160).

mass measuring 5.2×11.5 cm (Fig. 5). Pathologic diagnosis was made botryoid rhabdomyosarcoma (Fig. 6). She is on chemotherapy for management of rhabdomyosarcoma now.

### Discussion

Mitochondrial defects have been associated with neurological disorders, as well as cancers<sup>11</sup>. Some research showed an 'injury' to the respiratory chains such as mtDNA mutation, deletion or depletion can be a key event in carcinogenesis<sup>12, 13</sup>. In addition, several reports showed that mutations of mtDNA have been identified in various types of cancer including breast cancer, colon carcinoma, prostate cancer, pancreatic cancer, etc<sup>14</sup>. Also in some reports, decreased mitochondrial respiratory function was observed in accordance with increased invasiveness of cancer<sup>15</sup>.

### Summary

We report the 1st case of neonatal MRC defect with sarcoma botryoides confirmed by pathologic diagnosis suggesting a possible link between mitochondrial respiratory chain defect and rhabdomyosarcoma. Though there have been a few reports about mitochondrial dysfunction and certain types of cancer, there have not been attempts to study the relationship between MRC defect and rhabdomyosarcoma. So, further studies are needed to establish the relationship.

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