
Case Report

Sudden death in baby sling carrier of infant due to mitochondrial respiratory chain complex I activity deficiency

Masaru SHIMURA¹⁾, Atsushi KUMADA¹⁾, Shinichiro MORICHI¹⁾, Shigeo NISHIMATA¹⁾,
Kei MURAYAMA²⁾, Gaku YAMANAKA¹⁾, Hisashi KAWASHIMA¹⁾

¹⁾Department of Pediatrics, Tokyo Medical University

²⁾Department of Metabolism, Chiba Children's Hospital

Abstract

An injury alert concerning baby sling carriers issued in 2010 highlighted a case of suffocation and cardiopulmonary arrest. Here, the sudden death in a sling carrier of an infant due to decreased mitochondrial enzyme activity is reported. Symptoms arising from abnormalities of mitochondrial DNA can occur in any age group, with muscle weakness being common.

The infant was a 3-month-old baby girl who had produced watery diarrhea for several days before the fatal event. After feeding, the baby was carried by her mother in a sling for more than 40 minutes on a train. On reaching her destination, the mother noticed that the baby had nasal bleeding and a pale complexion. An ambulance was called, and the baby was found to be in state of cardiopulmonary arrest when it arrived. Liver autopsy revealed microvesicular fatty change and decreased enzyme activity of respiratory chain complex I.

The suggested casual pathway of this sudden death was mitochondrial deficiency leading to muscle weakness, causing upper airway obstruction. It is important to consider all potential pathologies when a child dies from what appears to be airway obstruction.

Introduction

Mitochondria constantly produce ATP, with the mitochondrial respiratory chain as the largest production area. Mitochondrial respiratory chain deficiency triggers a spectrum of diseases. It is caused by mutations of the mitochondrial (mtDNA) or nuclear genes¹⁾²⁾. Symptoms appear when it is inherited in the autosomal recessive or dominant forms, or by mitochondrial maternal heredity³⁾. Mitochondrial abnormalities appear over a broad age group. However, mitochondrial diseases in children are mostly caused by mutations of the nuclear DNA (90% to 95%). On the other hand, symptoms of mtDNA abnormalities can occur in all age groups, with muscle weak-

ness common.

Case

The baby girl was delivered under the normal procedure at full term (40 weeks) after an uneventful pregnancy. Her body weight was 3,250 g at birth. The baby's medical history showed nothing remarkable, apart from not meeting the target of an increase in body weight of 10 g per day at the 1-month check-up. The target rate of weight gain was subsequently reached, however. No historical episodes of muscle weakness were observed. The baby's family history was unremarkable and she had no siblings.

At the age of 3 months, the baby began to produce

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Corresponding author : Hisashi Kawashima, MD, Department of Pediatrics, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

TEL : +81-3-3342-6111 FAX : +81-3-3344-0643

watery diarrhea, and this continued for several days before the fatal event. Food intake also showed a slight decrease at this point. Just prior to the fatal event, and just after being fed, the baby was carried by her mother in a sling for more than 40 minutes on a train. On reaching her destination, the mother noticed that the baby had nasal bleeding and a pale complexion. An ambulance was summoned, and the baby was found to be in state of cardiopulmonary arrest when it arrived. The baby reached our hospital within 7 minutes. Cardiopulmonary resuscitation was performed, but there was no response.

No blood pressure was evident on palpation. The bulbar conjunctiva was not icteric, and the palpable conjunctiva was slightly anemic. The baby had no fascial abnormality. No lymph node enlargement was observed. The liver was palpable. It was located 3.5 cm below the costal margin and showed a smooth surface. No ecchymosis or petechiae was observed. The white blood cell count was 7,200/ μ l (neutrophils, 9.7%; lymphocytes, 86.5%; eosinophils, 1.1%; basophils, 0.7%; monocytes, 2%), and the hemoglobin level was 7.7 g/dl. The platelet count was 346×10^3 / μ l. The CRP level was normal. The AST, ALT, and γ -GTP levels were 471 (normal range: 13-30) IU/L, 339 (normal range: 10-42) IU/L, and 19 (normal range: 9-64) IU/L, respectively. The total bilirubin and direct bilirubin levels were 0.66 (normal range: 0.4-1.5) mg/dl and 0.13 (normal range: below 0.3) mg/dl, respectively. The ALP was 487 U/L. The serum glucose level was 128 mg/dl. The CPK level increased to 2,091 (normal range: 41-248) IU/l. The serum amylase level was 2 U/l. The results of the kidney function tests were normal. The PH and lactate levels were 6.44 mmol/l and 8 mmol/l, respectively. The HCO_3 level could not be assayed. The NH_4 concentration was extremely high. No laboratory study on lipid metabolism was performed. The influenza virus, RS virus, rotavirus, and adenovirus detection tests results were all negative. The results of bacterial culture were unremarkable, and those for metabolic screenings of the blood and urine were also negative.

After confirmation of death (1 hour later), autopsy imaging and liver biopsy were performed. Brain, abdominal, and chest CTs revealed no hemorrhage. The liver biopsy pathology revealed lymphocytic infiltration in the area of the central zone and hiatus of liver cells, which showed microvesicular steatosis on immunostaining with adipophilin and perilipin (Figure 1).

Respiratory chain complex I deficiency was subsequently diagnosed based on the liver pathology and enzyme data (Table 1).

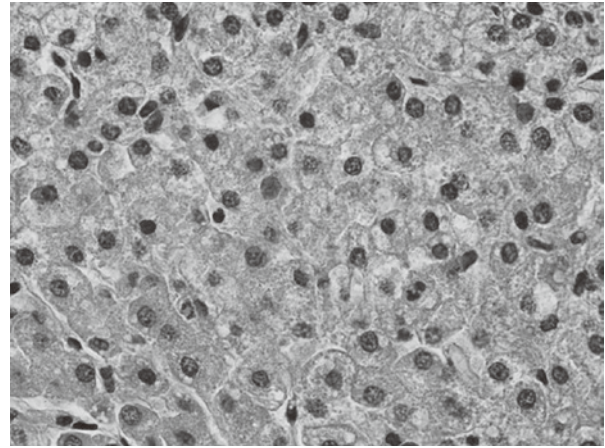


Fig. 1a Liver pathology (HE staining $\times 200$)
Liver biopsy pathology revealed lymphocytic infiltration central zone and hiatus of liver cells.

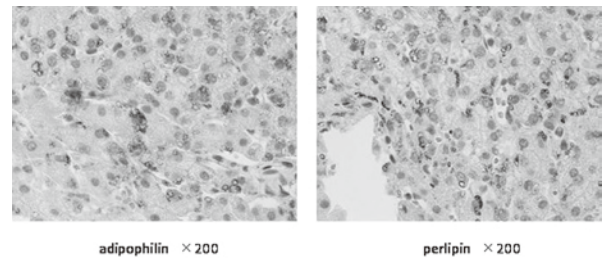


Fig. 1b Liver pathology (immunostaining $\times 200$; left: adipophilin, right: perilipin)
Liver biopsy pathology showed microvesicular steatosis on immunostaining with adipophilin and perilipin

Table 1 Enzyme activity of mitochondrial respiratory chain in liver tissue described previously¹³⁾¹⁴⁾. Complex I showed extremely low activity compared with that in normal control.

Liver					
	Co I	Co II	Co III	Co IV	CS
Control					
% of normal	131.5	126.0	136.5	193.5	140.5
CS ratio (%)	92.4	89.2	95.6	134.9	
CO II ratio (%)	94.7		158.8	192.0	
Pt					
% of normal	69.9	312.6	453.2	837.2	403.1
CS ratio (%)	17.1	77.1	110.7	203.4	
CO II ratio (%)	22.1		144.0	263.9	

Co I, complex 1; Co II, complex 2; Co III, complex 3; Co IV, complex 4; CS, citrate synthase

Discussion

In 2010, an injury alert concerning slings was issued by the Japanese Pediatric Society. It highlighted a case of suffocation and cardiopulmonary arrest⁴⁾. To our knowledge, this is the second report of sudden infant

death in a sling carrier in Japan. The causes of the sudden death were suspected to be upper airway obstruction, limitation of thoracic expansion, and abnormality of temperature control.

Many cases of sudden infant death in slings have been reported outside Japan. The U.S. Consumer Product Safety Commission has reported 14 cases of infant death since 1990. Of these 14 babies, 12 were less than 4 months old. Low birth weight and the common cold were reported in some of these cases⁵⁾. Health Canada (Canadian Ministry of Health) has reported 9 cases of sling accidents since 1995, 2 of which resulted in death⁶⁾.

In the present case, no special episode indicating mitochondrial disease, including muscle weakness after birth, was reported, and despite the increased transaminase level and hyperammonemia seen here, the other laboratory findings were all normal. Respiratory chain enzyme activity in the liver tissue revealed a decline in mitochondrial respiratory chain complex I activity. Mitochondrial respiratory chain complex I deficiency was subsequently diagnosed as the underlying disease based on the clinical and pathological data.

The symptoms of mitochondrial disorders include failure to thrive, sensorineural deafness, hypertrophic cardiomyopathy, muscular hypotonia, lactic acidosis, and hypoglycemia¹⁾²⁾⁷⁾. The prognosis of this condition is poor because these symptoms can easily lead to sudden death, such as in the case of infection. In an earlier study, this group reported 4 similar patients with neuromuscular disease accompanied by cardiac arrest after, or during, feeding⁸⁾.

Liver tissue commonly shows microvesicular steatosis in conventional respiratory chain complex I deficiency⁶⁾⁹⁾. Mitochondrial oxidative phosphorylation (OXPHOS) represents the final step in the conversion of nutrients into cellular energy. Genetic defects in the OXPHOS system have an incidence of between 1 : 5,000 and 1 : 10,000 live births. Among these mitochondrial diseases, isolated respiratory chain complex I deficiency is the most frequent type²⁾⁶⁾. Liver specimens from cases of sudden death often show microvesicular steatosis¹⁰⁾. The main symptom in such patients is leukodystrophy accompanied by hypotonia (60%). However, the correlation between genotype and phenotype is poor¹¹⁾. Although more than 35% of patients showed no single neurological symptom, nearly 50% with the fatal phenotype died before the age of 2 years¹²⁾. In the present case, there were no historical episodes of muscle weakness. However, the father, being a medical doctor, stated that he had noted sleep apnea after we informed him of the mitochondrial functional disorder and autopsy findings. The actual incidence might therefore be underestimated. Unfortunately, we did not have a chance to perform muscle biopsy and obtain other serum

data before the sudden death event. Muscle biopsy and more precise muscle diagnostic studies are needed to make a definitive diagnosis.

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スリング使用中に突然死を来したミトコンドリア呼吸鎖 I 欠損の乳児例

志村 優¹⁾ 熊田 篤¹⁾ 森地 振一郎¹⁾
 西亦 繁雄¹⁾ 村山 圭²⁾ 山中 岳¹⁾
 河島 尚志¹⁾

¹⁾東京医科大学小児科
²⁾千葉県子ども病院代謝科

【要旨】 スリング（子守帯）の危険性は窒息や心肺停止の報告から、2010年より、*Injury Alert*（傷害速報）がなされている。今回、スリング使用中に突然死を来したミトコンドリア呼吸鎖 I 欠損の乳児例を経験した。ミトコンドリア異常特に DNA 異常によるものは、あらゆる年齢で筋力の低下を発症する。

症例は、3か月の女児で数日前から水様性の下痢を認めていた。授乳後、40分間スリング中で電車にて移動。到着時に鼻出血と顔色不良に気づき、救急隊を要請した。救急隊到着時心肺停止の状態で蘇生に反応はなかった。剖検にて肝臓は小脂肪滴とミトコンドリア呼吸鎖 I の著減を認めた。

本症例の突然死の原因として、ミトコンドリア機能異常から筋力低下によるが機序の一つとして推察された。

〈キーワード〉 ミトコンドリア、呼吸鎖、突然死、無呼吸
