Case Report

Lethargy and hypotonia in a preterm neonate: Usual symptom with unusual diagnosis of mitochondrial trifunctional protein deficiency

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ABSTRACT

Methodical evaluation of a neonate with common clinical findings (hypotonia and lethargy) is important whenever it cannot be attributed to the frequent causes. This case report is on a preterm neonate with persistent hypotonia and metabolic acidosis who was evaluated and diagnosed with mitochondrial trifunctional protein deficiency. A preterm male baby, second born to second degree consanguineous parents, was found to have persistent lethargy and hypotonia with severe metabolic acidosis despite the shock being corrected. Strong clinical suspicion for inborn errors of metabolism (IEM) was considered despite negative reports of first tier investigations for IEM. He was started on carnitine and biotin. Whole exome sequencing of the baby and Sanger sequencing of mother revealed mutation in HADHA gene suggesting mitochondrial trifunctional protein (MTFP) deficiency. He was started on special infant formula containing medium chain triglycerides along with breastfeeding. When common causes cannot be attributed to the clinical picture, evaluation for uncommon aetiologies should be strongly considered. In case of IEMs, early diagnosis and appropriate therapeutic measures can have satisfactory growth and development in the child.

Key words: Acidosis, Hypotonia, Mitochondrial trifunctional protein, Preterm

Preterm infants are at risk for developing problems such as temperature instability, sepsis, apnea of prematurity, hyperbilirubinemia, hypoglycemia, and feeding difficulties. Due to their prematurity, they have hypotonia as compared to infants born at term gestation [1]. With experience, pediatricians and neonatologists often become used to and anticipate common things regularly. In the absence of underlying problems, if the hypotonia is out of proportion to prematurity, the infant has to be systematically approached for proper management and prognostication [2].

This report discusses the differential diagnoses of hypotonia in a preterm neonate, and on the final diagnosis of mitochondrial trifunctional protein (MTFP) deficiency. MTFP is an octameric multienzyme complex composed of 4 alpha and 4 beta subunits encoded by the Hydroxyacyl-CoA Dehydrogenase Trifunctional Multienzyme Complex A and B (HADHA and HADHB) gene respectively [3]. It is a rare autosomal recessive disease where long-chain fatty acid oxidation is impaired [4]. MTFP deficiency results in feeding difficulties, lethargy, hypoglycemia, hypotonia, hepatic dysfunction, cardiomyopathy, encephalopathy, and death. HADHA or HADHB genetic mutations lead to varying degrees of decline in MTFP activity that result in three types of phenotypes: severe neonatal-onset, hepatic infantile-onset, and late-onset neuromyopathic type. Since its description in 1992, only a few cases have been reported in the world literature.

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CASE REPORT

The proband is a preterm male baby born to second-degree consanguineous parents. He has an elder healthy male sibling. The mother had no significant past illnesses. There was no history of unexplained neonatal or infant deaths in the family. She had preterm premature rupture of membranes at 29 weeks of gestation for which, she was managed conservatively. There was no identified cause for preterm rupture of membranes. Pregnancy was terminated at 29+5 weeks by cesarean section due to failed induction of labor.

Preterm, 30 weeks, the male baby was delivered with a birth weight of 1140 g with APGAR scores of 7 and 8 at 1 and 5 min respectively. He was admitted to intensive care for preterm care and was started on intravenous fluids and injection caffeine. Early rescue surfactant was given by INtubate-Surfactant-Extubate to Continuous Positive Airway Pressure (CPAP) technique and the baby was connected to CPAP 6cm H2O and 30% FiO2. 10 h post surfactant, he developed shock with

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recurrent ABD (apnea, bradycardia, and desaturation) episodes. Blood gas revealed combined metabolic acidosis (pH-7.2, pCO2-58 mm Hg and HCO_3-17). Differential diagnoses considered were severe respiratory distress syndrome, early-onset neonatal sepsis (EONS), perinatal hypoxia, hypoglycemia, intracranial hemorrhage, and neonatal abstinence syndrome.

Reviewing the maternal records, there were no risk factors for EONS/neonatal abstinence. Perinatal hypoxia was ruled out since peripartum fetal heart rate tracings were normal and the baby had good respiratory efforts at birth with good Apgar scores. Workup for sepsis and blood sugar level were within normal limits. Chest roentgenogram and 2D echocardiogram was normal. Ultrasound cranium and Computed tomography brain did not show any evidence of intracranial hemorrhage. He was managed with ventilator support, inotropes (Dobutamine 15 mcg/kg/min), and maintenance fluids. Neither intermittent nor continuous infusions of sedatives were given. Expressed breast milk (EBM) was fed through a nasogastric tube at 14 h of life and graded up as the baby tolerated. Over the next 48 h, inotropes could be weaned as the shock got corrected (well felt peripheral pulses, normotensive and normal blood gas) but lethargy and hypotonia persisted.

Other differential diagnoses were considered that include disorders of neuromuscular, metabolic, genetic, and endocrine systems. Family history was negative for clues for such disorders. He had no dysmorphic features, the respiratory system was clear to auscultation, normal cardiac examination, the abdomen was soft with no organomegaly and neurologically he was hypotonic. Liver, renal and thyroid function test, and CK/CKMB were normal. Electrolytes were unremarkable and blood sugars were maintained with EBM through tube feeds. Serial blood gases showed persistent metabolic acidosis. He was extubated to CPAP and then changed to Oxygen by hood at the end of 6 days of life. The baby was tolerating feeds with stable vital parameters but had lethargy and hypotonia. In view of profound lethargy and hypotonia, with severe metabolic acidosis (pH ranging between 7.16 and 7.23 with HCO_3 between 11 and 18) further workup for underlying inborn error of metabolism was considered. Until the reports were available, breast milk was stopped, started on dextrose infusion with a glucose infusion rate of 8 mg/kg/min, syrup Levocarnitine 100 mg/kg/day, and tablet biotin 10 mg/day (latter two through a feeding tube).

First-tier investigations revealed elevated lactate (5.2 mmol/L), with normal levels of sugar (91 mg/dl), ammonia (56 μmol/L), and absent ketonemia. Urine organic acid analysis did not reveal any abnormal excretion of metabolites. Tandem mass spectrometry done in dried blood spots showed negative screening. Methionine, hydroxyproline, and aspartate were elevated in plasma amino acid analysis, which was inconclusive of any disorder. However, strong clinical suspicion of mitochondrial disorder was considered and genetic tests were done. The baby was restarted on EBM with simultaneous tapering of IV fluids and continued on syrup Levocarnitine 100 mg/kg/day and biotin 10 mg twice a day. Gradually, hypotonia improved, acidosis and lactate levels got corrected (1.8 mmol/L). It was clear that an Inborn error of metabolism was present, but the screening tests results had no specific abnormalities suspicious of several inborn errors including disorders of fatty acid, organic acid, and amino acid metabolism. Because some disorders cannot be differentiated by biochemical tests alone, either genetic testing or fibroblast enzyme testing are required to confirm the diagnosis, the parents were explained about genetic testing. Whole-exome and whole mitochondrial genome sequencing were done. The baby was discharged on day 38 while on direct breastfeeding with additional EBM through the cup, and oral medications. Whole-exome sequencing detected variant c.9147>C (p.IIe305Thr) in the HADHA gene in a heterozygous state with uncertain significance for the disorder MTFP deficiency (OMIM 609015) (Fig. 1a). The same gene mutation was confirmed in the mother by Sanger sequencing (Fig. 1b). Genetic counseling was done. The baby was started on special Medium-chain triglycerides (MCT) containing infant formula along with the continuation of breastfeeding. He was gaining weight and growing adequately, attained a social smile, and partial head control during his follow-up visit at 4 months of age. Parents have been advised regarding the need for close metabolic and dietary management, anticipatory screening for cardiomyopathy, and early interventions.

DISCUSSION

Mitochondrial fatty acid oxidation is essential to generate ATP for the normal functioning of vital organs. MTFP is an enzyme complex with three functional catalyzing activities at the second, third, and fourth steps of the mitochondrial fatty acid oxidation cycle namely long-chain enoyl-CoA hydratase, long-chain 3 hydroxy acyl-CoA dehydrogenase (LCHAD), and long-chain 3 ketoacyl-CoA thiolase. Isolated LCHAD deficiency and MTFP deficiency, two inherited autosomal recessive fatty acid oxidation disorders, occur due to mutations in either of the two genes (HADHA and HADHB) that encode this MTFP complex [5,6].

The reported prevalence of these disorders has been estimated to be 1:100,000–1:200,000 [7]. MTFP deficiency is closely related to LCHAD deficiency, autosomal recessive, extremely rare defect with high morbidity and mortality [7]. In this disorder, long-chain fatty acid oxidation is impaired leading to the accumulation of acylcarnitines and hydroxyl acyl fatty acid metabolites. Most infants with MTFP deficiency present with a generally mixed phenotype. There are three major varieties of clinical presentation. The neonatal form is severe with cardiomyopathy, arrhythmias, and hepatic encephalopathy. The infantile form has predominant liver involvement with encephalopathy, hypoketotic hypoglycemia induced by prolonged fasting. The third variety is milder presenting during later childhood with hypotonia, myopathy, and peripheral neuropathy with rhabdomyolysis [8-10].

Lotz-Havla *et al*. have reported two cases that were missed during newborn screening for MTP/LCHAD deficiency. In these cases, confirmatory testing was normal despite abnormal acylcarnitines in the initial screening that led to a rejection of MTP deficiency. Both cases presented with metabolic decompensation at around 4 months of life [11]. Genetic testing confirmed the

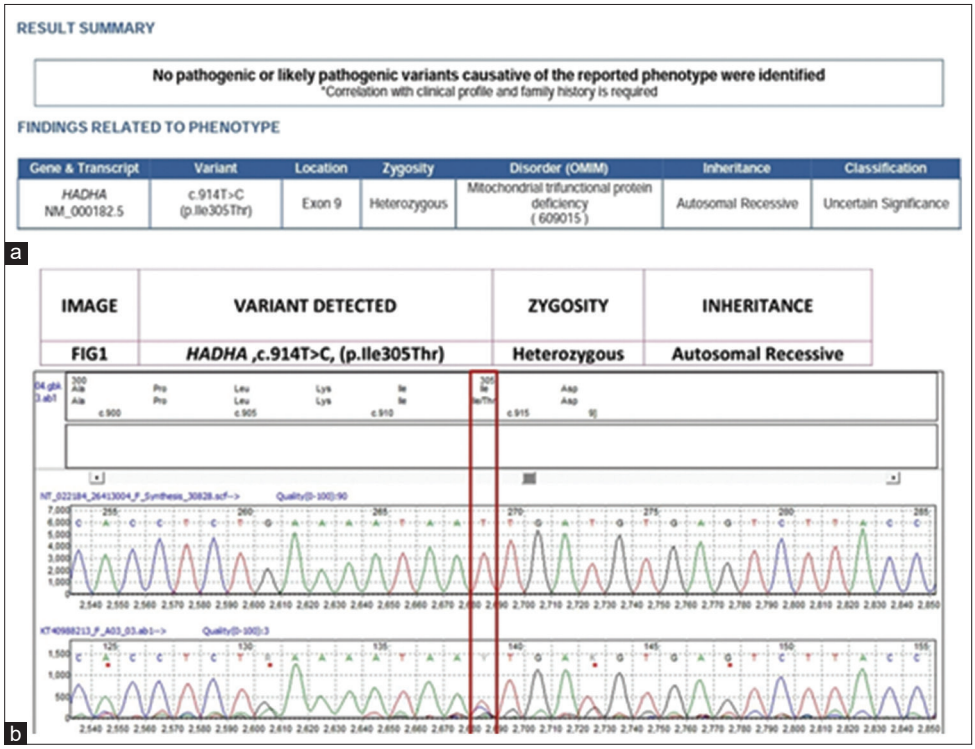

Figure 1: (a) Whole exome sequencing detected variant c.9147>C (p.IIe305Thr) in HADHA gene in heterozygous state with uncertain significance for the disorder MTFP deficiency; (b) Sanger sequencing data (electropherogram) for the provided sample showing nucleotide change at ch2:c.914T>C, in HADHA gene

diagnosis. Park *et al*. have reported a preterm 36 weeks of gestation who had respiratory distress, metabolic acidosis, seizures, and shock. TMS revealed an abnormal acylcarnitine level. MTP deficiency was diagnosed by genetic analysis [12]. Another reported case presented with gastrointestinal perforation was diagnosed with MTFP deficiency.TMS done showed elevated acylcarnitine levels. This infant had heterozygous mutations in the HADHA gene [13]. Anderson and Brooks have reported a preterm 36 weeks neonate who was asymptomatic till 36 h of age, developed lethargy, temperature instability, and hypoglycemia. This infant developed symptoms before the completion of newborn screening and on evaluation, was diagnosed with LCHAD deficiency [14].

The goals of treatment are to minimize long-chain fatty acid oxidation that can be achieved by avoidance of fasting, limiting long-chain fat intake instead of providing MCT, ensuring sufficient non-fat calories for adequate nutrition. Infants beyond 10 months can be given uncooked cornstarch (1–2.5 g/kg) at bedtime to prevent hypoglycemia overnight. The parents should be counseled about sick day management and danger signs should be explained. Infections and fever should be treated aggressively to prevent a catabolic state. Carnitine has to be supplemented if secondary carnitine deficiency is being documented. Intercurrent illnesses should be carefully managed along with biochemical monitoring of long-chain hydroxyl acylcarnitine and creatine kinase levels. During these times, intravenous dextrose infusions with glucose infusion rate between 7–10 mg/kg/min is necessary to prevent hypoglycemia. Most cases if diagnosed earlier, respond well with dietary modification, however, long-term complications cannot be prevented. Prognosis of MTP deficiency depends essentially on early diagnosis, fat-modified diet, avoiding catabolic stress situations, and aggressive treatment during intercurrent illness.

CONCLUSION

This report describes the importance of evaluation of a neonate with common clinical findings (hypotonia and lethargy) which cannot be attributed to the common causes. Despite negative screening, MTFP deficiency in the index case was diagnosed by genetic analysis. With timely diagnosis, optimizing the medical management, and anticipatory guidance specific to the diagnosis of MTFP deficiency, infants can have satisfactory growth and development. Furthermore, a definitive diagnosis will help guide the family with reproductive decision-making and ensure monitoring during subsequent pregnancies.

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