

Neuromyopathy due to mitochondrial trifunctional protein deficiency caused by novel HADHA mutation

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ABSTRACT

Mitochondrial trifunctional protein deficiency (MTP deficiency or MTPD) is a rare autosomal recessive disorder of oxidation of long-chain fatty acids. It is characterized by severe neonatal manifestations such as cardiomyopathy, hypoglycemia, metabolic acidosis, skeletal myopathy, neuropathy, liver disease, and death. It can also present with mild symptoms such as peripheral polyneuropathy, episodic rhabdomyolysis, and pigmentary retinopathy. Peripheral neuropathy is a known and long-term irreversible complication of MTPD. We report a rare case of a 5-year-old male child with slowly progressive limb weakness; genetic analysis was suggestive of MTPD with novel *HADHA* gene mutation. The present study comprehensively analyzed the cases, including exome sequencing, to the best of our knowledge, describing the first observation of homozygous novel mutation in the *HADHA* gene underlying this disorder in India.

Key words: *HADHA* gene mutation, Mitochondrial trifunctional protein deficiency, Neuromyopathy

Mitochondrial trifunctional protein (MTP), an enzymatic complex that catalyzes the last three steps of long-chain fatty acid oxidation, is an inner mitochondrial membrane-bound protein consisting of four α -subunits with long-chain 2,3-enoyl-CoA hydratase (LCEH) and long-chain 3-hydroxy acyl CoA dehydrogenase (LCHAD) activity, and four β -subunits with long-chain 3-ketoacyl-CoA thiolase activity. MTP deficiency is caused by *HADHA* or *HADHB* mutation and these are rare autosomal recessive fatty acid oxidation disorders. Patients homozygous for the common c.1528G>C variant in *HADHA* are classified as LCHAD deficient while homozygosity or compound heterozygosity for other genetic variants either in *HADHA* or *HADHB* result in MTPD [1].

They have been classified into three clinical phenotypes: lethal (neonatal-onset, severe form), hepatic (infantile-onset, intermediate form), and neuromyopathic (late adolescent-onset, mild form) and a deficiency in this heteromeric complex has diverse clinical consequences. The neonatal-onset severe form manifests as hepatic steatosis, cardiomyopathy, skeletal myopathy, and neuropathy and is usually fatal. A moderately severe form, with onset usually from the neonatal period to 18 months of age, presents primarily with hypoketotic hypoglycemia and metabolic acidosis. The mild form merges with the moderately

severe infantile form and can present from a few months of age until adolescence as a peripheral polyneuropathy with episodic rhabdomyolysis. This disorder presents with recurrent episodes of muscle weakness culminating in a severe attack of generalized muscle weakness and severe hypotonia and also there is respiratory failure associated with episodes of rhabdomyolysis. Pigmentary retinopathy may also develop over time. Despite this classification as milder phenotype, retinopathy, and neuropathy significantly can impair the quality of life and is usually irreversible [2].

We report a 5-year-old boy with gradual onset progressive lower limb weakness and tingling and numbness sensation; genetic analysis finally diagnosed MTP deficiency with novel *HADHA* mutation.


CASE REPORT

A 4-year-old male child, third by birth order born of the non-consanguineous marriage, presented with complaints of difficulty in walking and multiple falls for the past 1 month. This was associated with difficulty in wearing slippers and climbing stairs, difficulty in getting up from a sitting position, and tingling numbness of both hands and feet. There was no history of muscular pain and cranial nerve involvement. His intelligence quotient was claimed to be in the normal range.

The child was born by full-term vaginal delivery with a birth weight of 3000 g. There was no history of NICU stay. The child's

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Access this article online	
Received - 18 March 2022 Initial Review - 12 April 2022 Accepted - 03 May 2022	Quick Response code 
DOI: 10.32677/ijch.v9i5.3393	

motor development was within normal limits (held head steady at 4 months, rolled over at 5 months, could stand up at 10 months) until he began walking at 13 months. Starting at 3 years of age, he would often fall over when running. At 4 years of age, his parents noticed that he ran slower than his friends. His symptoms were progressive. From the age of 4 years onward, he had difficulty climbing stairs and getting up from a sitting position and had repeated episodes of falls. There were also complaints of slipping of footwear and tingling and numbness sensation. There was no history of swallowing difficulty, nasal regurgitation, and bowel or bladder disturbance.

There was a history of the death of an older sibling at 2.5 years of age due to similar complaints in the past. On general physical examination, the child had multiple scars over both knees due to repeated falls and slight lordosis was present. On central nervous system examination, the higher mental functions and cranial nerves were intact. Power was normal (5/5 of Medical Research Council [MRC] muscle power grading) in the proximal and distal group of muscles in both upper limbs, whereas it was affected (3/5) in the proximal and distal group of muscles in both lower limbs. The sensation of touch, pain, temperature, vibration, and position senses was preserved in all the dermatomes. Among superficial reflexes corneal, conjunctival, abdominal reflexes, and plantar were intact bilaterally. Among the deep tendon reflexes, biceps and triceps reflexes were normal (2+ of MRC grading of reflexes), whereas knee and ankle jerks were absent bilaterally. Gowers's sign was positive. There was no thinning and twitching of muscles.

The child was clinically suspected of having a neuromyopathic disorder. The differential diagnosis considered were Charcot-Marie-Tooth disease, mitochondrial myopathy, and muscular dystrophy. Serological analysis showed creatine kinase level to be elevated to 525 IU/L. The nerve conduction velocity test indicated a reduced amplitude in the compound motor action potential. Electromyographic and nerve conduction studies features were suggestive of chronic motor axonal degeneration. Panel diagnostics for genetic neuropathies were performed and yielded 2 pathogenic HADHA variants confirming MTPD. A homozygous missense mutation c.703 C>T p.Arg235Trp was detected in exon 8 of the HADHA gene (NM_000182.5) in the patient.

The child was advised to undergo physiotherapy, steroid therapy, and regular assessment for progressive muscle and cardiac/respiratory damage and dietary modification and consisted of a diet low in long-chain fats supplemented with medium-chain triglycerides (MCT), essential fatty acids, and low-dose carnitine (25 mg/kg/day).

DISCUSSION

The child had insidious onset slowly progressive lower limb weakness with exercise intolerance, which was associated with concomitant lethargy and weakness. Muscle disease was suspected and we confirmed it with increased CPK levels and peripheral nerve injury, which suggested a neuropathy and likely

episodes of muscular degeneration and it supported the diagnosis of metabolic neuromyopathy. The nerve conduction velocity test indicated a reduced amplitude in the compound motor action potential. Electromyographic and nerve conduction studies features were suggestive of chronic motor axonal degeneration. There was a death of a sibling with similar symptoms. Considering a significant family history, we next performed gene mutation analysis by next-generation sequencing, eventually discovering a novel HADHA homozygous mutation.

MTP is a multi-enzyme complex involved in long-chain hydroxyl acyl CoA metabolism. The trifunctional protein, composed of four α -subunits and four β -subunits, catalyzes three steps in mitochondrial beta-oxidation of fatty acids which are the LCHAD, LCEH, and long-chain thiolase (LCTH) steps [1]. The HADHA gene (2p23) encodes the LCEH and LCHAD enzymes and the HADHB gene (2p23) encodes the LCTH enzyme. Two mutations in either one of these two genes cause trifunctional protein deficiency. In MTP deficiency, β -oxidation of long-chain fatty acids is impaired; the deficiency is asymptomatic when energy supply and demand are in balance; however, if there is inadequate energy supply when infection, disease, exercise, or extended intervals between meals increase energy demand, the body cannot compensate for the energy shortage.

The mild form can present from a few months of age until adolescence as a peripheral polyneuropathy with episodic rhabdomyolysis triggered by prolonged fasting, illness, exercise, or exposure to heat or cold. There is respiratory failure associated with episodes of rhabdomyolysis. Pigmentary retinopathy may also develop over time [2].

In the case reported here, the child presented with progressive weakness of lower limbs and tingling and numbness sensation without hypoglycemia, acidosis, or cardiac involvement. This is a unique presentation: previously reported cases of deficiency usually presented with a variety of symptoms besides rhabdomyolysis, such as cardiomyopathy, oculopathy, or hypoglycemia. Progressive peripheral motor sensory neuropathy and progressive muscle weakness with onset between 1 and 6 years of age characterize a major phenotype of TFP deficiency [3].

A novel homozygous missense mutation c.703 C>T p.Arg235Trp was detected in exon 8 of the HADHA gene (NM_000182.5) in our patient. The deficiency of DHA may play a significant role in the progression of neuropathy and has been documented in several children with MTP deficiency who presented with peripheral neuropathy. With timely diagnosis, the prevention of life-threatening rhabdomyolysis and acute respiratory failure is possible, and DHA supplementation may reverse or slow the progression of the associated neuropathy [4]. DHA supplementation in children with progressive sensorimotor axonopathy with demyelination resulted in marked clinical and electrophysiological recovery [3].

Dietary restriction of long-chain fatty acids with supplementation of MCT present in coconut oil, palm kernel oil, milk, butter, yogurt, cheese, fat-soluble vitamins, and omega-3 oils may prevent death and reduce morbidity [5]. Fasting and exposure to environmental extremes must be strictly avoided

and exercise should be limited. The mild form has a favorable prognosis. Despite this, retinopathy and neuropathy significantly can impair the quality of life and is usually irreversible. Initiation of bezafibrate reduced the myopathic manifestations and lead to an improvement in quality of life [6].

CONCLUSION

MTP deficiency presents with non-specific symptoms making clinical diagnosis difficult. TFP deficiency must be included in the differential diagnosis of early-onset, progressive peripheral neuropathy. Unfortunately, despite early recognition and intervention, severe mitochondrial TFP deficiencies remain disorders with a poorer prognosis. In addition, an early and accurate diagnosis will help guide the family with reproductive decision-making and ensure maternal high-risk monitoring during subsequent pregnancies.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Vatkar A, Nishigandha SJ, Patil S, Shariff M. Neuromyopathy due to mitochondrial trifunctional protein deficiency caused by novel HADHA mutation. *Indian J Child Health*. 2022; 9(5):84-86.