A Variant in *SLC25A4* Leads to Mitochondrial DNA-Depletion Syndrome-12A Causing Neonatal Hypotonia and Hypoventilation

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J Pediatr Neurol

Abstract

Congenital hypotonia and hypoventilation is a rare association. We report a rare case of a female newborn with poor respiratory drive, ventilator dependency, severe hypotonia, cardiomyopathy, and premature death. Clinical-exome-sequencing revealed SLC25A4-related mitochondrial deoxyribonucleic acid (DNA) depletion syndrome-12A (cardiomyopathic type). This syndrome is apparent at birth and carries a poor prognosis.

Keywords

- neonatal hypotonia
- hypoventilation
- cardiomyopathy
- infant
- newborn

Introduction

Neonatal hypotonia is a relatively common presentation in the neonatal care units[1,2] however, its co-presentation along with severe hypoventilation necessitating chronic ventilation is relatively rarer.[2,3] The gamut of etiologies that can result in this clinical scenario includes neuromuscular, myopathic, neurometabolic, and syndromic genetic causes.[1,2] We report a female infant presenting at birth with severe hypotonia, persistent respiratory acidosis, hypoventilation, and ventilator dependency. The report outlines the detailed workup done, including results of genetic tests, to arrive at a rare molecular diagnosis of mitochondrial deoxyribonucleic acid (DNA)-depletion syndrome-12A (cardiomyopathic-type, MTDPS12A). This disease is known to be associated with profound hypotonia, hypoventilation, and death in infancy.[4,5] This report, a first documentation of MTDPS12A in the Indian subcontinent, hopes to sensitize the pediatrician and neonatologist about this rare disorder, while highlighting the growing scope and applications of modern genetics in clinical practice.

Case Report

A female child, of Asian descent, born to nonconsanguineous parents, was delivered at 38 weeks by elective cesarian section, due to cephalopelvic disproportion, to a primigravida mother. There was no history of any medical disease during pregnancy. The child cried immediately post-birth; however, the cry was weak. The APGAR scores were 7/10 at 1 and 5 minutes (scores of 7–10 at 5 minutes are considered reassuring).[6] Her birth weight was 3.7 kg (0 to +2Z score), length was 52 cm (0 to +2Z score), and head-circumference was 36 cm (+1 to + 2 Z score), as plotted on World Health Organization growth charts. The child developed mild respiratory distress shortly after birth and was shifted to our neonatal intensive care unit. On admission, she had shallow breathing and poor respiratory efforts, with generalized hypotonia. The child had severe hypoventilation in sleep as well as while awake. Cry, tone, activity, and neonatal reflexes were weak or incomplete.

There were poor spontaneous and absent antigravity movements in all four limbs. Deep tendon reflexes were not elicitable There were no obvious dysmorphic features.

received
November 7, 2020
accepted after revision
December 22, 2020

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1722954.
ISSN 1304-2580.

Arterial blood gas showed partial pressure of carbon dioxide ($PaCO_2$) of 90 mm Hg (normal range 38–42 mm Hg). After a brief trial of continuous positive airway pressure, she was intubated as $PaCO_2$ continued to rise. Chest skiagram was normal. She required minimal ventilator settings to maintain normoxia and normocarbia. Initial and repeat septic screens, electrolytes, calcium, renal, and liver functions were normal. Creatine-phosphokinase, thyroid functions, blood tandem mass spectroscopy, urine gas chromatography, and serum lactate were normal. Cranial ultrasonogram, cardiac echocardiogram, and color Doppler were reported normal. Multiple attempts at extubation met with failure with carbon-dioxide retention. On day of life 9 (DOL9, clinical exome sequencing (CES) targeting the genes associated with the given phenotype was ordered, to rule out congenital central hypoventilation syndrome (CCHS) and any single-gene neuromuscular disorder that could potentially cause this phenotype. The sequencing platform used for CES was Illumina-NextSeq 550. The libraries were prepared using Roche KAPA HyperPlus library preparation kit. Target enrichment was done selectively using capture probes targeted against coding regions of 4,100 genes of known clinical significance. We also ordered methylation-specific multiplex ligation probe-dependent amplification (MS-MLPA) to detect the methylation status of imprinted genes in 15q11-q13 region, to rule out Prader–Willi syndrome (PWS). There were two episodes of generalized convulsions. Electroencephalogram, electromyography, nerve conduction studies, and magnetic resonance imaging brain were reported as normal for her age. Ultrasonography of the neck and bronchoscopy showed normal anatomy. The infant was on full gavage feeds and gaining weight adequately. A repeat cardiac echocardiogram on DOL-57 done for increasing tachycardia and appearance of harsh systolic grade III murmur suggested hypertrophic cardiomyopathy, biventricular hypertrophy, and grade III diastolic dysfunction.

Genetic test results revealed normal MS-MLPA analysis ruling out PWS. CES revealed a heterozygous variant NM_001151.3:c.703C > G, p.Arg235Gly (chr4:g.186067017C > G), in exon 3 of *SLC25A4*gene, confirmed by Sanger sequencing (►**Fig. 1**). The variant was classified as pathogenic as per the American College of Medical Genetics (ACMG) guidelines.[7] This confirmed the diagnosis of autosomal-dominant mitochondrial DNA depletion syndrome-12A (cardiomyopathic type) (MTDPS12A) (OMIM #617184) in the child. Parental-targeted Sanger testing for the above specific variant to confirm its de novo origin in the proband was declined by the family. Appropriate genetic counselling was offered regarding the guarded prognosis in the proband. They opted for minimalistic care following the results. The child succumbed on DOL-92.

Discussion

Association of neonatal hypotonia, a common diagnosis, with hypoventilation, an uncommon diagnosis, is rare.[2,3] In a retrospective analysis of 138 patients of neonatal hypotonia, nearly 59% had a genetic etiology comprising the following—chromosomal disorders (trisomy 18, trisomy 21), syndromic causes (PWS, "dysmorphism-group" or joint hyperlaxity), metabolic causes (Zellweger syndrome, congenital disorders of glycosylation, inborn-errors-of-metabolism), and myopathic or neuromuscular disorders.[2] Thorough investigations in such cases should be initiated early, to dissect out the etiology from the spectrum of neuromuscular, myopathic, metabolic, syndromic/genetic, and respiratory causes, to arrive at a timely diagnosis,

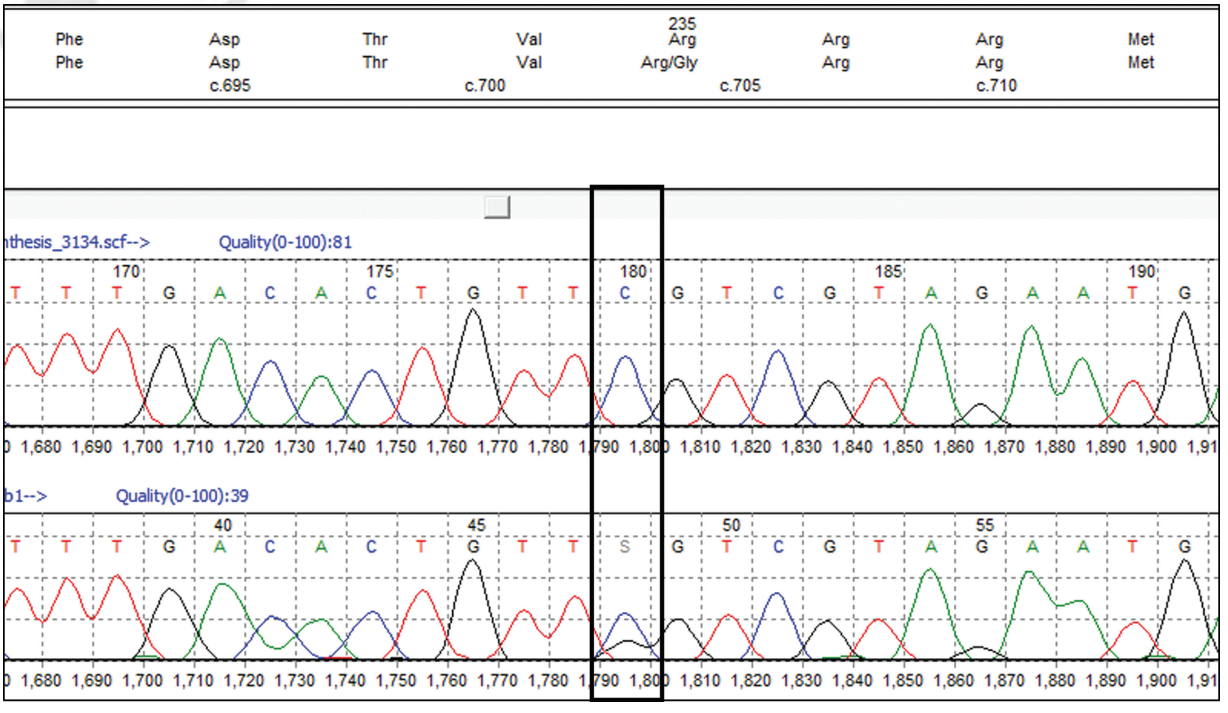

Fig. 1 Sanger sequencing data (electophoregram) of index case: showing nucleotide change at c.703C > G (p.Arg235Gly) in the SLC25A4 gene.

thus facilitating targeted management and counselling.[1,2] Our finding, the first case of MTDPS12A reported from India, with only seven cases reported worldwide,[5] highlights these aspects. The variant identified in our case is one of two recurrent variants reported in the context of MTDPS12A and has previously been described in three patients of MTDPS12A who succumbed, similarly, in early infancy.[4] Akin to the spectrum described before, our case had typical manifestations *viz* hypotonia, hyporeflexia, hypoventilation necessitating artificial ventilation, paucity of spontaneous movements, seizures, and hypertrophic cardiomyopathy. However, unlike other reports, our case did not document any raised serum lactate.[5]

MTDPS12A is characterized by a reduction in mt-DNA due to de novo variant in *SLC25A4*, leading to decreased synthesis of the respiratory complexes in different organs.[5] *SLC25A4* gene encodes an isoform of mitochondrial ADP/ATP carrier (AAC) known as AAC1, richly expressed in the skeletal and cardiac muscles, along with the brain.[5] The role of AAC1, like other forms of AAC, involves importing ADP into the mitochondria and exporting of ATP into the intermembrane space.[5] Understandably, thus, aberrations in the encoding of AAC1 protein due to variants in *SLC25A4* are associated with important clinical implications.[5]

Literature describes three distinct disease entities associated with variants in *SLC25A4*.[5] These include autosomal recessive MTDPS type-12 (MIM 615418) due to biallelic variants in *SLC25A4* causing mitochondrial myopathy and cardiomyopathy, autosomal-dominant adult-onset external ophthalmoplegia (MIM 609283) associated with heterozygous variants in *SLC25A4*, and lastly, autosomal dominant MTDPS12A as highlighted in this report.[5]

The likely factors contributing to respiratory insufficiency in MTDPS12A could be cerebral, myopathic, and/or neurogenic.[4,5] The unique nature of our case is that it had neurogenic respiratory insufficiency and hypertrophic cardiomyopathy without skeletal-muscle myopathy or any documented central nervous system lesion. The symptom-complex in our case made us consider CCHS as the primary differential.[3] A comparison of our differential versus final diagnosis, with the impact on the subsequent management and counselling, is presented in ►**Table 1**.[3,4] Clinically, though, the presence of hypoventilation in sleep as well as awake state, and the absence of the typical non-neurological spectrum described in CCHS (►**Table 1**), is pointer against it. Hence, we opted for next-generation sequencing (NGS)-based CES that covered CCHS as well as other single-gene disorders that can cause similar or

Table 1 Comparison of congenital central hypoventilation syndrome and mitochondrial DNA depletion syndrome-12A[3,4]

Parameters	Name of the disease	
	CCHS	MTDPS12A
Gene associated	PHOX2B	SLC25A4
Inheritance	AD (de novo)-commoner AD (inherited from a parent)	AD (de novo)
Incidence	Uncommon >1,000 cases reported worldwide	Very rare 7 cases reported worldwide
Age of presentation	Usually neonatal, milder cases can be later in childhood/adulthood	Neonatal onset
Clinical features	*CNS:* Central hypoventilation more severe during sleep, no hypotonia, seizures, neurocognitive deficits	*CNS:* Central hypoventilation even during awake hours as well as sleep, profound hypotonia, hyporeflexia, paucity of spontaneous movements, seizures, encephalopathy
	CVS: Transient cardiac asystoles, prolonged sinus pauses, syncope, autonomic disturbances	*CVS:* Hypertrophic cardiomyopathy
	GIT: Hirschsprung's disease, (20%), constipation, esophageal dysmotility	Not reported
	Oncogenic: Sympathetic nervous system and neural crest tumors	Not reported
	Ophthalmology: Decreased/absent pupillary light response, Anisocoria, Strabismus, lack of convergent gaze, Marcus Gunn phenomenon, jaw winking	Not reported
	Others: Decreased baseline body temperature, poor heat tolerance, hyperinsulinism, hypoglycemia, hyperglycemia, psychiatric disturbances	Raised blood and CSF lactate (not reported in our case)
Treatment options	Supportive care, tracheostomy, hospital-based and later home- based ventilation, diaphragmatic pacing, cardiac pacing for prolonged sinus pauses	Supportive care, tracheostomy, hospital-based and later home- based ventilation
Prognosis	With improving awareness, early genetic tests, proactive management, home ventilation, and multidisciplinary care children grow into adulthood and report a good quality of life; concerns for long term neurocognitive concerns	Ventilator dependence, most children die in early infancy. Longest known survivor aged 6 years (wheelchair-bound, tracheostomized, ventilator- dependent, unable to speak independently)
Risk of recurrence in future sibs	AD (de novo): more than general population, not zero (due to possibility of germline mosaicism) AD (if inherited from either parent): 50%	AD (de novo): more than general population, not zero (due to possibility of germline mosaicism)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CCHS, congenital central hypoventilation syndrome; CSF, cerebrospinal fluid; MTDPS, mitochondrial DNA depletion syndrome-12A.

overlapping clinical features. We were thus able to establish an early albeit a rare diagnosis of MTDPS12A.

Conclusion

Congenital hypotonia and hypoventilation should be a red flag to suspect an underlying genetic disorder, early in the course. Timely definitive diagnosis has an impact on patient management, prognostication as well as counselling regarding prevention of recurrence of the same condition in the next child. Rational use of NGS-based tests can shorten the diagnostic odyssey in such cases.

Authors' Contributions

K.P.S. Clinical management and manuscript preparation.
S.B.: Clinical management and manuscript preparation.
S.M.: Clinical management and manuscript preparation.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We would like to thank the parents of the child, who granted us the kind permission to share their child's clinical journey. We would also like to extend our sincere gratitude to Dr. Nagaraja M Phani, Senior Manager, Molecular Genetics and Dr. Venu Seenappa, Manager, Molecular Genetics, Lifecell International Pvt. Ltd., for sharing the Sanger pictogram of the variant as well as for guiding us toward drafting certain molecular and laboratory details of the manuscript.

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