HIDEA Syndrome: A rare cause of congenital hypoventilation in a premature infant

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Abstract

Background: HIDEA syndrome is a rare and novel disease characterised by hypotonia, hypoventilation, intellectual disability, epilepsy and eye abnormalities. Diagnosis is made by genetic testing with exclusion of other causes of hypoventilation. We present a case of a neonate born premature to a pair of consanguineous parents with an atypical course of bronchopulmonary dysplasia subsequently diagnosed with HIDEA syndrome. Conclusion: This is the first case report of HIDEA syndrome in South East Asia, broadening our understanding of the full phenotypic pattern of HIDEA syndrome. Patients with HIDEA syndrome are at risk of prematurity and hypothyroidism. Early diagnosis is crucial to optimise adequate ventilatory management including early tracheostomy as many require lifelong continuous or intermittent ventilation. This minimises the complications of chronic hypoxia and reduces mortality risk. HIDEA syndrome is an important differential diagnosis in the consideration of an infant who presents with hypoventilation.

Introduction

Hypoventilation in infants is rare and can be derived from a peripheral or central cause. Central hypoventilation has its origins in the brainstem respiratory center and can be secondary to drugs or the central nervous system diseases. Primary central hypoventilation syndromes present a wide spectrum of clinical manifestations, usually either in association with a clinically and genetically well determined disease (e.g., Prader Willi syndrome, familial dysautonomia) or as congenital central hypoventilation syndrome (CCHS) most commonly secondary to *PHOX2B* anomalies . Peripheral causes include cardiac arrhythmias, underlying neuromuscular disease and mitochondrial diseases . In premature infants, the most common cause of hypoventilation is apnea of prematurity

We describe a patient who was born premature in our hospital and required extensive work up for his hypoventilation with a diagnosis of HIDEA syndrome (hypotonia, hypoventilation, intellectual disability, dysautonomia, epilepsy and eye abnormalities) based on whole exome sequencing showing homozygous likely pathogenic variants in*P4HTM* . This is the first case report of HIDEA syndrome in a premature neonate in South East Asia, and it is a rare and novel differential diagnosis in a child who presents with central hypoventilation.

Case Report

The patient was born to Chinese parents whom are first cousins; mother is a 35-year-old Gravida 3 Para 2 (previous two pregnancies were born at term and are currently well). The pregnancy was unremarkable with normal antenatal ultrasound scans, liquor volume and fetal movements. Mother attended our hospital with per vaginal bleeding at 32 weeks gestation, obstetric assessment on admission noted fetal bradycardia and thus concern of abruption placentae was raised. The patient was immediately delivered via a crash caesarean section. The patient was born with a birth weight of 2 kg (52^{nd} centile), length 42.5 cm (39^{th} centile) and

occipital-fontal circumference of 31.1 cm (74^{th} centile). He initially required positive pressure ventilation but subsequently transferred to our neonatal intensive care unit (NICU) on continuous positive airway pressure (CPAP) support.

On clinical examination, he was noted to have baseline bradycardia and intermittent bradypnea with good respiratory effort. He did not have myopathic facies nor any dysmorphism. He was slightly hypotonic but had good anti-gravity movements and normal reflexes throughout.

His post-natal course was significant for severe respiratory distress syndrome requiring intubation at one hour of life. He required three doses of surfactant, and this was also complicated by a right pneumothorax requiring chest drain insertion. He was extubated at day 6 of life to CPAP and failed multiple trials of high flow nasal cannula in view of multiple apneas and increased work of breathing. Thus, he was maintained on CPAP 6 cmH_2O with a fraction of inspired oxygen at 23 – 25% until he reached term. The 2-dimesional echocardiography showed a small atrial septal defect, patent foramen ovale, and hypertrabeculation of the left ventricle apex and a 12-lead electrocardiogram (ECG) showed sinus bradycardia.

The patient's clinical course was atypical for bronchopulmonary dysplasia. He was not an extremely low birth weight or low gestation infant and yet, he required significant respiratory support at term. He was also noted to be significantly bradypnoeic at times with respiratory rates 10 – 15 breaths per minute which was also atypical for prematurity. Since birth, he was also noted to be bradycardic with baseline heart rates 70 – 90 beats per minute.

He was referred to the neurology team to investigate for a possible central pathology in view of the significant bradypnea and multiple apneic episodes while on ventilation. A normal magnetic resonance imaging of the brain ruled out a structural central cause and a normal creatinine kinase level 46 U/L was not in keeping with an underlying congenital muscular dystrophy. Electroencephalogram (EEG) did not reveal any seizures.

His serial chest radiographs showed bilateral mild reticular lung markings suggesting mild bronchopulmonary dysplasia. This was also reflected in his capillary blood gases which showed compensated respiratory acidosis with hypercarbia. He underwent an initial pulse oximetry study on CPAP 6 cmH_2O which showed a desaturation index of 131.4 events/hour with an oxygen saturation nadir of 58% as illustrated in Figure 1. Thus, he was converted to bi-level positive airway pressure (BiPAP) at settings of 10 cm H_2O / 6 cmH_2O. Polysomnogram done showed multiple hypopneic and apneic episodes with significant desaturations and thus, it was recommended to continue the adjusted BiPAP settings. Tracheostomy was recommended for a definitive airway and in view of his frequent hypoventilation episodes. A bedside nasoendoscopy did not reveal any upper airway abnormalities. Since he had persistent oxygen requirements, a computed tomography (CT) of the lungs was performed which showed diffuse reticular lung markings in both lungs.

Another possibility was congenital central hypoventilation syndrome and thus, we referred him to our Genetics team. He underwent *PHOX2B*gene testing which returned negative. Subsequently, trio whole exome sequencing was done which identified homozygous variants (NM_1777938.2:c.72G>A; p.Trp24*) in *P4HTM* (prolyl 4-hydroxylase, transmembrane), in keeping with the diagnosis of autosomal recessive HIDEA syndrome. His parents were heterozygous carriers; the pedigree is illustrated in Figure 2. Based on the ACMG-AMP guidelines, this *P4HTM* variant would be classified as "likely pathogenic" .

His other postnatal issues included pyloric stenosis for which he presented with multiple episodes of vomiting. Ultrasound abdomen confirmed this and he underwent a pylorotomy at a post menstrual age of 44 weeks. He also has hypothyroxinaemia of prematurity for which he currently remains on L-thyroxine replacement. He was also noted to have roving eye movements and ophthalmology will continue to follow up and assess for possible cortical blindness.

He is currently 2.5 months old corrected age and was discharged home when his parents were competent of taking care of his medical needs at home. He was discharged on BiPAP 24 cm H_2O / 9 cm H_2O, Rate 35 breaths per minute, Oxygen 2 L/min and three hourly bolus nasogastric tube feeding. He was also referred to the community palliative care team in view of the poor prognosis.

Discussion

In recent years, advancement in genetic science has solved many 'atypical' cases with no definite diagnosis. Defining the phenotype allows physicians to actively screen for associated medical problems and help with prognostication. Having a genetic diagnosis also helps with future family planning .

HIDEA syndrome is a rare and novel autosomal recessive condition. It is characterized by hypotonia, hypoventilation, intellectual disability, dysautonomia, epilepsy, and eye abnormalities. Clinical presentation of HIDEA syndrome may overlap with other genetic syndromes such as Prader-Willi syndrome, Down syndrome and rapid onset obesity, hypoventilation with autonomic dysfunction (ROHHAD syndrome) .

The first link between P4HTM and a human phenotype was described in 2014 in a large Finnish family where six family members had hypotonia, profound intellectual disability, strabismus and coarse facial features . In 2019, another 7 patients were reported with HIDEA syndrome with an update of the previously reported 6 patients. 77% (N=10/13) were noted to have epilepsy and 62% (N=6/13) were noted to have obstructive sleep apnea. 69% (N=9/13) of patients had pneumonia or recurrent pneumonias. The patients were also noted to have dysautonomia including constipation (46%, N=6/13), hypothermia or hyperthermia and reduced sweating. 46% (N=6/13) had a body mass index of more than 25 kg/m2.

In the reported literature of 21 patients presenting with HIDEA syndrome so far, the clinical picture is usually associated with moderate to severe neonatal hypotonia, central hypoventilation, severe to profound intellectual disability, dysautonomia including constipation and thermal dysregulation, high incidence of seizures (48%), and abnormal visual behavior including roving or rotatory eye movements. There does not seem to be any characteristic structural brain or structural eye abnormalities. Brain magnetic resonance imaging were normal in most patients 50% (9/18) of those who survived beyond infancy learned how to walk. 44 % (8/18) never developed speech . 17 % (3/18) died in infancy from respiratory tract infections, and 17% (3/18) died during childhood from febrile respiratory illness. The oldest reported patient died at 61 from acute pneumonia . One other patient was also reported to have hypothyroidism like the patient we report.

Out of the 21 reported patients with HIDEA syndrome (Table 1), 33% (6/18) had obstructive sleep apnea. 58% (11/19) were reported to have hypoventilation of which six had formal sleep studies and were confirmed to have central hypoventilation. This is unlike peripheral hypoventilation seen in patients with underlying neuromuscular disease Amongst the initial 13 patients that were reported, 38% (5/13) required nocturnal BiPAP, 7% (1/13) required BiPAP support throughout the day and 7% (1/13) required high frequency nasal cannula support. Our patient was similar with mixed central and obstructive apnea seen on polysomnography and he also required BiPAP support throughout the day. Table 1 summarizes the clinical features of patients with HIDEA syndrome including our patient for comparison.

Prolyl 4-hydroxylases (P4Hs) are important enzymes in the synthesis of collagen and the control of oxygen homeostasis. Two groups of P4Hs are recognized: those that hydroxylate proline resides in collagen and those that hydroxylase proline resides in hypoxia inducible factors (HIFs). Endoplasmic reticulum transmembrane prolyl-4-hydroxylase (*P4HTM*), encoded by the *P4HTM* gene, is a special P4H localized to the endoplasmic reticulum membrane, with the highest expression in the brain and eye. The genetic defect leads to premature stop codons or affect protein folding yielding an insoluble protein product that results in the clinical characteristics of the syndrome. *P4HTM* deficiency is postulated to be a mitochondrial disorder although the precise molecular mechanisms leading to mitochondrial dysfunction remains unknown. Abnormal HIF-1α levels have been reported in primary genetic mitochondrial disease. Other possible targets for *P4HTM* include the large subunit of RNA polymerase II and activating transcription factor 4 (ATF4) of all nuclear-encoded mRNAs. Impaired function of RNA polymerase II may affect mitochondrial function. These abnormalities could explain the mitochondrial dysfunction observed in patients with HIDEA syndrome.

Our case is a second reported premature infant to be diagnosed with HIDEA syndrome. The first was an infant born at 32 weeks of gestation with a low birth weight of 1.9 kg. He had persistent feeding difficulties and was subsequently diagnosed with hypothyroidism at 1 month old. In view of his poor weight gain, he

was started on nasogastric tube feeding at 8 months old and was admitted to the Pediatric Intensive Care Unit at 12 months old with frequent apneas during an episode of bronchiolitis. He was also noted to have global developmental delay with marked hypotonia. During his admission, he developed oxygen dependence related to hypoventilation and bradypnea. He subsequently required gastrostomy with fundoplication for severe gastro-esophageal reflux. He also had spinal dural arteriovenous fistula, mild hepatomegaly and left grade 2 hydronephrosis. His EEG had evidence of focal seizures although he did not manifest any clinically . Our patient is the first South East Asian patient to be formally diagnosed with HIDEA syndrome. We postulate that infants with HIDEA syndrome may have an increased risk of preterm birth and congenital hypothyroidism and possibly even pyloric stenosis. Unlike other cases reported in literature, this infant's autonomic dysfunction manifested as significant bradycardia since birth as well.

Thus, in consideration of the underlying etiology when faced with a neonate with central hypoventilation, consideration should be made for HIDEA syndrome as one of the differential diagnoses, especially when hypoventilation is associated with neonatal hypotonia. While no treatment exists for the intellectual disability and developmental delay, establishing the clinical diagnosis can impact management of hypoventilation, feeding issues and dysautonomia . Infant should undergo a thorough evaluation including bloods investigations to rule of an underlying neuromuscular disease, genetic syndrome, and mitochondrial disease. Once diagnosed an infant should undergo polysomnography and thyroid function tests. Early diagnosis of central hypoventilation will allow for possible early tracheostomy which will help to protect the airway especially as infants with HIDEA syndrome are prone to significant bradypnea which may be more pronounced during intercurrent respiratory tract infections which may result in significant morbidity and mortality. Looking at the current available literature and comparing the phenotypes reported to our case, our patient seems to have a severe form of HIDEA syndrome requiring such high ventilator support at a young age and thus, prognosis is guarded.

Conclusion

Genetic testing should be considered early in an infant who presents with central hypoventilation and hypotonia. When considering genetic causes for hypoventilation, HIDEA syndrome is an important differential when associated with hypotonia and other multisystemic features. Early diagnosis can help with prognostication and counselling about future pregnancies as well. More importantly, early diagnosis is crucial to optimise adequate ventilatory management including early tracheostomy as many require lifelong continuous or intermittent ventilatory dependence. This minimises the complications of chronic hypoxia and reduces mortality risk.

Conflict of Interest

All authors declare that no conflict of interest exists.

Author Contributions

YHT and AML contributed to the conception of the manuscript and were responsible for drafting the manuscript. PLT, NKV, NF and GCV revised the manuscript critically. AML, PLT, NKV, NF, GCV and YHT approved its final version.

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References

Figure 1. Abnormal Pulse oximetry

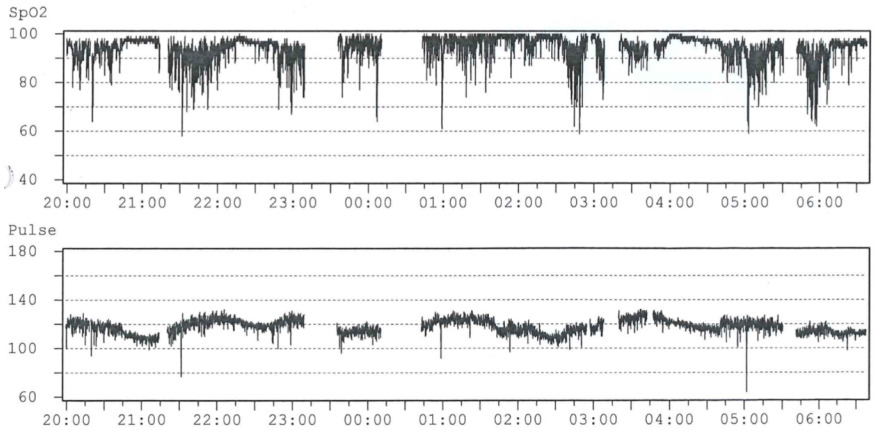

Figure 2. Pedigree of the family

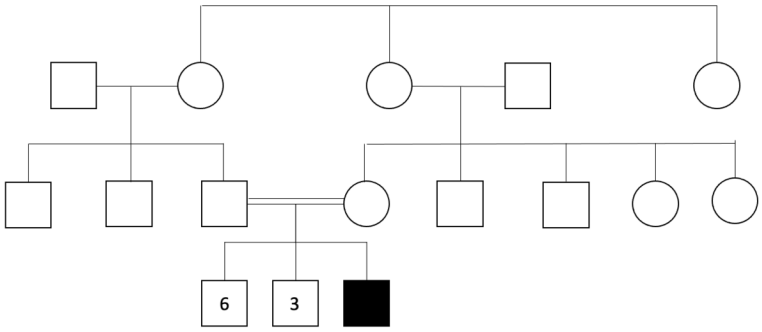

Table 1: Clinical features of HIDEA syndrome compared with our patient

	Patients with HIDEA syndrome in literature	Current patient	Total (%)
Subject Characteristics	Subject Characteristics	Subject Characteristics	Subject Characteristics
Male	13/21	Male	14/22 (64)
Consanguineous	7 (13 NR)	+	
Ethnicity	10 Middle eastern 8 Caucasian 3 Turkish	Asian	
Death Age of death (Median, years)	7 5 (7 months – 61 years)	Alive	15/21 (71)

	Patients with HIDEA syndrome in literature	Current patient	Total (%)
Clinical Features	Clinical Features	Clinical Features	Clinical Features
Dysmorphism	16/16	+	17/17 (100)
Thermoregulation abnormalities	4/15	-	4/16 (25)
Neurological Features	Neurological Features	Neurological Features	Neurological Features
Microcephaly	5/21	-	5/22 (23)
Failure to thrive	2/21	-	2/22 (9)
Hypotonia	21/21	+	22/22 (100)
GDD/ID	21/21	+	22/22 (100)
Poor/Absent speech	13/18 3 NA	NA	13/18 (72)
Seizures	10/21	-	10/22 (45)
Independent walking	9/18	NA	9/18 (50)
MRI Abnormalities	4/7	-	4/8 (50)
Ophthalmological features	Ophthalmological features	Ophthalmological features	Ophthalmological features
Poor vision	6/6	NA	
Refractive error/strabismus	13/14	NA	
Abnormal eye movements (Nystagmus, rotatory eye movements)	12/21	+	13/22 (59)
Respiratory features	Respiratory features	Respiratory features	Respiratory features
Hypoventilation/bradypnea	11/19	+	12/20 (60)
Sleep Apnea	6/18	+	7/19 (36)
Respiratory support (BiPAP/HFNC)	6/13	+	7/14 (50)
Gastrointestinal	Gastrointestinal	Gastrointestinal	Gastrointestinal
Constipation	11/20	-	11/21(52)
Skeletal	Skeletal	Skeletal	Skeletal
Scoliosis	3/9	-	3/10 (30)