Growing Spectrum of Episodic Apnea with Hypotonia in a Young Infant

To the editor,

A 48-day-old infant presented with 1-day history of altered breathing pattern and poor feeding of 20 days. Her perinatal period was uneventful. She was a full-term (38 weeks of gestation) first child born to third-degree consanguineous parents with a birth weight of 2.5 kg and head circumference of 31 cm. She was on mixed feeds with early introduction of cow milk owing to poor sucking at the breasts. History of failure to thrive was prominent. At admission, she had two episodes of self-limiting tonic seizures. She was lethargic with the poor state to state variability and irregular breathing pattern. She was afebrile and also underweight (2.25 kg, <-3z), stunted (50.5 cm, <-3z), and microcephalic (32 cm, <-3z). Receding anterior hairline was noteworthy. Focused neurological examination revealed generalized hypotonia with hypoactive reflexes and extensor plantar response. Tongue fasciculations were conspicuously absent. Infant continued to have episodic apnea with poor respiratory efforts and recurrent desaturation requiring positive pressure ventilatory support. Clinical differential diagnoses considered were neuromuscular disorders such as congenital myasthenia, dystroglycanopathy, and mitochondrial Leigh's disease. Blood gas analysis showed compensated respiratory acidosis (pH-7.3, PCO_2-56 mmHg). Blood lactate (5.45 mmol/L [Normal = 1.1–2.3 mmol/L]) and serum ammonia (134 µmol/L[Normal = 11–35 µmol/L]) were elevated. Serum creatine kinase was normal (112 U/L). Magnetic resonance imaging (MRI) of the brain revealed nonspecific cerebellar white matter hyperintensities. Cerebrospinal fluid analysis was acellular with normal glucose (89 mg/dL) and increased protein (68 mg/dL [normal range: 20–45 mg/dL]). Tandem mass spectrometry and gas chromatography were normal. The child was initiated on megavitamin supplements and required 2 weeks of respiratory assistance prior to discharge. Exome sequencing revealed a pathogenic heterozygous frameshift variation in Exon 1 of the *PURA* gene *(chr5:g. 140114334_140114335insG; Depth: 75x)* that resulted in frameshift and premature truncation of the protein 147 amino acids downstream to codon 54 *(p.Leu54AlafsTer147; ENST0000033132.5)* validated by Sanger sequencing. Parental screening for pathogenic variation was negative. The child was initiated on early rehabilitation services and at 3-month follow-up, the child had no further episodes of breathing dysfunction. Reproduction counselling has been offered to the parents.

The list of clinical differential diagnoses for episodic apnea with generalized hypotonia in a young infant is exhaustive. Metabolic disorders like mitochondrial respiratory chain disorders, Leigh's disease, glycine encephalopathy, and citrullinemia; neurotransmitter disorders like aromatic amino acid decarboxylase deficiency; neuromuscular disorders like congenital myasthenia and dystroglycanopathy; structural causes like Joubert syndrome and congenital central hypoventilation syndrome merit evaluation. In addition, the above features can also be seen in a lesser-known developmental encephalopathy due to mutations of purine-rich element binding protein A (PURA) in chromosome 5q entitled "PURA syndrome."[1] The literature on PURA syndrome is sparse and should be suspected in infants with the constellation of 4H comprising hypotonia, hypoventilation, hypothermia, and hypersomnolence.[2] A review of 54 cases by reijnders *et al*. reported that the earliest presentation is by excessive hiccups in utero and post-term delivery (>41 weeks) as seen in more than 50% of the cases (55%–56%). Hypotonia from birth (96%) is the most common manifestation of the condition leading to feeding difficulties (77%) that may require tube feeding. Hypersomnolence (66%), breathing difficulties that include apneas and congenital hypoventilation (57%), exaggerated startle response (44%), and hypothermia (35%) were the next common clinical features.[1] The association of infantile spasms, myotonia was also reported.[3,4] Older children present with moderate-to-severe intellectual impairment, absent speech, seizures, spasticity, unstable gait, and motor delay.[5] Uncontrolled seizures in some cases may result in loss of achieved milestones mimicking neuroregression. Movement disorders, seizure-like movement, and ataxic movements were reported in 20% of cases.[1] Peripheral neuropathy can occur at a younger age. The hypotonia can also lead to swallowing problems at later age, drooling, and constipation in up to 60% of the cases. Dysmorphic features

like higher anterior hairline, myopathic face, full cheeks, and almond-shaped palpebral fissures have been described in cases of PURA syndrome.[1,2] However, the clinical phenotype is nonspecific with no diagnostic criteria, and diagnosis is strictly genetic by exome analysis. A multiorgan screening for structural heart defects, genitourinary abnormalities, strabismus, and hip dysplasia and scoliosis, metabolic and endocrine abnormalities like vitamin D deficiency, hypothyroidism, and short stature is warranted in children with PURA syndrome. Screening in the index child on follow-up was unremarkable. Nonspecific white matter changes and delayed myelination (30%), similar to the index case, are the frequently reported abnormality in MRI neuroimaging. Corpus callosal abnormalities, lateral ventricular widening, mild parenchymal atrophy were also described.[6] Treatment for this condition is largely supportive with the institution of early intervention services. In conclusion, PURA-related developmental disorders should be suspected in a young infant with generalized hypotonia and episodic apnea. Early recognition is essential to assist in reproductive counselling.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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