PURA Syndrome: A Rare Case of Neonatal Hypotonia with a Novel Multi-gene Deletion at 5q31.2q31.3 Diagnosed with rWES

Mahesh Chikkannaiah,[1,2] Laura D. Fonseca,[1] Irma Reyes,[1,2] Samuel Dzodzomenyo, [1,2] Gogi Kumar [1,2]

[1]Department of Neurology, Dayton Children's Hospital, Dayton, OH

[2]Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton, OH

INTRODUCTION

- PURA syndrome is a rare neurodevelopmental disorder due to alterations in the purine-rich binding element protein alpha (PURA) gene in chromosome 5q31.2q31.3
- The genetic defect is either due to a heterozygous pathogenic sequence variant (90%) or a deletion of 5q31.3 encompassing all or part of PURA gene (10%).[1]
- Common clinical features of PURA syndrome are detailed in Table 1.[1,2]
- Congenital heart defects, urogenital malformations, skeletal and endocrine abnormalities occur, but are less common (Table 2).

CASE SUMMARY

- A 9-day old boy admitted to the NICU was consulted with pediatric neurology for concerns of hypotonia, difficulty weaning off ventilatory support and seizure like activity reported as episodes of eye rolling and bilateral lower extremity twitching.
- He was born at 39+1 weeks via induced vaginal delivery with no pregnancy or delivery complications. APGAR scores were 8 and 9 at 1 and 5 minutes.
- Respiratory distress was noted soon after birth; he was admitted to the NICU and was placed on continuous positive airway pressure (CPAP).
- He failed to wean from CPAP until day 7 of life when he was transitioned to high flow oxygen via nasal canula. However, due frequent apneic events and increased FiO2 requirement, patient was intubated and on ventilator support.
- Head ultrasound was negative; continuous EEG monitoring was negative for seizures.
- Neurological exam was significant for low muscle tone, weak cry, poor suck reflex and intact reflexes.
- Given clinical history and examination, neuromuscular etiology was considered and rapid whole exome sequencing (rWES) was recommended.
- rWES was positive and showed a heterozygous multi-gene deletion at 5q31.2q31.3 consistent with PURA syndrome.
- Other diagnostic testing that was considered included genetic testing for myotonic dystrophy, CK, thyroid function testing and MRI brain.
- He was weaned back to CPAP and then to 1 liter per minute oxygen via nasal cannula at time of discharge.
- As of most recent follow-up at 20 months, he is diagnosed with hypotonic cerebral palsy with global developmental delay, sensorineural hearing loss requiring hearing aids, and on bilevel positive airway pressure (BiPAP) during sleep for hypoventilation and obstructive sleep apnea.

TABLES

Table 1. Clinical features of PURA Syndrome

Neonatal Period	Infants and Children
Hypotonia	Hypotonia
Hypothermia	Moderate-to-severe neurodevelopmental delay with absent speech
Hypersomnolence	Moderate-to-severe intellectual disability
Apnea and hypoventilation	Non-epileptic movements (e.g., dystonia, dyskinesia, and disconjugate eye movements)
Feeding difficulties	Epilepsy

Table 2. Extra-Neurological manifestations

Body System	PURA Syndrome Manifestations
Cardiovascular	Atrial and ventricular septal defect, persistent foramen ovale, persistent ductus arteriosus, pulmonic stenosis, bicuspid aortic valve, and aberrant left subclavian artery
Respiratory	Apnea and hypoventilation
Gastrointestinal	Feeding difficulties and/or gastroesophageal reflux disease, dysphagia, and constipation
Urogenital	Cryptorchidism, congenital hydronephrosis, urinary reflux, kidney stones, and prolapsed uterus
Skeletal	Scoliosis, hip dysplasia, and osteoporosis/osteopenia.
Endocrine	Hypothyroidism, elevated prolactin levels, precocious puberty and blunted cortisol response
Ophthalmologic	Strabismus, Brown syndrome, cortical visual impairment, hypermetropia, and optic nerve pallor

DISCUSSION

- PURA syndrome should be considered in the differential diagnosis of neonates with hypotonia, hypersomnolence, feeding difficulties and apnea/hypoventilation with difficulty weaning from respiratory support.
- Differential diagnosis of PURA syndrome in the neonatal period include neuromuscular conditions (i.e., congenital myasthenic syndrome, myotonic dystrophy, spinal muscular atrophy, congenital muscular dystrophies and myopathies), congenital central hypoventilation syndrome and Prader-Willi syndrome, among others.
- Currently there is no specific treatment for PURA syndrome.
- Management includes symptomatic treatment and multidisciplinary care.

CONCLUSION

- PURA syndrome should be an important diagnostic consideration in neonatal hypotonia.
- Where available ultra-rapid or rapid whole exome sequencing (rWES) can be an important diagnostic tool for neonates with hypotonia and can be helpful for early and accurate diagnosis, and aide in the management and prognosis.[3]

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For questions contact Mahesh Chikkannaiah, MD at ChikkannaiahM@childrensdayton.org

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