Fellows Column: Early Identification of PURA Syndrome in a Neonate: Implications on Diagnosis and Management

Samir Alsalek, BS, Lucas J. Saporito, BS, Grace J. Noh, MD, Michael S. Chang, MD, Huy N. Truong, MD

Abstract:

Background: *Protein-rich element binding protein A (PURA) syndrome is a genetic neurodevelopmental disorder that results in profound neurodevelopmental delay and intellectual disability. Few cases of PURA syndrome have been recognized in neonatal life, partly due to heterogenous clinical presentation, low clinical suspicion, and symptom progression that results in a more thorough workup later in life.*

Case Presentation: *We report the case of a newborn who presented with hypotonia, feeding difficulties, and respiratory distress within the first hours of birth. Neonatal screening, infectious workup, and imaging were unremarkable. Clinical exome sequencing revealed de-novo, a pathogenic variant in the PURA gene. The patient received comprehensive rehabilitative care and social support. At one-year follow-up, the patient continued to experience feeding difficulties and apneic events and demonstrated significant neurodevelopmental delay.*

Conclusion: *This report documents the consideration and diagnosis of PURA syndrome in the neonatal period and describes the implications of early diagnosis on prompt symptomatic management and patient outcomes at 1-year follow-up.*

Introduction:

PURA syndrome is a rare genetic, neurodevelopmental disorder that arises from variants in the *PURA* gene and presents with neonatal hypotonia, feeding difficulties, and severe global intellectual and developmental delay. The syndrome was first described in 2014 and is often identified in early childhood in individuals with unexplained severe intellectual disability and neurodevelopmental delay, using clinical or whole exome sequencing (1-3). The *PURA* gene is located on chromosome 5q31.3 and encodes PUR-α, a ubiquitous, purine-rich, DNA- and mRNA-binding protein essential in mammalian brain development (4-6). *PURA*-related disorders typically occur de novo, but inheritance from an unaffected mosaic parent has also been reported (3).

"PURA syndrome is a rare genetic, neurodevelopmental disorder that arises from variants in the PURA gene and presents with neonatal hypotonia, feeding difficulties, and severe global intellectual and developmental delay...PURA-related disorders typically occur de novo, but inheritance from an unaffected mosaic parent has also been reported (3)."

Notably, most reported cases of PURA syndrome in the current literature have been detected in late infancy or early childhood. This is expected given that the intellectual and developmental features of the condition become more pronounced with age, prompting thorough investigation. However, detection of PURA syndrome in the neonatal period has seldom been reported, and the implications of early detection on prognosis and management remain unclear (7,8). Diagnosis in the neonatal period is difficult mainly due to the low index of suspicion and broad, non-specific presentation. In this report, we present the case of a neonate with PURA syndrome that was identified and promptly managed during the first few weeks of life. We report follow-up outcomes at one year of life and discuss the potential implications of early diagnosis.

"A 6-hour-old female infant was born to a 36-year-old G6P5 at 39 weeks and 3 days gestation via spontaneous vaginal delivery. The infant weighed 3910g and had APGAR scores of 7 and 9 at 1 and 5 minutes, respectively. At birth, the infant was in the 87th percentile for weight, 94th percentile for length, and 67th percentile for head circumference. Pregnancy was complicated by polyhydramnios, maternal obesity, clindamycin-resistant Group B Strep, and Varicella non-immunity."

Case Presentation:

A 6-hour-old female infant was born to a 36-year-old G6P5 at 39 weeks and 3 days gestation via spontaneous vaginal delivery. The infant weighed 3910g and had APGAR scores of 7 and 9 at 1 and 5 minutes, respectively. At birth, the infant was in the 87th percentile for weight, 94th percentile for length, and 67th percentile for head circumference. Pregnancy was complicated by polyhydramnios, maternal obesity, clindamycin-resistant Group B Strep, and Varicella non-immunity. The parents are of Hispanic descent and non-consanguineous, with four other children. There is a family history of isolated Down Syndrome on the maternal side but no history of neuromuscular disorders, major birth defects, developmental delay, or other significant inherited conditions in the family. Shortly after birth, the infant was noted to be hypotonic, with absent suckling during the first 6 hours and intermittent, poor suckling at 12 hours. The infant also had intermittent episodes of slowed respiration and desaturation, which improved on the nasal cannula. X-ray imaging of the chest and abdomen revealed no abnormalities (**Figure 1**). The infant was subsequently transferred to a different facility's neonatal intensive care unit (NICU) for further evaluation and management. During transportation, the infant was placed on non-invasive intermittent positive pressure ventilation (NIPPV) due to respiratory insufficiency and started on antimicrobial therapy for suspected infectious disease.

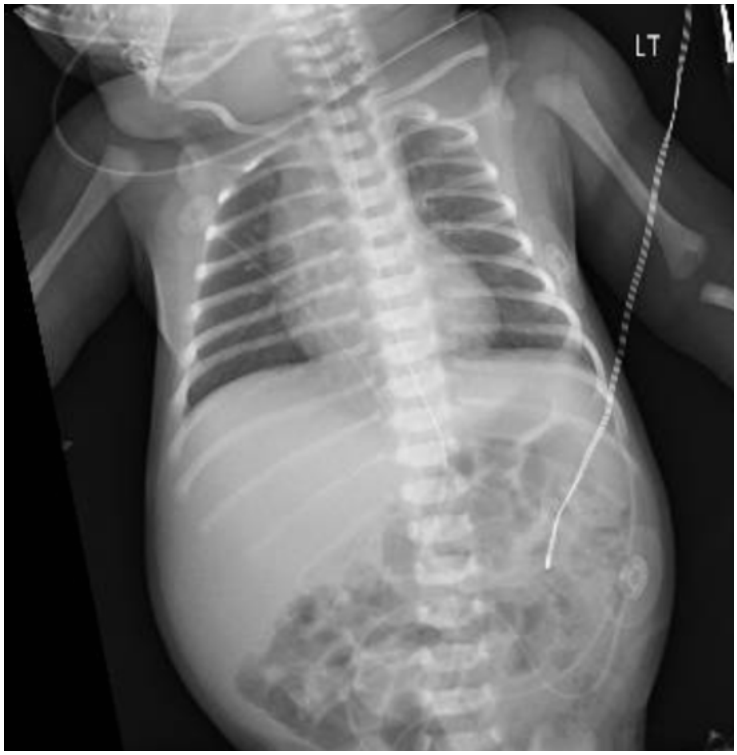


Figure 1. X-ray imaging of the chest and abdomen demonstrating no evidence of active respiratory infection or bowel obstruction. A nasogastric tube tip can be seen in the distal stomach.

Upon arrival to the NICU, the infant continued to have decreased tone, poor suckling and feeding, hypotonia, and absence of the Moro reflex. No dysmorphic facial features or asymmetric muscle activity were noted. Blood cultures investigating neonatal sepsis were negative, and an ultrasound of the head revealed no evidence of intraventricular hemorrhage. Routine newborn screening also revealed no abnormalities. A nasogastric tube was placed to provide feeds due to persistently poor feeding. On day 2, the infant was noted to have intermittent, brief ankle jerks and was later observed to have stronger, single jerks of the right upper extremity. Due to concern for seizures, phenobarbital was initiated, and cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG), and magnetic resonance imaging (MRI) studies were obtained. Neurologic evaluation of the infant revealed moderate-to-severe hypotonia and seizures with normal reflexes, normal eye movements, and no other focal neurologic deficits. The results of the CSF analysis were normal. EEG was normal, with no extremity jerks or seizure activity observed during the study. MRI of the brain showed normal neonatal myelination pattern and structure, with mild enlargement of the subarachnoid spaces but no evidence of effusion or hydrocephalus (**Figure 2**). Microarray and methylation testing for Angelman and Prader-Willi syndrome were also negative. Hypersomnolence was noted on day 4 of life, and the phenobarbital maintenance dose was reduced. Due to persistent hypotonia and feeding difficulties, clinical whole exome sequencing was obtained on day 29 of life, revealing de-novo, heterozygous pathogenic variant (c.573del; p.(A192Rfs*33)) in the *PURA* gene.

"...clinical whole exome sequencing was obtained on day 29 of life, revealing de-novo, heterozygous pathogenic variant (c.573del; p.(A192Rfs*33)) in the PURA gene."

Following the diagnosis of PURA syndrome, seizure prophylaxis was switched to levetiracetam to minimize somnolence. A second EEG study continued to show normal activity, and no further convulsive episodes were observed. Due to continued poor feeding, a gastrostomy tube was placed for enteral feeds and weight-gain support. The patient's family was counseled after the diagnosis, and appropriate follow-up appointments, support, and resources were provided. The infant was discharged two months after birth and was breastfeeding around 75% of all intakes at discharge. The infant was neurologically stable on levetiracetam with increased activity and marked improved respiratory status on the nasal cannula.

On follow-up examination at three months of age, the patient had improvement in feeding and was in the 85th percentile for head circumference, 98th percentile for weight, and 91st percentile for height. The infant continued to demonstrate developmental delay and had episodes of feeding-associated respiratory distress, including inspiratory stridor, aspiration, and cough, requiring supplemental oxygen. At 1-year follow-up, the patient displayed significant developmental delay, including absence of expressive language and delay of fine motor function. The infant relied on supplemental nighttime oxygen for mixed central and obstructive apneic events and gastrostomy for most feeds and received speech, physical, and pulmonary therapy services.

"PURA syndrome is a genetic, heterogenous, neurodevelopmental disorder characterized by neonatal hypotonia, feeding difficulties, respiratory distress, seizures, and progression to moderate-to-severe developmental delay and learning disability. It may additionally present with hypersomnolence, movement abnormalities, epilepsy, and congenital disabilities of the heart, urogenital tract, and skeleton. Infants with PURA syndrome may or may not have dysmorphic features, including high anterior hairline, hypotonic face, almond-shaped palpebral fissures, full cheeks, well-defined philtrum, and retrognathia (2, 3, 6)"

Discussion:

PURA syndrome is a genetic, heterogenous, neurodevelopmental disorder characterized by neonatal hypotonia, feeding difficulties, respiratory distress, seizures, and progression to moderate-to-severe developmental delay and learning disability. It may additionally present with hypersomnolence, movement abnormalities (e.g., dystonia, dyskinesia, dysconjugate eye movements), epilepsy, and congenital disabilities of the heart, urogenital tract, and skeleton. Infants with PURA syndrome may or may not have dysmorphic features, including high anterior hairline, hypotonic face, almond-shaped palpebral fissures, full cheeks, well-defined philtrum, and retrognathia (2, 3, 6). Despite these features, PURA syndrome remains difficult to diagnose in practice, with low rates of detection in neonatal life (7).

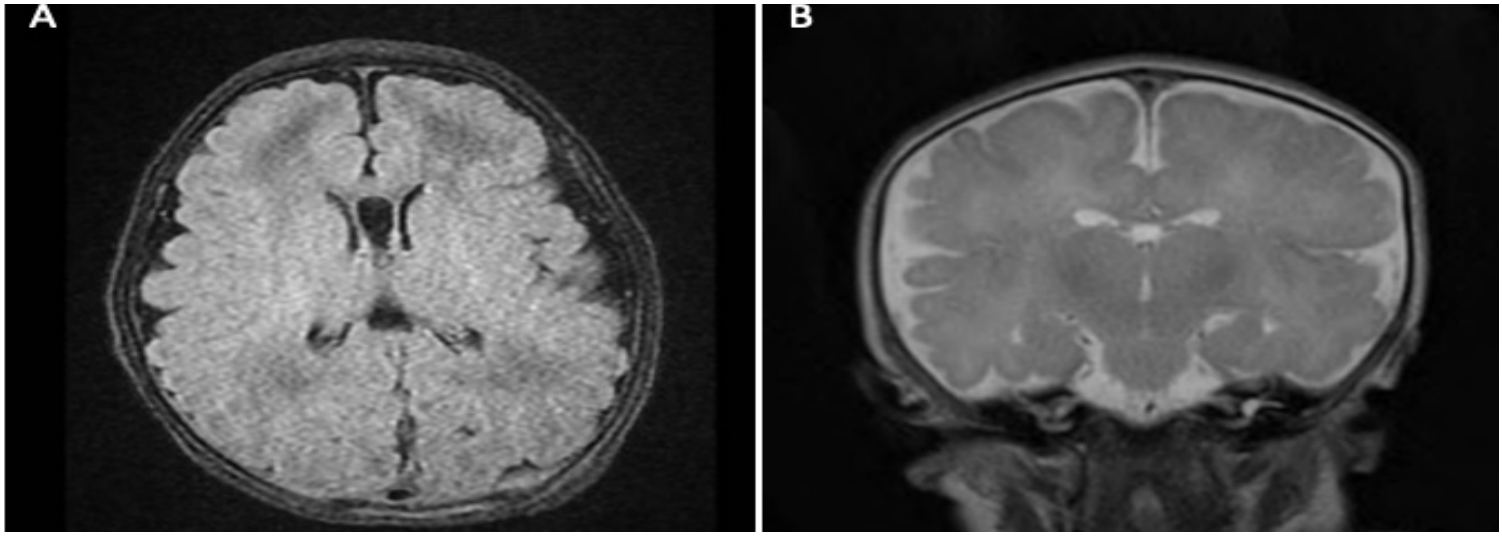


Figure 2. Axial (A) and coronal (B) MRI imaging of the brain demonstrating mild enlargement of the subarachnoid spaces with no extra-axial or subdural effusion and no hydrocephalus. No evidence of parenchymal or intraventricular hemorrhage is seen.

As a recently described genetic syndrome with variable and multi-system phenotypic presentation, PURA syndrome has no definitive treatment, and the mainstay of management is through symptomatic, respiratory, and nutritional support, along with rehabilitation, social support, and parental education. Recent reports have suggested that PURA may share clinical features and pathophysiology with neuromuscular junction disorders (e.g., congenital myasthenic syndrome), indicating potential benefit for acetylcholinesterase inhibitors (8,9). Our patient experienced significant respiratory failure in early life and continues to display respiratory distress at one-year follow-up, which may add clinical support to this hypothesis. However, more query is needed into the exact pathophysiology of the disease and the value of neuromuscular therapies in improving respiratory outcomes. Nonetheless, supportive care should be initiated as early as possible in suspected PURA cases, ideally by a multidisciplinary team of providers, including neonatologists, neurologists, geneticists, respiratory therapists, gastroenterologists, and speech and physical therapists. Special attention should be given to the close monitoring and support of respiration, feeding difficulties, and seizure prophylaxis (6).

"As a recently described genetic syndrome with variable and multi-system phenotypic presentation, PURA syndrome has no definitive treatment, and the mainstay of management is through symptomatic, respiratory, and nutritional support, along with rehabilitation, social support, and parental education."

Our report presents one of the few documented cases of PURA syndrome detection in a neonate. Our patient had profound hypotonia, respiratory distress, and feeding difficulties within the first few hours of life. Although symptomatic management was initiated promptly, extensive workup and genetic sequencing allowed for the precise diagnosis and mobilization of additional resources for the patient and family. This included social support, rehabilitation, and longitudinal patient engagement and education. In addition to excluding alternative diagnoses, early detection of PURA may allow for complete care planning, early coordination between the clinician and family, and prospective follow-up of prognosis and treatment outcomes. In this case, diagnosis within neonatal life allowed for our patient's early rehabilitative and psychosocial services. Future research should investigate the long-term developmental and physical outcomes of PURA patients with early identification and therapy.

Conclusion:

Despite its rarity and heterogeneous presentation, the present case demonstrates how clinical suspicion and genetic analysis can lead to a successful neonatal diagnosis of PURA syndrome in the setting of a non-specific constellation of symptoms. Early detection of PURA syndrome allows for prompt initiation of appropriate symptomatic management, care planning, and access to supportive resources for the patient and family. Further research is needed to determine how early management impacts long-term outcomes in PURA syndrome patients.

"Early detection of PURA syndrome allows for prompt initiation of appropriate symptomatic management, care planning, and access to supportive resources for the patient and family."

References:

1. Bonaglia MC, Zanotta N, Giorda R, D'Angelo G, Zucca C. Long-term follow-up of a patient with 5q31.3 microdeletion syndrome and the smallest de novo 5q31.2q31.3 deletion involving PURA. Mol Cytogenet. 2015;8:89. Published 2015 Nov 14. doi:10.1186/s13039-015-0193-9

2. Hunt D, Leventer RJ, Simons C, et al. Whole exome sequencing in family trios reveals de novo mutations in PURA as a cause of severe neurodevelopmental delay and learning disability. J Med Genet. 2014;51(12):806-813. doi:10.1136/jmedgenet-2014-102798

3. Reijnders MRF, Janowski R, Alvi M, et al. PURA syndrome:

clinical delineation and genotype-phenotype study in 32 individuals with review of published literature. J Med Genet. 2018;55(2):104-113. doi:10.1136/jmedgenet-2017-104946

4. Johannesen KM, Gardella E, Gjerulfsen CE, et al. PURA-Related Developmental and Epileptic Encephalopathy: Phenotypic and Genotypic Spectrum. Neurol Genet. 2021;7(6):e613. Published 2021 Nov 15. doi:10.1212/NXG.0000000000000613

5. Molitor L, Bacher S, Burczyk S, Niessing D. The Molecular Function of PURA and Its Implications in Neurological Diseases. Front Genet. 2021;12:638217. Published 2021 Mar 11. doi:10.3389/fgene.2021.638217

6. Lalani SR, Zhang J, Schaaf CP, et al. Mutations in PURA cause profound neonatal hypotonia, seizures, and encephalopathy in 5q31.3 microdeletion syndrome. Am J Hum Genet. 2014;95(5):579-583. doi:10.1016/j.ajhg.2014.09.014

7. Liu Y, Liu R, Xu T, Zhou YX, Zhang SC. Neonatal PURA syndrome: a case report and literature review. Transl Pediatr. 2021;10(1):194-203. doi:10.21037/tp-20-248

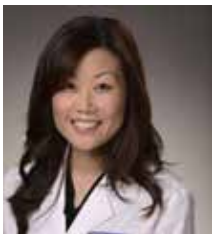
8. Wyrebek R, DiBartolomeo M, Brooks S, Geller T, Crenshaw M, Iyadurai S. Hypotonic infant with PURA syndrome-related channelopathy successfully treated with pyridostigmine [published correction appears in Neuromuscul Disord. 2022 Aug;32(8):e1]. Neuromuscul Disord. 2022;32(2):166-169. doi:10.1016/j.nmd.2022.01.005

9. Iyadurai S, Geller T, Wyrebek R, et al. PURA syndrome: Neuromuscular junction manifestations with potential therapeutic implications [published online ahead of print, 2022 Nov 4]. Neuromuscul Disord. 2022;S0960-8966(22)00703-9. doi:10.1016/j.nmd.2022.11.001

Disclosures: The authors have no relevant disclosures.

NT

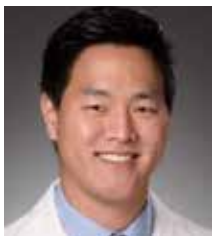
Lucas J. Saporito, BS
Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, United States
Email: Lucas.J.Saporito@kp.org



Grace J. Noh, MD
Kaiser Permanente Fontana Medical Center, Fontana, United States
Email: Grace.J.Noh@kp.org

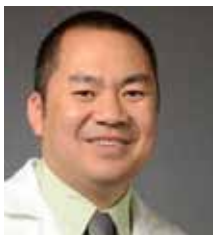
Corresponding Author

Samir Alsalek, BS
Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, United States
Email: Samir.x.alsalek@kp.org



Michael S. Chang, MD
Kaiser Permanente Fontana Medical Center, Fontana, United States
Email: Michael.S.Chang@kp.org

Corresponding Author



Huy N. Truong, MD
Kaiser Permanente Fontana Medical Center, Fontana, United States
Kaiser Permanente Fontana Medical Center Department of Pediatrics, Fontana, United States
Email: Huy.A.Truong@kp.org

Fellow's Column is published monthly.

- Submission guidelines for “Fellow's Column”:
- 2000 word limit not including references or title page. Exceptions will be made on a case by case basis
- QI/QA work, case studies, or a poster from a scientific meeting may be submitted..
- Submission should be from a medical student, resident, fellow, or NNP in training.
- Topics may include Perinatology, Neonatology, and Younger Pediatric patients.
- No more than 20 references.
- Please send your submissions to:

Elba Fayard, MD, Interim Fellowship Column Editor
or Sandeep Lankireddy, OMS IV Fellowship Column Assistant Editor: LomaLindaPublishingCompany@gmail.com