PURA syndrome in a child with severe developmental delay: a challenging diagnosis

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Accepted:
03.09.21.

Conflict of interests:
The authors have no conflicts of interest to declare.

How to cite this article:
Nogueira M, Melo C, Grangeia A, Magalhães T, Soares C, Dias R, et al. PURA syndrome in a child with severe developmental delay: a challenging diagnosis. Rev Neurol 2022; 74: 170-3. doi: 10.33588/rn.7405.2021068.

Versión española disponible en www.neurologia.com

Introduction. PURA syndrome is a rare autosomal dominant condition caused by de novo pathogenic variants in PURA gene and characterized by a multisystemic phenotype that includes global neurodevelopmental delay, early hypotonia, absence of speech, feeding difficulties, hypersomnolence, epilepsy and movement disorders.

Case report. We report a 9-year-old girl with hypotonia and feeding difficulties with failure to thrive since the neonatal period. At the age of 3 years motor and intellectual delay were evident, she had a wide-based gait, no speech and an exaggerated acoustic startle response. She developed hand-mouthing stereotypies and epilepsy at 6 years old. The 24 hours continuous electroencephalogram monitoring revealed global slow activity and frequent epileptiform activity in left temporal and centrotemporal areas. The brain MRI revealed delayed myelination. At 6 years old the clinical exome sequencing identified a heterozygous pathogenic variant in the PURA gene, c.153delA p.(Leu54CysfsTer24).

Conclusion. PURA syndrome has clinical features similar to other neurological disorders but the association with some clinical features, not as common in other neurological entities, like never being able to speak but being able to follow simple orders and exaggerated acoustic startle response, should raise the suspicion of PURA syndrome and genetic analysis must be performed to confirm the diagnosis and provide early multidisciplinary intervention.

Key words. Developmental delay. Neurological disorders. Next generation sequencing. PURA gene. PURA syndrome. Speech delay.

Introduction

PURA syndrome is a rare autosomal dominant condition characterized by a spectrum of phenotypes including moderate to severe global neurodevelopmental delay, early hypotonia, apneas, feeding difficulties, hypothermia, hypersomnolence, motor delay and intellectual disability with language delay affecting mostly the expressive language. Many patients also have epilepsy and abnormal non-epileptic movements like dystonia, dyskinesia and dysconjugate eye movements. Less frequently the patients may have congenital heart disorders and other abnormalities of the urogenital, skeletal and endocrine systems [1-6].

In 2014, using next generation sequencing (NGS) analysis, this disorder was first reported as being caused by *de novo* heterozygous pathogenic variants in purine-rich element binding protein A (*PURA*) gene in a group of patients with consistent neurological features, previously described in 5q31.3 microdeletion syndrome [6-8]. *PURA* gene is localized at chromosome 5 and encodes a transcriptional activator protein Pur-alpha (Pura), which is involved in neuronal growth and division, dendrite maturation and synapses transmission [5,8].

To our knowledge, there are, at least, 77 reported and well-characterized cases of PURA syndrome associated with 62 different variants in *PURA* gene [1,2].

We report the case of a 9-year-old girl that presents severe developmental delay associated with a *de novo* heterozygous pathogenic variant in *PURA* gene.

Case report

A 9-year-old girl was the second child of a young, healthy and non-consanguineous couple. Pregnancy and family history were unremarkable. During the first month of life, the newborn developed hypotonia and feeding difficulties with failure to thrive. The metabolic workup and thyroid function analysis were normal. At 4-months-old, brain magnetic resonance imaging (MRI) and electromyogram were normal. Karyotype and microarray-

based comparative genomic hybridization testing were also normal.

At 5 months old, she was admitted to the pediatric intensive care unit due to a severe influenza A (H1N1) infection. Hypotonia, hypersomnolence and feeding problems got worse and a gastroesophageal reflux was diagnosed.

The head circumference and weight remained stable in the 10th percentile and she was growing in the 5th percentile. Regarding developmental milestones, head control was achieved by the age of 6 months, she sat unsupported at 12 months and at 3 years old she was able to walk with support with a wide-based and unstable gait. She was never able to speak, but receptive language skills were less affected and she could follow simple instructions. Other clinical features included dolichocephaly, bilateral epicanthus, strabismus, deep palmar and plantar creases, hypertrichosis, sialorrhea, axial hypotonia and apendicular spasticity. Hand motor stereotypies, such as hand-mouthing, were very prominent, most of all in the midline. She had frequent vomiting and constipation. Up to the age of 3 years, exaggerated acoustic startle response was noticed. At 8 years old she also presented hip dysplasia that was surgically corrected.

Seizures started at 6 years old with multiple daily episodes of loss of tonus and staring with or without associated loss of consciousness. She started valproic acid, and subsequently clobazam, with seizures control. The 24 hours continuous electroencephalogram monitoring revealed basal cerebral electrogenesis in wakefulness with globally slow activity and frequent epileptiform activity in left temporal and centrotemporal areas. The following MRI of the brain revealed delayed myelination, especially in temporal areas and prominent periventricular spaces due to a mild parenchymal atrophy.

At the age of 6 years, the clinical exome sequencing (CES) was performed and identified a heterozygous pathogenic variant in the exon 1 of the *PURA* gene, c.153delA (p.Leu54CysfsTer24). The CES consisted in a large sequencing panel that included more than 4000 clinically relevant genes and focuses on the sequencing of the coding (exons) and flanking regions (splicing sites) of genes already associated with clinical phenotypes listed on Human Gene Mutation Database (HGMD) and Online Mendelian Inheritance in Man (OMIM). After sequencing, detected variants were annotated regarding their effect on protein function, allele frequency in the general population, and prior evidence of disease causality and filtered to select likely pathogenic DNA variants. The selected variants were then reviewed and reported according to their relevance and association with the clinical information and phenotype of the patient.

Discussion

PURA syndrome was recently discovered as a cause of moderate to severe neurodevelopmental delay [5,6]. Using NGS, it was possible to identify in our patient a heterozygous frameshift variant in *PURA* gene that occurred *de novo* and consists in a nucleotide base deletion (c.153delA) causing an out of frame transcript and a premature stop codon. It is predicted that this aberrant transcript will be targeted by nonsense-mediated mRNA decay. This pathogenic variant has never been reported in the population database (gnomAD), but in 2018, Reijinders *et al* reported the same pathogenic variant in an individual with PURA syndrome with similar phenotype features [9].

Marked hypotonia and feeding difficulties that were found early in our patient are one of the most characteristic manifestations of PURA syndrome, reaching 97% and 81%, respectively, in a recent series of 32 cases [1,5,9].

Hypersomnolence and exaggerated acoustic startle response that was noticed in our case are also frequently described features (66% and 58%, respectively, in Reijinders et al series) [2,3,5,9].

Apneas and hypoventilation in neonatal period are reported in about half of the patients [3,9]. In our patient these manifestations were only seen during an Influenza A respiratory infection at the age of 5 months.

Gastroesophageal reflux disease and constipation were seen in 28-33% and 50-62% of the patients, respectively, and may need medical or surgical intervention [3,9]. Our patient was successfully controlled with medical treatment.

All patients with PURA syndrome have moderate to severe intellectual disability and most of them remain non-verbal, with expressive language being more affected than the receptive language skills. Gait is unstable and broad based but it may not be achieved at all [3,9]. Stereotypic hand-mouthing movements noticed in our patient occur in 36% of the cases and are similar to those seen in Rett syndrome patients [9]. A less frequent feature found in our patient was spasticity of extremities, reported in 9% of the cases [9]. Movement disorders are also frequently described but were not seen in our pa-

tient [3,9]. A recent case report described for the first time myotonia in a patient with PURA syndrome, which was not present [2].

Epilepsy is an important manifestation of PURA syndrome, occurring in half of the patients, more frequently at the age of 2-4 years [1,3,5-7,9]. In our patient it was noticed at the age of 6 years.

Delayed myelination is the most common finding in the brain MRI [9]. A recent paper described a large brainstem in a patient with PURA syndrome, which was not found in our patient [1].

Progressive hip dysplasia was described in about 23% of the patients.

Endocrine problems such as thyroid function abnormalities or premature thelarche were previously described but they were excluded in our patient [1,4,9].

Other congenital malformations, such as cardiac and urogenital abnormalities, were rarely reported [9].

Conclusion

PURA syndrome is a rare disorder characterized by a spectrum of multisystemic manifestations, including some similar features seen in other neurological diseases. The association with some particular features not as common in other neurological entities, such as feeding difficulties since neonatal period, never being able to speak but being able to follow simple orders and exaggerated acoustic startle response, should raise the suspicion and genetic analysis must be performed to confirm the diagnosis and provide early multidisciplinary intervention.

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Síndrome PURA en una niña con retraso grave del desarrollo: un diagnóstico desafiante

Introducción. El síndrome PURA es una condición autosómica dominante poco común causada por variantes patogénicas *de novo* en el gen *PURA* y que se caracteriza por un fenotipo multisistémico que incluye retraso del neurodesarrollo global, hipotonía temprana, ausencia de habla, dificultades para alimentarse, hipersomnolencia, epilepsia y trastornos del movimiento.

Caso clínico. Presentamos una niña de 9 años con hipotonía y dificultades para alimentarse con retraso del crecimiento desde el período neonatal. A la edad de 3 años era evidente el retraso motor e intelectual, tenía una marcha de base amplia, no hablaba y una respuesta de sobresalto acústico exagerada. Desarrolló estereotipias de mano-boca y epilepsia a los 6 años. La monitorización electroencefalográfica continua de 24 horas reveló una actividad lenta global y una actividad epileptiforme frecuente en las áreas temporal izquierda y centrotemporal. La resonancia magnética del cerebro reveló un retraso en la mielinización. A los 6 años, la secuenciación clínica del exoma identificó una variante patógena heterocigótica en el gen *PURA,* c.153delA p. (Leu54CysfsTer24).

Conclusión. El síndrome PURA tiene características clínicas similares a otros trastornos neurológicos, pero la asociación con algunas características clínicas, no tan comunes en otras entidades neurológicas, como no poder hablar, pero poder seguir órdenes simples, y una respuesta de sobresalto acústico exagerado, deben ser factores de sospecha de síndrome

PURA y servir para realizar un análisis genético para confirmar el diagnóstico y proporcionar una intervención multidisciplinar precoz.

Palabras clave. Gen *PURA.* Retraso del desarrollo. Retraso en el habla. Secuenciación de última generación. Síndrome PURA. Trastornos neurológicos.