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CASE REPORT: PURA SYNDROME CAUSED BY A DE NOVO c.345_346del VARIANT IN A 6-YEAR-OLD BOY WITH REFRACTORY EPILEPSY AND DIAGNOSTIC DELAY

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ABSTRACT

Background: PURA syndrome is a rare neurodevelopmental disorder caused by heterozygous pathogenic variants in the PURA gene, characterized by neonatal hypotonia, epilepsy, and developmental delay. Diagnostic delay is common when acquired neonatal insults co-exist and mask the underlying genetic etiology.
Methods: We describe a 6-year-old boy with a de novo PURA c.345_346del (p.Asp116LeufsTer84) variant identified by trio clinical exome sequencing after negative SCO2 sequencing and chromosomal microarray. Clinical course, EEFeG, neuroimaging, and 6-year follow-up were analyzed retrospectively.
Results: The patient presented with hypotonia, feeding difficulties, and neonatal seizures complicated by bacterial meningitis, grade I intraventricular hemorrhage, and hyperbilirubinemia. Seizures evolved into refractory epilepsy with tonic, hypermotor, and focal impaired awareness seizures despite four antiseizure medications. Additional features included non-verbal status, GMFCS V, strabismus, cryptorchidism, and hypothyroidism requiring replacement therapy.
Conclusion: Co-occurring acquired insults may mask monogenic etiology and prolong diagnostic odyssey. Early access to exome sequencing and multidisciplinary follow-up are critical for family counseling and care planning.

KEYWORDS
PURA Syndrome, Refractory Epilepsy, Diagnostic Odyssey, Exome Sequencing

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1. Background

PURA syndrome (OMIM #616158) is a rare neurodevelopmental disorder first delineated in 2014 by Lalani et al. [1] and Hunt et al. [2], following the identification of de novo pathogenic variants in the PURA (purine-rich element binding protein A) gene located on chromosome 5q31.3. To date, more than 700 genetically confirmed cases have been reported worldwide, with an estimated incidence of 1 in 1,000,000 live births [3,11]. The disorder is characterized by neonatal hypotonia, feeding difficulties, moderate-to-severe global developmental delay, epilepsy, and multisystem involvement [4,5,6].

PURA encodes Pur-alpha, a ubiquitously expressed 322-amino acid protein with highly conserved nucleic acid-binding domains that play critical roles in DNA replication, transcriptional regulation, mRNA transport and translation, and neuronal development [3,7]. PURA knockout mice die shortly after birth with profound defects in brain and hematopoietic development, and surviving adults display megalencephaly with axonal swellings and neurofilament hyperphosphorylation, underscoring the essential role of Pur-alpha in postnatal brain development [8,9]. Haploinsufficiency of Pur-alpha is the proposed pathogenic mechanism in PURA syndrome, supported by evidence that PURA syndrome-causing mutations impair PUR-domain structural integrity and disrupt RNA binding and P-body association [10].

Pathogenic variants in PURA include point mutations (~93% of cases) and 5q31.3 microdeletions (~7%), with over 345 different pathogenic variants reported in public databases [3,11]. The vast majority (~99%) occur de novo [3,12], although rare inherited cases with milder phenotypes have been described [13]. The p.Phe233del variant is the most common, accounting for approximately 6% of the patient population [3].

The neonatal period in PURA syndrome is typically complicated by profound hypotonia, feeding difficulties, and respiratory insufficiency, often prompting extensive metabolic, infectious, and neurological workups before a genetic etiology is considered [4,5,6,14]. Current guidelines from the American College of Medical Genetics and Genomics (ACMG) recommend exome or genome sequencing as a first-tier test for pediatric patients with congenital anomalies or intellectual disability [15].

2. Methodology

Study design: Single case report based on retrospective chart review.

Data collection: Medical records spanning the period from birth (2019) through the most recent follow-up (early 2026) were reviewed. Data sources included neonatal intensive care records, outpatient neurology, cardiology, endocrinology, genetics, and ophthalmology consultations, EEG reports, cranial ultrasound, brain MRI, genetic testing results (SCO2 sequencing, chromosomal microarray, clinical exome sequencing, parental Sanger sequencing), and hospitalization records. Three-generation family history was obtained.

Analysis: Descriptive analysis of clinical course, EEG evolution, neuroimaging findings, and genetic results. Variant classification was performed according to ACMG/AMP guidelines.

3. Case Presentation

3.1. Neonatal Period and Acquired Complications

The patient, a boy born at term (38 weeks gestation, G II P II, spontaneous vaginal delivery, birth weight 3280 g, Apgar score 10), was admitted to the neonatal intensive care unit shortly after birth due to hypotonia, feeding difficulties, and abnormal movements. The pregnancy was complicated by maternal thrombocytopenia and recurrent urinary tract infections. From the first day of life, desaturation episodes, reduced vitality, and yellowing of the skin were observed. Initial laboratory workup revealed marked inflammatory parameters (procalcitonin [PCT] 18.9 ng/mL), and blood culture yielded a positive result without definitive bacterial identification. On day 3 of life, "tremors and seizures of independent limbs" were documented, and an ICD-10 diagnosis of P90 (Neonatal seizures) was assigned.

The neonatal course was further complicated by the following acquired conditions:

- Neonatal bacterial meningitis (ZOMR) of unknown etiology. Lumbar puncture performed on day 6 revealed lymphocytic pleocytosis (27 cells/μL), elevated protein (123 mg/dL), and glucose of 41 mg/dL; cerebrospinal fluid culture was subsequently negative. Empirical antibiotic therapy was initiated with ampicillin + gentamicin, and subsequently escalated to cefotaxime + vancomycin following confirmation of bacterial meningitis. A control lumbar puncture demonstrated decreasing pleocytosis and a negative culture, confirming treatment response.
- Congenital pneumonia, requiring passive oxygen therapy (incubator care). Lung ultrasound on day 22 was normal at that time, suggesting resolution.
- Grade I intraventricular hemorrhage (IVH), identified on cranial ultrasound, with associated thalamic vasculopathy. The Levene ventricular index was 14 mm. No surgical intervention was required, and the hemorrhage resolved spontaneously.
- Early-onset hyperbilirubinemia (neonatal jaundice), managed with phototherapy from the first days of life. No exchange transfusion was required.

Additional neonatal findings included a cardiac evaluation showing a systolic murmur (grade 1/6 at Erb's point) with echocardiography demonstrating additional trabeculae in the left ventricle but otherwise normal cardiac anatomy. Holter monitoring revealed sinus rhythm (mean 125/min, range 66–174/min) with several sinus pauses (longest up to 1.5 seconds) but no ventricular or supraventricular ectopy. The patient was referred for ongoing cardiology follow-up.

These acquired complications were initially considered the primary etiology of the neurological presentation, and a genetic cause was not pursued at this stage. Phenobarbital (Luminal, 10 mg/kg/day loading dose) was administered for seizure control during the neonatal period. Additional symptomatic treatment included 0.9% NaCl, Euphyllina, and incubator care. TORCH screening was negative. Due to the complex neonatal course, the patient was referred for expanded metabolic workup (blood gas analysis, lactate, ammonia, urinary organic acids by GC-MS, and tandem MS/MS), all of which yielded normal results. Routine vaccinations were withheld; only BCG and two doses of hepatitis B vaccine were administered.

The developmental milestones attained by the patient are summarized in Table 1.

Table 1. Developmental milestones and age of attainment

Developmental Milestones	Age of attainment
Lifting head while in prone position	13 months
Rolling over	18 months
Sitting without support	2 years
Cruising (walking while holding onto furniture)	3 years
Pointing / Gesturing for objects	2 years
Responding to name	2 years
Walking independently	not achieved

3.2. Dysmorphic Features and Ophthalmologic Findings

Facial dysmorphism was noted, consistent with the PURA syndrome phenotype described in the literature [1,4]. Ophthalmologic consultation confirmed alternating convergent strabismus with a normal fundus. No nystagmus was documented. Ophthalmologic abnormalities, including strabismus and nystagmus, have been reported in 40–50% of PURA syndrome patients (n=32) [4,5,16], with strabismus (particularly esotropia) being the most commonly reported finding.

3.3. Urogenital Anomalies

Urologic and genetic documentation confirmed the presence of genitourinary anomalies:

- Right-sided cryptorchidism with suspected agenesis or hypoplasia of the right testis, status post orchiopexy.
- Penile hypospadias (discrete preputial split).

Genitourinary anomalies, including cryptorchidism and hypospadias, are recognized features of PURA syndrome in male patients and are thought to reflect the role of Pur-alpha in genitourinary development [1,4,5]. The combination of cryptorchidism and hypospadias in this patient is consistent with the previously described phenotypic spectrum.

3.4. Genetic Findings

Prior to clinical exome sequencing, the patient underwent an extensive diagnostic workup. In October 2020, targeted Sanger sequencing of the SCO2 gene (c.418G>A, p.Glu140Lys) was performed due to clinical suspicion of mitochondrial cytopathy - the result was negative. In January 2021, a genome-wide chromosomal microarray (CytoScan 750K, Affymetrix) was performed, which revealed a normal male karyotype with no pathogenic copy number variants. These negative results, together with normal metabolic screening (urinary organic acids by GC-MS, tandem MS/MS), further prolonged the diagnostic odyssey and underscored the difficulty of reaching a molecular diagnosis in neonatal encephalopathy of unclear etiology.

Clinical exome sequencing (CES) was performed at the Institute of Mother and Child (Instytut Matki i Dziecka) in Warsaw. Genomic DNA was extracted from peripheral blood samples of the patient and both parents (trio design). Sequencing was performed using the Twist Human Core Exome Plus Kit (Twist Bioscience) on an Illumina NovaSeq 6000 platform (2 × 100 bp paired-end reads). Bioinformatic analysis was conducted by CeGaT GmbH (Tübingen, Germany). Reads were aligned to the GRCh38/hg38 reference genome.

Analysis revealed a heterozygous variant in the PURA gene (NM_005859.5): c.345_346del, resulting in a frameshift and premature termination codon: **p.Asp116LeufsTer84*. This variant introduces a premature stop codon 84 amino acids downstream of aspartic acid at position 116.

Sanger sequencing of parental DNA confirmed that the variant was absent in both the mother and father, establishing its de novo origin. Parental testing reports from the Institute of Mother and Child confirmed PURA variant status as negative for both parents, providing definitive evidence of a de novo event in the proband.

The variant was classified as likely pathogenic according to ACMG/AMP guidelines [17], fulfilling: - PVS1_Strong (null variant - frameshift - in a gene where haploinsufficiency is a known mechanism of disease; downgraded from full PVS1 to PVS1_Strong because PURA is a single-exon gene and canonical nonsense-mediated decay [NMD] is not expected, per the ClinGen Sequence Variant Interpretation recommendations for PVS1 [25]), - PS2 (de novo in a proband with confirmed paternity and maternity), - PM2 (absent from population databases including gnomAD v4.1).

The combination of PVS1_Strong (strong) + PS2 (strong) + PM2 (moderate) meets ACMG criteria for likely pathogenic.

Because PURA is a single-exon gene, canonical nonsense-mediated decay (NMD) is not expected to be triggered, as NMD requires a downstream exon-exon junction for exon-junction complex (EJC)-dependent recognition [4,10]. Consequently, the premature termination codon may lead to a truncated protein product or, more likely, result in mRNA instability and haploinsufficiency, which is the proposed pathogenic mechanism in PURA syndrome [4,10]. Recent structural biology studies have demonstrated that PURA syndrome-causing mutations impair PUR-domain integrity and disrupt the protein's ability to bind RNA and associate with P-bodies, providing a molecular framework for understanding how diverse variants converge on a shared pathogenic mechanism [10].

3.5. Neuroimaging

Cranial ultrasound performed in the neonatal period revealed grade I intraventricular hemorrhage with associated thalamic vasculopathy. The Levene ventricular index was 14 mm. No other structural abnormalities of the central nervous system were identified at that time.

Brain magnetic resonance imaging (MRI) performed at 2.5 years of age revealed heterogeneous white matter signal in regions posterior to the bodies of the lateral ventricles. The interpreting radiologist indicated that these findings could represent either areas of incomplete myelination or hypoxic-ischemic changes. Brain abnormalities, including delayed myelination, white matter changes, and corpus callosum abnormalities, have been reported in PURA syndrome [4,5,6,18,22]. The observed white matter changes may represent a combination of the underlying genetic leukodystrophy-like process and sequelae of the neonatal acquired insults (IVH grade I, meningitis). Delayed myelination is a recognized imaging feature of PURA syndrome, reflecting the critical role of Pur-alpha in oligodendrocyte maturation and myelin formation [3,4].

3.6. Epilepsy: Evolution and Current Status

Seizure Onset and Early Course

Seizures were first documented in the neonatal period (day 3 of life), with the clinical description of "tremors, seizures of independent limbs." Phenobarbital (Luminal) was used during the neonatal period. At age 3 years, a detailed seizure history was documented at the Neurology Clinic, describing a recurrence of polymorphic seizures of varying morphology, predominantly tonic in character:

- Tonic seizures (the predominant seizure type): episodes of sustained muscle contraction with stiffening of the limbs, lasting seconds to minutes.
- Hypermotor seizures: The boy positions himself on all fours on the floor, flexes his limbs at the joints, rocks, and performs purposeless movements of the upper limbs.
- Focal seizures with altered awareness: Eye blinking, facial grimacing, episodes of "switching off" with clouding of consciousness.

The seizure semiology is therefore polymorphic, with tonic seizures representing the most frequent and prominent morphology, accompanied by hypermotor and focal seizures with altered awareness, consistent with ILAE 2017 classification of multiple seizure types.

Two electroencephalographic studies were performed:

- EEG (August 2021, age ~1.5 years): Performed during daytime sleep using the international 10-20 system with 19 scalp electrodes. The recording showed slow-wave sleep without clear stage differentiation. A notable finding was slowing of activity in the temporal lobes, characterized by continuous sinusoidal delta-theta activity (3–7 Hz, amplitude up to 150 μV). No clear epileptiform discharges were identified at this time.
- EEG (December 2022, age ~3 years): Performed during spontaneous sleep with NREM stages I–III documented, using the international 10-20 system. The recording demonstrated episodic generalized paroxysmal changes, including short-lived generalized groups of sharp waves and spike-wave complexes superimposed on slow waves (5–7 Hz, amplitude up to 70 μV). Additionally, numerous single and grouped slow waves (2–2.5 Hz, amplitude up to 90 μV) were recorded bilaterally in the temporal-occipital-parietal regions. The conclusion was: "record with episodic generalized paroxysmal changes."

The evolution of EEG findings - from isolated temporal slowing in 2021 to generalized epileptiform activity in 2022 - parallels the clinical evolution from neonatal seizures to refractory polymorphic epilepsy.

Current Antiepileptic Regimen

Despite multiple antiepileptic drugs, the patient's epilepsy remains refractory. The most recent medical summary (discharge: February 2026) documents the following regimen:

Drug	Dose	Route
Levetiracetam (Cezarius 100mg/ml)	2 × 5 ml	Oral
Valproate (Depakine)	450 mg +0+ 450 mg	Oral
Cannabidiol (Epidyolex 100mg/ml)	2 × 2 ml	Oral
Clobazam (Frisium)	1 x 5 mg	Oral

Rescue medication: Buccolam (midazolam) 7.5 mg buccally for seizures lasting >2–3 minutes. The patient is also taking the off-label medication pyridostigmine (Mestinon)- 4 x 15mg to improve neuromuscular conduction and increase skeletal muscle strength.

The patient carries a definitive diagnosis of refractory epilepsy (ICD-10: G40.9) as of the most recent neurological assessment. An earlier note from the 3-year visit recorded temporary improvement with "significant lengthening of the time interval between seizures," but seizures subsequently proved resistant to pharmacological control across this four-drug regimen. Serum valproate level at the time of the most recent admission was 82.5 μg/mL (therapeutic range: 50–100 μg/mL).

Epilepsy develops in approximately 50–60% of PURA syndrome patients [4,19], making it one of the most common and clinically significant complications. In the largest reported PURA cohort (Johannesen et al. [19]), the seizure semiology included myoclonic, generalized tonic-clonic, focal seizures, and epileptic spasms, with Lennox-Gastaut syndrome being the most common epilepsy syndrome [19]. The seizure semiologies observed in this patient - predominantly tonic seizures, accompanied by hypermotor seizures and focal seizures with altered awareness, with EEG findings of both localized (temporal) and generalized epileptiform abnormalities - are consistent with the heterogeneous and polymorphic epileptic phenotype described in PURA syndrome [19]. The prominent tonic semiology in our patient is consistent with the Lennox-Gastaut-compatible EEG pattern of generalized slow spike-wave activity observed on the 2022 EEG, as tonic seizures are a core seizure type in Lennox-Gastaut syndrome. The evolution from neonatal seizures to refractory polymorphic epilepsy despite a four-drug regimen underscores the severity of the epileptic encephalopathy associated with PURA syndrome, with only 33.3% of patients (47/142) in the largest cohort achieving seizure freedom [19]. A recent study comparing epilepsy phenotypes between PURA point mutations and 5q31 microdeletions confirmed that PURA is the key contributor to developmental delay and epilepsy severity, with 5q31 microdeletions involving PURA producing the most severe phenotypes [20]. Movement disorders, including dystonia, chorea, and hyperkinetic movements, frequently co-occur with epilepsy in PURA syndrome and may complicate both diagnosis and management [21].

3.7. Endocrine Involvement

The patient is under ongoing endocrinology care for hypothyroidism, documented alongside the PURA mutation and refractory epilepsy. Endocrine problems have been reported in 42% of PURA syndrome patients (n=32) in the largest genotype-phenotype cohort study [4], and endocrine abnormalities are recognized as part of the multisystem involvement in PURA-NDD [3,24]. However, the specific types of endocrine dysfunction have not been systematically characterized in the literature. The patient receives thyroid replacement therapy and is monitored regularly by an endocrinologist.

The association between hypothyroidism and PURA syndrome in this patient is uncertain. Valproate, which the patient has been receiving as part of his antiepileptic regimen, is known to interfere with thyroid function and has been associated with biochemical hypothyroidism in pediatric patients. Therefore, valproate-induced thyroid dysfunction cannot be excluded as an alternative or contributing explanation. This finding should be regarded as a coincidental observation of uncertain association with PURA syndrome rather than a novel phenotypic manifestation.

3.8. Recent Hospitalization

The most recent hospitalization (late December 2025 – early January 2026) at a regional pediatric department was prompted by community-acquired pneumonia, immune thrombocytopenic purpura (platelet count 29,000/μL, treated with IVIG 1 g/kg, partial response to 66,000/μL), and anemia (hemoglobin 10.0 g/dL). The patient had recovered from varicella in the preceding weeks. Treatment included combined antibiotic therapy, corticosteroids, bronchodilators, and oxygen therapy, with significant clinical improvement by discharge. Whether these complications reflect intrinsic susceptibility associated with PURA syndrome or coincidental events cannot be determined from a single case.

3.9. Developmental Course and Current Status

At the time of the most recent follow-up (late 2025 – early 2026), the patient is 6 years old. His clinical status is as follows:

- Psychomotor development: Severely delayed. No verbal communication. Most individuals with PURA syndrome are minimally verbal or non-speaking, with stronger receptive language skills compared to expressive language skills [3,4].
- Motor function: Severe central hypotonia with quadriparesis. The patient is non-ambulatory and does not achieve verticalization, corresponding to GMFCS level V. Independent ambulation is achieved only by a minority of PURA syndrome patients [4].
- Seizure control: Refractory polymorphic epilepsy (predominantly tonic seizures) despite a four-drug antiepileptic regimen (valproate, cannabidiol, clobazam, and levetiracetam).
- Endocrine status: Hypothyroidism, under endocrinology care with thyroid replacement therapy (of uncertain association with PURA syndrome; see Section 2.7).
- Ophthalmologic status: Alternating convergent strabismus, normal fundus.
- Urogenital status: Status post right orchiopexy (right cryptorchidism/hypoplasia); discrete penile hypospadias.
- Cardiac status: Systolic murmur (grade 1/6, Erb's point), additional left ventricular trabeculae on echocardiography; under cardiology follow-up.
- Rehabilitation: The patient receives ongoing multidisciplinary supportive care involving a neurologist, cardiologist, endocrinologist, geneticist, surgeon, and speech-language therapist.
- Vaccination status: Incomplete - only BCG and two doses of hepatitis B vaccine have been administered; all other vaccinations have been withheld. This incomplete vaccination status likely contributed to the development of varicella and may have increased susceptibility to community-acquired pneumonia.

4. Discussion

PURA syndrome was first delineated in 2014 [1,2], with more than 700 genetically confirmed cases reported worldwide [3,11]. The disorder is characterized by neonatal hypotonia, feeding difficulties, moderate-to-severe global developmental delay, epilepsy, and multisystem involvement [4,5,6].

Diagnostic Delay and Confounding Acquired Insults

A notable aspect of this case is the diagnostic trajectory, significantly influenced by co-occurring acquired neonatal complications. The patient presented with neonatal hypotonia, seizures, and feeding difficulties - the classic PURA triad - but these findings were initially attributed to acquired insults (meningitis, grade I IVH, pneumonia, hyperbilirubinemia). The diagnostic trajectory was further prolonged by negative SCO2 sequencing and normal chromosomal microarray. This extensive exclusionary workup consumed over a year before clinical exome sequencing identified the pathogenic PURA variant. Current ACMG guidelines recommend exome or genome sequencing as a first- or second-tier test for pediatric patients with congenital anomalies, developmental delay, or intellectual disability[15]. Had CES been performed earlier, the prolonged diagnostic odyssey might have been avoided.

Genotype-Phenotype Considerations

The c.345_346del (p.Asp116LeufsTer84) variant identified in this patient results in a frameshift with a premature termination codon 84 amino acids downstream. As PURA is a single-exon gene, canonical nonsense-mediated decay (NMD) - which requires a downstream exon-exon junction for EJC-dependent recognition - is not expected to be triggered [4,10]. In accordance with the ClinGen Sequence Variant Interpretation recommendations for applying PVS1 to variants in genes without NMD [25], the PVS1 criterion was applied at the Strong level rather than the full (Very Strong) level. This suggests two possible pathogenic mechanisms: (1) production of a truncated, likely non-functional protein, or (2) mRNA instability leading to haploinsufficiency. The prevailing model of PURA syndrome pathogenesis supports haploinsufficiency as the primary disease mechanism, where loss of one functional copy of PURA results in insufficient Pur-alpha protein for normal neuronal development [1,4,10]. Recent structural biology work by [10] has demonstrated that PURA syndrome-causing mutations impair PUR-domain structural integrity and disrupt the protein's ability to bind RNA and associate with P-bodies, providing a convergent molecular mechanism for diverse pathogenic variants [10].

The de novo origin of the variant was confirmed through Sanger sequencing of both parents, with parental PURA variant testing confirmed negative at the Institute of Mother and Child. This provides definitive

evidence of a de novo event, consistent with the overwhelming majority (~99%) of reported PURA syndrome cases [1,2,3,12]. Although rare inherited cases with milder phenotypes have been described [13], the severe phenotype observed in our patient is consistent with the typical de novo presentation. The variant was not found in gnomAD v4.1, supporting its pathogenicity.

Epilepsy Phenotype

Epilepsy develops in approximately 50–60% of PURA syndrome patients [4,19], making it one of the most common and clinically significant complications. In the largest reported PURA cohort (n=142), [19] found that seizure semiologies included myoclonic, generalized tonic-clonic, focal seizures, and/or epileptic spasms, with Lennox-Gastaut syndrome being the most common epilepsy syndrome [19]. The seizure semiologies observed in our patient - predominantly tonic seizures, accompanied by hypermotor seizures and focal seizures with altered awareness, with EEG findings of both localized (temporal) and generalized epileptiform abnormalities - are consistent with the heterogeneous and polymorphic epileptic phenotype described in PURA syndrome [19]. Notably, while Johannesen et al. listed generalized tonic-clonic seizures (which include a tonic phase) and identified Lennox-Gastaut syndrome - which characteristically features tonic seizures as a core seizure type - as the most common epilepsy syndrome, isolated tonic seizures as the predominant seizure morphology have not been specifically emphasized as a distinct semiology in the PURA literature. The prominent tonic semiology in our patient is consistent with the Lennox-Gastaut-compatible EEG pattern of generalized spike-wave activity observed on the 2022 EEG. The evolution from neonatal seizures to refractory polymorphic epilepsy despite a four-drug regimen (valproate, cannabidiol, clobazam, and levetiracetam) underscores the severity of the epileptic encephalopathy associated with PURA syndrome, with only 33.3% of patients (47/142) in the Johannesen cohort achieving seizure freedom [19]. The temporary improvement reported at age 3, followed by pharmacoresistance, illustrates the typically progressive or fluctuating nature of PURA-related epilepsy [4,19] demonstrated that PURA is the key contributor to epilepsy severity in the 5q31 region, with 5q31 microdeletions involving PURA producing more severe epileptic phenotypes than point mutations alone [20]. A case-based review by [23] also documented the potential benefit of the ketogenic diet in PURA-related epilepsy, though this has not yet been attempted in our patient [23]. Movement disorders frequently co-occur with epilepsy in PURA syndrome and may complicate both diagnosis and management [21].

Ophthalmologic and Urogenital Findings

The alternating convergent strabismus with normal fundus observed in this patient is consistent with the reported prevalence of ophthalmologic abnormalities in 40–50% of PURA syndrome patients (n=32) [4,5,16]. Strabismus, particularly esotropia, is the most commonly reported ophthalmologic finding [4,5]. The absence of nystagmus in our patient does not contradict the literature, as nystagmus is less frequently documented than strabismus.

Genitourinary anomalies, including cryptorchidism and hypospadias, are recognized features of PURA syndrome in male patients [1,4,5]. The combination of right-sided cryptorchidism (with suspected testicular hypoplasia/agenesis) and penile hypospadias in this patient adds to the phenotypic evidence supporting the role of PURA in genitourinary development.

Endocrine Involvement

The presence of hypothyroidism should be interpreted with caution. Endocrine problems were documented in 42% of patients (n=32) in the [4] cohort, but the specific types have not been systematically characterized. [24] listed endocrine disorders among recognized extra-neurological features. However, the association between hypothyroidism and PURA syndrome is uncertain: the patient has been receiving valproate, which is known to interfere with thyroid function. Without pre-valproate thyroid function tests and anti-thyroid antibody testing, valproate-induced thyroid dysfunction cannot be excluded. This finding should be regarded as a coincidental observation of uncertain association rather than a novel phenotypic manifestation.

Neuroimaging

The heterogeneous white matter signal on MRI at 2.5 years, posterior to the lateral ventricles, represents a non-specific finding that could reflect either incomplete myelination or hypoxic-ischemic sequelae. Brain abnormalities including delayed myelination, white matter changes, and ventricular abnormalities have been reported in PURA syndrome [4,5,6,18,22]. In this case, the neonatal cranial ultrasound demonstrated grade I IVH with thalamic vasculopathy, suggesting early vascular involvement. The subsequent MRI findings may represent a convergence of the underlying genetic process and sequelae of IVH, thalamic vasculopathy, and neonatal meningitis. This dual etiology underscores the challenge of attributing neurological findings solely to acquired or genetic causes when both are present.

Limitations

This case report has several important limitations that should be considered when interpreting the findings:

1. Confounding acquired neonatal insults. The patient experienced four significant acquired neonatal complications - bacterial meningitis, congenital pneumonia, grade I IVH with thalamic vasculopathy, and hyperbilirubinemia - all of which can independently produce neurological findings overlapping with PURA syndrome (hypotonia, seizures, developmental delay, white matter changes). It is not possible to definitively attribute individual clinical features to PURA syndrome versus acquired insults. Features such as cryptorchidism, hypospadias, and alternating strabismus are more specifically attributable to PURA syndrome, as they are not explained by the acquired insults.
2. Valproate as a confounder for hypothyroidism. The patient has been receiving valproate as part of his antiepileptic regimen. Valproate is known to interfere with thyroid function and has been associated with biochemical hypothyroidism in pediatric patients. Without pre-valproate thyroid function tests and without anti-thyroid antibody testing, the contribution of valproate to the observed hypothyroidism cannot be excluded.
3. Incomplete vaccination status. The patient received only BCG and two doses of hepatitis B vaccine, with all other vaccinations withheld. This likely contributed to the development of varicella and may have increased susceptibility to community-acquired pneumonia. The attribution of these infections to PURA-related immune vulnerability is therefore confounded by the incomplete vaccination status.
4. ITP as a potentially coincidental finding. Immune thrombocytopenic purpura is a relatively common pediatric condition and may have occurred independently of PURA syndrome. While Pur-alpha plays roles in hematopoietic development [8], a causal link between PURA syndrome and ITP has not been established.
5. Four-drug antiepileptic polypharmacy. The concurrent use of four antiepileptic drugs (valproate, cannabidiol, clobazam, and levetiracetam) introduces potential drug interactions and cumulative side effects that may confound the clinical picture, including effects on thyroid function, liver enzymes, and overall neurodevelopmental status.
6. Lack of functional validation and n=1 design. No functional studies (e.g., RNA binding assays, P-body association studies) were performed to confirm the pathogenic effect of the c.345_346del variant at the protein level. As a single case report, no generalizable conclusions can be drawn, and genotype-phenotype correlations cannot be established. The variant classification as likely pathogenic is based on in silico prediction and ACMG criteria alone, without experimental evidence of altered protein function.

5. Conclusions

This case report describes a 6-year-old boy with PURA syndrome caused by a de novo c.345_346del (p.Asp116LeufsTer84) variant, classified as likely pathogenic (PVS1_Strong + PS2 + PM2). The patient presented with the classic triad of neonatal hypotonia, feeding difficulties, and seizures, complicated by refractory polymorphic epilepsy with predominantly tonic seizures consistent with a Lennox-Gastaut-compatible pattern, severe psychomotor delay (GMFCS V), and multisystem involvement. The neonatal course was further complicated by bacterial meningitis, grade I IVH, and hyperbilirubinemia - all of which initially masked the underlying genetic etiology. Prior negative genetic testing (SCO2, microarray) illustrate the diagnostic odyssey. This case highlights the importance of early clinical exome sequencing when acquired insults do not fully explain the clinical picture, and cautious interpretation of co-occurring findings potentially confounded by medication effects.

Ethics Approval and Consent to Participate

Case report exempt per policy of Medical University of Lublin. Consent for publication obtained from parents. All identifying information has been removed to protect patient anonymity in accordance with GDPR requirements.

Consent for Publication: Consent for publication of clinical details was obtained from the parents of the patient.

Conflicts of Interest: No conflicts of interest to declare.

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Declaration on Off-Label Medication Use: Mestinon (pyridostigmine) mentioned in this report may be used off-label in some jurisdictions. All medications were prescribed by treating neurologists in accordance with local clinical guidelines.

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