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Case Report

LNPK-Related Neurodevelopmental Disorder with Refractory Epilepsy and Developmental Regression: A Case Report

Hadeel Haj Taher[1]*, Rahaf Egbarieh[1], Maisoon Masarwa[1] and Itidal Ahmed Naji[2]

[1]*Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine*

[2]*Faculty of Medicine and Health Sciences, Al-Quds University, Jerusalem, Palestine*

***Corresponding Author:** Hadeel Haj Taher, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine. Email ID: s11940985@stu.najah.edu

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Abstract

Background: LNPK-related neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum (NEDEHCC), also known as Lunapark deficiency syndrome, is an extremely rare autosomal recessive disorder caused by pathogenic variants in the LNPK gene. The disorder is characterized by global developmental delay, developmental regression, intellectual disability, refractory epilepsy, and variable neuroimaging abnormalities. Fewer than 20 affected families have been reported worldwide, and the clinical spectrum and optimal management remain poorly defined.

Case Presentation: We report the case of a 5-year-old boy with genetically confirmed LNPK-related neurodevelopmental disorder caused by a homozygous pathogenic LNPK variant who presented with recurrent generalized tonic-clonic and myoclonic seizures triggered by an acute respiratory infection. His medical history was notable for severe global developmental delay, developmental regression following seizure onset, and drug-resistant epilepsy requiring treatment with multiple antiseizure medications. On admission, he was febrile, hypoxemic, and exhibited respiratory distress with radiographic evidence of left-sided pneumonia. Electroencephalography demonstrated persistent epileptiform activity despite multidrug antiseizure therapy. The patient required pediatric intensive care unit admission, continuous intravenous midazolam infusion, optimization of antiseizure medications, respiratory support, enteral nutritional management, and broad-spectrum antimicrobial therapy. Although his respiratory status and inflammatory markers gradually improved, seizure activity remained difficult to control, highlighting the refractory nature of epilepsy associated with LNPK deficiency.

Conclusion: This case illustrates the severe neurological phenotype and therapeutic challenges associated with LNPK-related neurodevelopmental disorder. The combination of profound developmental impairment, developmental regression, and refractory epilepsy complicated by intercurrent infection underscores the importance of early genetic diagnosis, multidisciplinary management, and prompt treatment of seizure-provoking conditions. Reporting additional cases is essential to expand the current understanding of the phenotypic spectrum, natural history, and management strategies for this exceptionally rare disorder.

Keywords: *LNPK; Lunapark Deficiency; Neurodevelopmental Disorder; Refractory Epilepsy; Developmental Regression*

Introduction

LNPK-related neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum (NEDEHCC), commonly referred to as Lunapark deficiency syndrome, is a recently recognized, ultra-rare autosomal recessive neurodevelopmental disorder caused by biallelic pathogenic variants in the LNPK (Lunapark) gene. The LNPK protein is a highly conserved endoplasmic reticulum membrane protein that plays a critical role in maintaining the architecture of the endoplasmic reticulum (ER) network by stabilizing three-way junctions within the tubular ER. Disruption of ER morphology resulting from LNPK dysfunction is believed to impair neuronal development and synaptic function, ultimately leading to severe neurological manifestations [1,2].

The disorder was first described in 2021, and only a limited number of affected individuals and families have subsequently been reported worldwide. Consequently, the full clinical spectrum, genotype-phenotype correlations, disease progression, and long-term outcomes remain incompletely understood [3-5]. Most reported patients present during infancy or early childhood with global developmental delay, hypotonia, intellectual disability, epilepsy, and varying degrees of developmental regression. Additional neurological manifestations include movement disorders, spasticity, visual abnormalities, feeding difficulties, and progressive motor impairment [2,5,6].

Epilepsy is among the most disabling manifestations of LNPK deficiency, occurring in approximately three-quarters of reported patients. Seizure onset ranges from early infancy to childhood and encompasses multiple seizure types, including myoclonic, tonic-clonic, tonic, focal, and epileptic spasms. Importantly, epilepsy is frequently drug-resistant, necessitating treatment with multiple antiseizure medications and occasionally prolonged intensive care management during episodes of status epilepticus or breakthrough seizures precipitated by intercurrent illness [2,5,7].

Neuroimaging findings are variable. Although hypoplasia of the corpus callosum represents the characteristic radiological feature reflected in the disorder's nomenclature, several patients have normal brain magnetic resonance imaging, particularly during early disease stages. Other reported abnormalities include cerebellar atrophy, cerebral atrophy, delayed myelination, ventricular enlargement, and progressive neurodegenerative changes, suggesting considerable phenotypic heterogeneity [3,5,8].

The diagnosis of LNPK-related neurodevelopmental disorder relies primarily on molecular genetic testing, most commonly whole-exome sequencing, owing to the nonspecific clinical presentation and broad differential diagnosis of developmental delay and early-onset epilepsy. Early genetic diagnosis facilitates accurate counseling, avoids unnecessary investigations, and enables multidisciplinary management involving pediatric neurology, rehabilitation, nutrition, respiratory care, and clinical genetics [4,6,9].

Given the rarity of this condition, every additional well-characterized case contributes valuable information regarding its clinical presentation, natural history, treatment response, and prognosis. Herein, we report a child with genetically confirmed LNPK-related neurodevelopmental disorder presenting with severe refractory epilepsy triggered by community-acquired pneumonia, highlighting the clinical complexity and management challenges encountered in this exceptionally rare disorder [2,5,10].

Case Presentation

Patient information

A 5-year-old boy with a genetically confirmed diagnosis of Lunapark deficiency syndrome (LNPK-related neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum [NEDEHCC]) was admitted to the pediatric intensive care unit (PICU) because of recurrent breakthrough seizures associated with fever and respiratory distress. The diagnosis had been established by whole-exome sequencing at 4 years of age after extensive evaluation for global developmental delay and refractory epilepsy.

History of present illness

The patient had been in his usual state of health until one day before admission, when he developed cough and harsh breathing followed by recurrent episodes of generalized tonic-clonic seizures involving all four limbs with upward eye deviation. Each episode lasted less than one minute and resolved spontaneously; however, the seizures recurred multiple times over the following three days. On the day of presentation, he developed fever with a maximum recorded axillary temperature of 38°C. There was no history of vomiting, diarrhea, cyanosis, or skin rash.

He initially presented to the emergency department while actively seizing and received intravenous midazolam, which successfully terminated the seizure. Hospital admission was recommended; however, the family declined because of financial constraints. He subsequently presented to another emergency department with recurrent seizures, where a second dose of intravenous midazolam was administered, followed by a loading dose of levetiracetam. Despite initial seizure control, he experienced another breakthrough seizure requiring an additional dose of midazolam. At that time, he was febrile (38.9°C), hypoxemic with an oxygen saturation of 90% on room air, and had bilateral chest crepitations and pharyngeal congestion. Because pediatric intensive care beds were unavailable at the referring hospital, he was transferred to our institution for further management.

Past medical history

The patient had severe global developmental delay and drug-resistant epilepsy secondary to LNPK deficiency syndrome. A brain magnetic resonance imaging (MRI) study performed approximately two years before admission was unremarkable, whereas electroencephalography (EEG) performed during early childhood demonstrated epileptiform activity. He had no previous surgical history or known drug allergies.

Developmental history

Developmental delay was first recognized during infancy. At the time of admission, the patient was unable to walk, sit independently, or maintain head control. He was nonverbal and communicated only through nonspecific vocalizations. Although he recognized his parents, he had no functional hand grasp.

Notably, he had experienced significant developmental regression following seizure onset. Before the onset of epilepsy at approximately 2.5 years of age, he had acquired several developmental milestones, including grasping and transferring objects, cruising along furniture, and speaking approximately five to six meaningful words. These motor and language skills were progressively lost after seizure onset, resulting in profound neurodevelopmental impairment.

Birth and family history

The patient was born at term by cesarean section because of breech presentation with a birth weight of 3.1 kg. The neonatal period was uncomplicated, and immunizations were appropriate for age.

The parents were first-degree cousins. One younger sibling had the same pathogenic LNPK mutation with associated developmental delay, whereas another sibling was developmentally normal. The family history was consistent with autosomal recessive inheritance.

Genetic evaluation

Whole-exome sequencing identified a homozygous pathogenic variant in the LNPK gene (NM_030650.3:c.751dup; p.Arg251Profs), confirming the diagnosis of LNPK-related neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum (NEDEHCC). Earlier chromosomal microarray analysis had demonstrated a likely benign Yq11.223 microdeletion that was considered unrelated to the patient's phenotype. Previous metabolic investigations, including brain MRI, echocardiography, abdominal ultrasonography, and extensive metabolic screening, were otherwise unremarkable.

Medications before admission

At presentation, the patient was receiving combination antiseizure therapy consisting of levetiracetam, lamotrigine, topiramate, sodium valproate, and primidone.

Physical examination

On admission, the patient weighed 15 kg. His temperature was 37.7°C, heart rate 116 beats/min, respiratory rate 18 breaths/min, blood pressure 117/68 mmHg, and oxygen saturation 92% while receiving supplemental oxygen via nasal cannula.

He appeared sleepy and hypoactive but was not actively seizing. Neurological examination demonstrated bilateral reactive pupils, marked central and peripheral hypotonia, absent voluntary motor power in all four limbs, brisk lower-extremity deep tendon reflexes, normal upper-extremity reflexes, bilateral ankle equinus deformities, and no signs of meningeal irritation.

Respiratory examination revealed bilateral coarse crackles with noisy breathing and excessive airway secretions. Cardiovascular examination was unremarkable, with normal heart sounds and no murmurs. The abdomen was soft, non-distended, and non-tender without organomegaly. Hyperkeratotic skin changes were noted over both upper and lower extremities, and examination of the oropharynx demonstrated pharyngeal congestion.

Investigations

Initial laboratory investigations demonstrated mild microcytic anemia (hemoglobin 10.8 g/dL), leukocytosis with neutrophil predominance, and mildly elevated inflammatory markers. Serum electrolytes, renal function, liver enzymes, and coagulation studies were largely within normal limits. Arterial blood gas analysis revealed metabolic acidosis with partial respiratory compensation.

Chest radiography demonstrated left-sided pulmonary infiltrates consistent with pneumonia. Continuous EEG showed persistent epileptiform discharges with frequent seizure activity and burst-suppression patterns despite ongoing antiseizure therapy. During hospitalization, C-reactive protein increased from 1.83 mg/L to 19.03 mg/L in association with recurrent fever before declining to 8.32 mg/L following escalation of antimicrobial therapy. Serial blood and urine cultures remained sterile throughout admission. Stool examination performed because of persistent watery diarrhea was negative for bacterial pathogens, parasites, rotavirus, and adenovirus. CT scan of the brain showed mild ventriculomegaly associated with prominence of the basal cisterns (Figure 1).

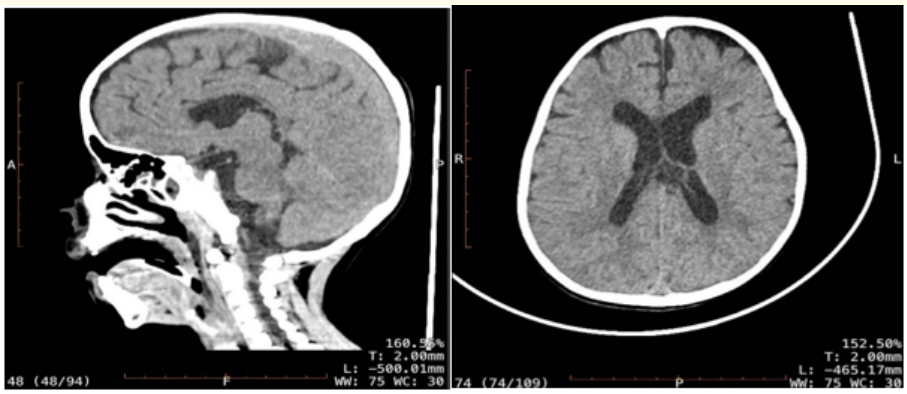

Figure 1: *CT findings.*

Hospital course

The patient was admitted to the PICU for management of refractory seizures and acute respiratory infection. Continuous intravenous midazolam infusion was initiated for seizure control while maintenance antiseizure medications, including levetiracetam, sodium valproate, topiramate, lamotrigine, and primidone, were resumed. Despite therapy, he continued to experience intermittent myoclonic seizures and persistent epileptiform activity on EEG. Owing to ongoing seizure activity, pediatric neurology recommended escalation of the midazolam infusion, optimization of antiseizure medications, addition of clonazepam, prolonged EEG monitoring, neuroimaging, lumbar puncture after brain imaging, and consideration of endotracheal intubation because of worsening respiratory status.

Respiratory management included supplemental oxygen, nebulized budesonide, hypertonic saline inhalation, airway suctioning, and empirical antimicrobial therapy. Chest radiographs consistently demonstrated left-sided pulmonary infiltrates with abundant airway secretions. The patient's oxygen requirement gradually resolved, although noisy breathing and secretion burden persisted.

Initially, enteral nutrition was withheld, and intravenous fluids were administered. Feeding was subsequently initiated via an orogastric tube and gradually advanced to full nasogastric feeding. During hospitalization, the patient developed persistent watery diarrhea without vomiting. Stool investigations remained negative for infectious pathogens, abdominal examinations remained unremarkable, and body weight remained stable.

Empirical azithromycin was initiated at admission because of suspected lower respiratory tract infection. Recurrent fever with rising inflammatory markers prompted escalation to piperacillin-tazobactam while repeat blood and urine cultures were obtained. All cultures remained negative, inflammatory markers subsequently improved, and azithromycin was discontinued. Throughout the admission, the patient remained hemodynamically stable without cardiovascular complications.

Final diagnosis

The patient was diagnosed with refractory epilepsy secondary to LNPK-related neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum (Lunapark deficiency syndrome), presenting with recurrent breakthrough generalized tonic-clonic and myoclonic seizures precipitated by community-acquired pneumonia. His clinical course was complicated by persistent epileptiform activity requiring continuous midazolam infusion, recurrent fever requiring broad-spectrum antimicrobial therapy, and prolonged PICU admission for intensive neurological and respiratory support.

Discussion

LNPK-related neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum (NEDEHCC), also referred to as Lunapark deficiency syndrome, represents one of the most recently recognized and rare forms of developmental and epileptic encephalopathy. Since its initial characterization, only a limited number of affected individuals and families have been reported worldwide, leaving substantial gaps in the understanding of its natural history, phenotypic variability, and optimal management [8,9]. Consequently, each additional case contributes valuable information toward refining the clinical spectrum of the disorder and improving recognition by pediatric neurologists, geneticists, and intensivists. The present case illustrates many of the hallmark features of LNPK deficiency, including profound developmental impairment, developmental regression, refractory epilepsy, and the need for intensive care management during acute neurological deterioration.

The LNPK gene encodes Lunapark, a highly conserved membrane protein that localizes to the endoplasmic reticulum (ER), where it plays a fundamental role in maintaining the highly interconnected tubular ER network by stabilizing three-way junctions. The ER is essential for numerous cellular processes, including protein synthesis, calcium homeostasis, lipid metabolism, intracellular signaling, and organelle communication. In neurons, proper ER organization is particularly important because of their large size, polarized structure,

and high metabolic demands. Pathogenic variants affecting LNPK disrupt ER morphology, resulting in neuronal dysfunction, impaired synaptic activity, and abnormal neurodevelopment. Although the precise mechanisms linking ER disorganization to epilepsy remain incompletely understood, experimental studies suggest that disruption of ER integrity may alter neuronal excitability, intracellular calcium signaling, and neuronal survival, thereby predisposing affected individuals to severe epileptic encephalopathy [10-12].

Consistent with previously reported cases, our patient exhibited profound global developmental delay beginning during infancy. Early developmental milestones were markedly delayed, with impairment in gross motor, fine motor, and language domains. Such findings appear to be among the earliest manifestations of LNPK deficiency and frequently precede the onset of epilepsy [8,10]. Most reported patients demonstrate delayed acquisition of head control, sitting, crawling, and walking, while expressive language development is often severely impaired. In several published cases, developmental delay was initially considered nonspecific until the emergence of epilepsy prompted more extensive neurological and genetic evaluation [9,11].

One of the most striking features of the present case was the marked developmental regression that followed seizure onset. Before developing epilepsy, the patient had acquired several meaningful developmental skills, including the ability to grasp and transfer objects, cruise along furniture, and produce several recognizable words. These abilities were progressively lost after the onset of recurrent seizures, ultimately resulting in profound motor and language impairment. Developmental regression has emerged as a characteristic feature of LNPK-related disease and may represent an important distinguishing characteristic from other genetic developmental disorders in which developmental progress simply plateaus rather than regresses [8,12].

The mechanisms underlying regression remain uncertain but are likely multifactorial. Frequent epileptic discharges may interfere with normal cortical maturation and synaptic plasticity, while recurrent seizures themselves may contribute to neuronal injury and disruption of developing neural networks. Furthermore, the underlying ER dysfunction caused by LNPK deficiency may promote progressive neurodegeneration, rendering the developing brain particularly susceptible to functional deterioration following epileptic activity [10,13]. Similar patterns of regression have been described in other developmental and epileptic encephalopathies, including disorders associated with STXBP1, CDKL5, and SCN2A variants; however, the combination of severe hypotonia, profound regression, and refractory epilepsy appears particularly characteristic of LNPK deficiency [14].

Epilepsy remains the most clinically significant manifestation of LNPK-related disease and is responsible for much of the associated morbidity. Approximately three-quarters of reported patients develop epilepsy, although seizure onset varies considerably, ranging from early infancy to several years of age [8,10]. The seizure phenotype is highly heterogeneous and includes generalized tonic-clonic seizures, myoclonic seizures, tonic seizures, focal seizures, epileptic spasms, and mixed seizure types. Our patient demonstrated recurrent generalized tonic-clonic seizures accompanied by persistent myoclonic activity, findings that closely resemble the seizure patterns described in previously published cohorts [9,12].

Another notable feature illustrated by this case is the remarkable resistance of seizures to pharmacological therapy. At the time of presentation, the patient was receiving five antiseizure medications, including levetiracetam, sodium valproate, topiramate, lamotrigine, and primidone, yet continued to experience frequent breakthrough seizures requiring emergency treatment with intravenous benzodiazepines and continuous midazolam infusion. Drug-resistant epilepsy has consistently been reported in LNPK deficiency and represents one of the greatest therapeutic challenges for clinicians [8,11]. Many affected children require multidrug therapy with limited success, and complete seizure freedom is rarely achieved. This pattern suggests that the underlying disease mechanism involves diffuse neuronal network dysfunction rather than isolated abnormalities in individual neurotransmitter pathways [13].

The electroencephalographic findings in the present patient further support the diagnosis of severe developmental and epileptic encephalopathy. Continuous epileptiform discharges with burst-suppression activity persisted despite aggressive treatment and

prolonged sedation. Previous reports have described diverse EEG abnormalities, including generalized spike-and-wave discharges, multifocal epileptiform activity, hypsarrhythmia, burst-suppression patterns, and diffuse slowing [8,9]. Although no single EEG pattern is considered pathognomonic for LNPK deficiency, persistent diffuse epileptiform abnormalities appear to correlate with disease severity and poor neurodevelopmental outcomes. The persistence of epileptiform activity despite intensive pharmacological treatment in our patient highlights the intrinsic epileptogenic nature of the disorder rather than inadequate antiseizure therapy alone [12,15].

Interestingly, brain MRI performed in our patient before admission was reported as normal. While the disorder is designated as "neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum," increasing evidence indicates that neuroimaging findings are considerably more heterogeneous than initially recognized [8]. Although hypoplasia of the corpus callosum remains the most frequently reported structural abnormality, several patients have demonstrated normal MRI findings, particularly during infancy or the early stages of disease [9,10]. Other reported abnormalities include cerebellar hypoplasia or atrophy, delayed myelination, ventricular enlargement, cerebral atrophy, and progressive neurodegenerative changes [11,13]. The absence of structural abnormalities in our patient therefore does not exclude the diagnosis and emphasizes the importance of molecular genetic testing in children presenting with unexplained developmental delay and refractory epilepsy.

The genetic diagnosis in this patient was established by whole-exome sequencing, which identified a homozygous pathogenic variant in the LNPK gene. Earlier chromosomal microarray analysis revealed only a likely benign microdeletion that did not explain the clinical phenotype. This diagnostic sequence mirrors the experience reported in many published cases, where conventional metabolic testing, neuroimaging, chromosomal microarray analysis, and targeted investigations were unrevealing before whole-exome sequencing established the diagnosis [9,14]. As next-generation sequencing becomes increasingly accessible, earlier genetic diagnosis is expected to shorten the prolonged diagnostic journey experienced by many families of children with rare developmental epileptic encephalopathies.

The family history in this case provides additional support for the autosomal recessive inheritance pattern of LNPK deficiency. The patient's parents were first cousins, and another sibling carried the same pathogenic variant with similar developmental abnormalities. Consanguinity has been reported in a substantial proportion of published LNPK families, reflecting the autosomal recessive mode of inheritance and the increased likelihood of homozygous pathogenic variants in populations with a high prevalence of consanguineous marriage [8,10]. Recognition of this inheritance pattern has important implications for genetic counseling, family screening, reproductive planning, and prenatal diagnosis. Carrier parents should be informed of the 25% recurrence risk in each pregnancy, while molecular confirmation enables targeted prenatal testing and preimplantation genetic testing in future pregnancies [15].

An important aspect of the present case was the temporal relationship between respiratory infection and seizure exacerbation. The patient presented with fever, hypoxemia, abundant respiratory secretions, and radiographic evidence of left-sided pneumonia immediately preceding the dramatic increase in seizure frequency. Acute systemic infections are well-recognized precipitants of seizure exacerbation in children with developmental epileptic encephalopathies. Fever, systemic inflammation, metabolic stress, hypoxia, sleep disruption, and altered pharmacokinetics of antiseizure medications may all contribute to lowering the seizure threshold [16-18]. Although respiratory infections have not been specifically emphasized in previous reports of LNPK deficiency because of the rarity of the condition, the present case suggests that intercurrent infections may represent important triggers for neurological decompensation in these patients. Prompt recognition and aggressive treatment of infectious illnesses may therefore reduce seizure burden and prevent progression to status epilepticus requiring intensive care management.

The coexistence of severe neurological impairment and respiratory compromise also illustrates the multidimensional clinical challenges encountered in children with advanced developmental epileptic encephalopathies. Profound hypotonia, impaired airway protection, ineffective cough, excessive respiratory secretions, and reduced mobility substantially increase the risk of aspiration and lower respiratory tract infections [19,20]. Consequently, respiratory illnesses often result in prolonged hospitalization and may further

aggravate underlying neurological dysfunction. Multidisciplinary management involving pediatric neurologists, intensivists, respiratory therapists, physiotherapists, nutrition specialists, and rehabilitation teams is therefore essential to optimize both acute management and long-term outcomes in these medically complex children.

The management of epilepsy in patients with LNPK-related neurodevelopmental disorder remains largely supportive because no disease-specific therapy is currently available. Similar to other genetic developmental and epileptic encephalopathies, treatment focuses primarily on seizure control, prevention of seizure-related complications, optimization of neurodevelopmental function, and improvement of quality of life [21]. However, as demonstrated in the present case, seizure control is often difficult to achieve despite the use of multiple antiseizure medications. Our patient required long-term treatment with levetiracetam, sodium valproate, topiramate, lamotrigine, and primidone before admission, yet experienced recurrent breakthrough seizures necessitating repeated intravenous benzodiazepines and continuous midazolam infusion in the pediatric intensive care unit. This clinical course is highly consistent with previous reports describing medically refractory epilepsy as one of the defining features of LNPK deficiency [8,11,16].

An important lesson highlighted by this case is the value of continuous EEG monitoring in critically ill children with developmental epileptic encephalopathies. Clinical observation alone may underestimate seizure burden because many seizures are subtle or entirely electrographic, particularly in sedated patients receiving continuous anesthetic infusions. Continuous EEG therefore provides an objective assessment of seizure frequency, guides titration of antiseizure medications, and assists in determining the adequacy of therapeutic interventions [18]. In our patient, persistent epileptiform discharges despite aggressive treatment confirmed ongoing cortical hyperexcitability and justified continued intensive neurological management.

Respiratory complications represented another major contributor to the patient's clinical deterioration. Children with severe neurodevelopmental disorders frequently exhibit impaired airway clearance resulting from generalized hypotonia, bulbar dysfunction, reduced cough effectiveness, abnormal swallowing, and prolonged immobility. These factors predispose affected individuals to recurrent aspiration, retained secretions, atelectasis, and lower respiratory tract infections [19]. In our patient, pneumonia likely developed through a combination of impaired airway protection and infection, resulting in hypoxemia, abundant respiratory secretions, and increased respiratory effort. Respiratory compromise not only necessitated supplemental oxygen and intensive respiratory care but also likely contributed to seizure exacerbation by increasing metabolic stress and reducing the seizure threshold [16,20].

Management therefore appropriately extended beyond seizure control to include aggressive respiratory support through supplemental oxygen, frequent airway suctioning, nebulized hypertonic saline, inhaled corticosteroids, and antimicrobial therapy. The gradual improvement in oxygenation without the need for prolonged mechanical ventilation demonstrates the importance of early multidisciplinary respiratory intervention in neurologically impaired children. Nevertheless, the persistence of excessive secretions throughout hospitalization suggests that chronic respiratory morbidity may remain an important long-term challenge in patients with severe LNPK deficiency [19].

Nutritional management constitutes another important component of comprehensive care in children with severe developmental disabilities. Our patient initially required intravenous fluid therapy followed by gradual initiation of enteral nutrition through an orogastric tube and subsequent transition to nasogastric feeding. Enteral feeding ensured adequate nutritional intake while minimizing the risk of aspiration during the acute phase of illness. The subsequent development of persistent watery diarrhea complicated nutritional management but did not result in significant weight loss or evidence of infectious gastroenteritis. Although gastrointestinal manifestations have not been consistently described as part of the LNPK phenotype, feeding difficulties, swallowing dysfunction, and nutritional compromise are frequently encountered in children with severe neurological impairment irrespective of the underlying genetic diagnosis [21]. Early involvement of dietitians and speech and swallowing specialists may therefore improve nutritional status and reduce aspiration-related complications.

The differential diagnosis of children presenting with developmental regression and refractory epilepsy remains broad and includes numerous inherited metabolic disorders, mitochondrial diseases, structural brain abnormalities, and other developmental and epileptic encephalopathies. Disorders such as nonketotic hyperglycinemia, pyridoxine-dependent epilepsy, glucose transporter type 1 deficiency, mitochondrial encephalopathies, and several monogenic epileptic syndromes may initially present with overlapping clinical features [22]. Similarly, pathogenic variants involving genes such as STXBP1, SCN2A, SCN8A, CDKL5, FOXG1, KCNT1, and PCDH19 are well-established causes of developmental delay with early-onset refractory epilepsy [14,22]. Consequently, diagnosis based solely on clinical presentation is extremely challenging.

Our patient's diagnostic evaluation illustrates the increasingly important role of comprehensive genomic testing in pediatric neurology. Initial investigations, including neuroimaging, metabolic studies, chromosomal microarray analysis, echocardiography, and abdominal ultrasonography, were largely unrevealing. Only whole-exome sequencing established the definitive diagnosis by identifying a homozygous pathogenic variant in LNPK. This diagnostic trajectory mirrors that of many recently described neurogenetic disorders, in which traditional diagnostic investigations frequently fail to identify an etiology while next-generation sequencing provides a rapid and definitive molecular diagnosis [9,23]. Early implementation of exome sequencing in children with unexplained developmental delay and drug-resistant epilepsy may therefore reduce unnecessary investigations, shorten the diagnostic odyssey, facilitate accurate prognostication, and enable appropriate genetic counseling.

The present case also highlights the progressive nature of LNPK-related neurological dysfunction. Although developmental delay was recognized during infancy, the patient initially acquired several meaningful developmental milestones before experiencing substantial regression following seizure onset. This temporal sequence supports the hypothesis that progressive epileptic activity contributes significantly to neurological decline. Recurrent seizures, continuous epileptiform discharges, and repeated episodes of status epilepticus may accelerate deterioration by disrupting normal synaptic maturation during critical periods of brain development [13,18]. Whether earlier seizure control could alter long-term neurological outcomes in LNPK deficiency remains unknown; however, this possibility reinforces the importance of prompt recognition and aggressive management of epilepsy in affected children.

The family history observed in our patient further emphasizes the importance of genetic counseling in populations where consanguineous marriage is common. Autosomal recessive disorders constitute a substantial proportion of pediatric neurogenetic diseases in these populations, and identification of the underlying molecular diagnosis carries implications extending well beyond the affected individual [24]. Carrier testing, prenatal diagnosis, and preimplantation genetic testing may all become available once the familial pathogenic variant has been identified. Furthermore, molecular diagnosis enables cascade screening of siblings and extended family members, allowing earlier recognition and intervention in affected relatives.

From a scientific perspective, this case contributes additional evidence supporting the expanding clinical spectrum of LNPK-related neurodevelopmental disorder. Although the principal manifestations observed in our patient—including profound developmental delay, developmental regression, hypotonia, and drug-resistant epilepsy—are consistent with previously reported cases, the detailed description of his acute presentation with pneumonia-triggered neurological deterioration requiring prolonged pediatric intensive care management provides valuable insights into the natural history of severe disease. The principal limitation inherent to this report is that it describes the clinical course of a single patient, thereby limiting generalizability. Nevertheless, this limitation is unavoidable given the exceptional rarity of LNPK deficiency. Rare disease research relies heavily on carefully documented case reports because each additional patient contributes incrementally to the understanding of disease mechanisms, clinical variability, treatment response, and prognosis. Future international collaboration through multicenter registries and longitudinal natural history studies will be essential to define genotype-phenotype correlations, identify prognostic biomarkers, evaluate therapeutic interventions, and ultimately establish evidence-based management recommendations for this rare disorder [24,25].

Conclusion

LNPK-related neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum is an exceptionally rare developmental and epileptic encephalopathy characterized by severe developmental delay, developmental regression, generalized hypotonia, and highly refractory epilepsy. The present case demonstrates the considerable neurological and medical complexity associated with this condition, particularly when acute systemic infection precipitates seizure exacerbation requiring pediatric intensive care management. Our findings reinforce the importance of considering rare monogenic disorders in children with unexplained developmental regression and drug-resistant epilepsy, even in the absence of characteristic neuroimaging abnormalities. Early molecular diagnosis through next-generation sequencing facilitates accurate diagnosis, informs genetic counseling, and supports multidisciplinary management. Given the limited number of reported patients worldwide, continued publication of well-characterized cases is essential to expand current knowledge of the phenotypic spectrum, improve understanding of disease pathophysiology, refine genotype-phenotype correlations, and guide the development of future therapeutic strategies for this devastating neurodevelopmental disorder.

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