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Case Report

Pilarowski–Bjornsson Syndrome with Congenital Heart Defect: A Case Report and Literature Review

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Abstract

Introduction

Pilarowski–Bjornsson syndrome (PILBOS) is a rare autosomal dominant neurodevelopmental disorder caused by heterozygous variants in chromodomain helicase DNA-binding protein 1 (CHD1), a gene encoding an adenosine triphosphate (ATP)-dependent chromatin remodeler. Since its initial description in 2018, only a limited number of cases have been reported in the literature.

Case Presentation

A 4-month-old male infant presented with persistent hypotonia and recurrent focal seizures beginning in the neonatal period, accompanied by severe global developmental delay. Brain magnetic resonance imaging (MRI) was structurally normal. Whole exome sequencing identified a heterozygous de novo CHD1 variant (NM_001270.4: c.797C>T; p.Pro266Leu), classified as a variant of uncertain significance. Echocardiography revealed a medium-sized secundum atrial septal defect with right-sided chamber dilatation. The clinical course was complicated by recurrent lower respiratory tract infections and progressive respiratory distress.

Literature Review

Review of eight previously reported cases confirms global developmental delay and hypotonia as universal features of PILBOS (8/8, 100%). Dysmorphic craniofacial findings were present in 7/8 (87.5%) cases, and seizures occurred in 3/8 (37.5%). Intellectual disability was confirmed in 3/8 (37.5%) and not assessable in a further 3/8 (37.5%). Respiratory complications were documented in 1/8 (12.5%) cases. De novo inheritance was confirmed in 4/8 (50%) cases. No structural cardiac defects have been documented in any previously reported case, and all 8/8 (100%) patients were alive at last follow-up.

Conclusion

Findings from this case suggest that structural congenital heart defects may represent an underrecognized component of the PILBOS phenotypic spectrum. Further case reports and functional investigations are required to establish whether cardiac involvement constitutes a consistent feature of CHD1-related disease.

1. Introduction

Chromatin remodeling is essential for embryonic development, regulating gene expression through adenosine triphosphate (ATP)-dependent modulation of nucleosome architecture [1]. Chromodomain helicase DNA-binding protein 1 (CHD1) is a key chromatin remodeler that maintains open chromatin states and facilitates transcriptional elongation required for cellular differentiation [2]. Disruption of chromatin remodeling pathways has increasingly been implicated in neurodevelopmental disorders, including autism spectrum disorder and intellectual disability [3].

Pilarowski–Bjornsson syndrome (PILBOS) is a rare Mendelian disorder of the epigenetic machinery caused by heterozygous CHD1 variants, first described in 2018, with eight reported cases in the peer-reviewed literature [4-6]. The phenotype is characterized primarily by global developmental delay (GDD), hypotonia, seizures, and craniofacial dysmorphism [4]. Genes encoding chromatin remodeling proteins play critical roles in both neural and cardiac development, and large-scale genomic studies demonstrate enrichment of damaging de novo variants in chromatin regulators among individuals with congenital heart defects (CHD) [7,8]. The clinical spectrum of CHD1-related disease has thus far been defined largely by neurodevelopmental involvement.

The aim of the study is to report a patient with PILBOS caused by a de novo heterozygous CHD1 missense variant, presenting with severe early-onset neurodevelopmental impairment (NDI) in association with a CHD. The report was prepared in accordance with the CaReL guidelines [9], and the literature was systematically reviewed for relevance [10].

2. Case Presentation

2.1. Patient information

A 4-month-old male infant was referred for evaluation of persistent hypotonia and recurrent focal seizures. He was the first child of non-consanguineous parents, with no family history of epilepsy, neurological disorders, or known genetic conditions. He was born at term via spontaneous vaginal delivery. The perinatal period was complicated by birth asphyxia requiring admission to the neonatal intensive care unit (NICU). No congenital anomalies were identified at birth. Since the neonatal period, he developed recurrent focal seizures associated with generalized hypotonia, poor feeding, and severe delay in developmental milestones appropriate for his age. His clinical course was further complicated by recurrent chest infections and respiratory distress, leading to multiple hospital admissions.

2.2. Clinical findings

On physical examination, the infant demonstrated generalized hypotonia and delayed motor responses. No obvious dysmorphic facial or structural abnormalities were observed. Cardiovascular examination revealed a cardiac murmur.

2.3. Diagnostic assessment

Brain magnetic resonance imaging (MRI) demonstrated normal cerebral gray and white matter signal intensities, a normal ventricular system and basal cisterns, and normal sellar and parasellar structures. The cerebellum and brainstem appeared normal, with no evidence of focal lesions or midline shift. Echocardiography revealed mild dilatation of the right atrium and right ventricle with a medium-sized secundum atrial septal defect (ASD). Left ventricular wall thickness and systolic function were normal, and all cardiac valves were structurally normal.

Abdominal ultrasonography showed normal liver size and echotexture without focal lesions, a normal gallbladder without stones or biliary dilatation, normal spleen and pancreas, and normal kidneys without hydronephrosis. No ascites or pleural effusion was identified. Laboratory investigations revealed mild leukocytosis with neutrophilia and thrombocytosis. Stool calprotectin levels were within the normal range for age.

Whole exome sequencing identified a heterozygous de novo variant in the CHD1 gene (NM_001270.4), c.797C>T, resulting in a p.Pro266Leu amino acid substitution. The variant was classified as a variant of uncertain significance and is associated with PILBOS, an autosomal dominant disorder. Additional carrier findings included a pathogenic variant in NDUFAF6, associated with an autosomal recessive mitochondrial disorder, and a pathogenic variant in HERC1, associated with an autosomal recessive neurodevelopmental disorder. Based on the clinical presentation and genetic findings, a diagnosis of PILBOS due to a de novo heterozygous CHD1 variant was made, with an associated medium-sized secundum ASD.

2.4. Therapeutic intervention

The patient received ongoing medical therapy for seizure control along with supportive management for hypotonia and feeding difficulties. Recurrent respiratory infections were managed during multiple hospital admissions. Cardiology follow-up and potential future intervention for the ASD were planned; however, the patient died before these could be completed.

2.5. Follow-up and outcomes

During the observed clinical course, he continued to demonstrate profound hypotonia, severe GDD, and persistent focal seizures requiring ongoing anti-seizure medication (ASM). His condition was further complicated by recurrent lower respiratory tract infections, resulting in multiple hospitalizations. He ultimately developed severe, treatment-resistant pneumonia. Despite appropriate antimicrobial treatment and intensive supportive care, his respiratory status progressively worsened, leading to his death. He passed away before additional diagnostic investigations, serial neurodevelopmental evaluations, and planned cardiology interventions could be completed.

3. Discussion

Pilarowski–Bjornsson syndrome belongs to the expanding group of Mendelian disorders of the epigenetic machinery [4]. Several chromatin remodeler genes are linked to distinct neurodevelopmental syndromes, including Snijders Blok-Campeau syndrome, Sifrim-Hitz-Weiss syndrome, and CHARGE syndrome [5]. CHD1 is expressed across multiple tissues, with the highest levels found in the cerebellum and basal ganglia, and patient-derived fibroblasts have shown a global increase in closed chromatin modification, providing functional evidence for a dominant-negative disease mechanism [4,6].

A literature review of eight previously reported cases demonstrates that GDD and generalized hypotonia are universal features, each present in 8/8 (100%) of reported individuals. Intellectual disability was confirmed in 3/8 (37.5%), not assessable in 3/8 (37.5%), and absent in 1/8 (12.5%). Dysmorphic craniofacial features were reported in 7/8 (87.5%) cases. Seizures occurred in 3/8 (37.5%) cases. Respiratory complications were documented in 1/8 (12.5%). No cardiac findings were identified in any previously reported case. Reported patients ranged from 7 months to 17 years of age, and included both sexes, although 7/8 (87.5%) were female. De novo inheritance was confirmed in 4/8 (50%) cases, could not be determined in the remaining 4/8 (50%). All 8/8 (100%) previously reported patients were alive at last follow-up (Table 1) [4-6].

Pathogenic variants in PILBOS are predominantly heterozygous missense changes, and the absence of a neurological phenotype in individuals with CHD1 deletions supports a dominant-negative rather than haploinsufficiency mechanism [4]. Phenotypic variability across reported cases has been attributed to this altered-function mechanism [4–6]. The variant identified in this patient (c.797C>T; p.Pro266Leu) is consistent with this variant class. Although classified as a variant of uncertain significance under ACMG criteria, its confirmed de novo occurrence provides moderate evidence supporting pathogenicity [11], and the clinical phenotype is consistent with previously reported PILBOS cases, supporting the diagnosis.

Clinically, this patient demonstrated profound neonatal hypotonia and severe GDD, consistent with the established phenotype. Brain MRI was structurally normal, consistent with prior reports of normal neuroimaging in PILBOS [4]. However, the neurological course was notable for early-onset recurrent focal seizures requiring ongoing ASM. Seizures occur variably in PILBOS, present in 2/6 individuals in the original cohort [4], absent in the case reported by Sunwoo et al. [5], and limited to febrile convulsions in the truncating variant case [6]. Disruption of chromatin remodeling pathways has been implicated in epilepsy through dysregulation of gene expression essential for neuronal differentiation and synaptic stability [3]. In the present case, recurrent focal seizures began in early infancy and required ongoing ASM, representing a more severe seizure phenotype than previously reported in PILBOS, despite structurally normal neuroimaging.

Respiratory complications have not been uniformly described in PILBOS. Although absent in the initial cohort [4] and in the case reported by Sunwoo et al. [5], neonatal respiratory distress and aspiration pneumonia were documented in one individual with a truncating variant [6]. This patient experienced recurrent lower respiratory tract infections and progressive respiratory compromise beginning in early infancy, necessitating repeated hospitalizations. This pronounced respiratory involvement could plausibly be attributed to severe hypotonia, which may impair airway protection and increase susceptibility to aspiration and recurrent infections.

Structural CHDs have not previously been reported in association with CHD1-related disease, making the identification of a medium-sized secundum ASD with right-sided chamber dilatation in this patient noteworthy. Chromatin remodeling genes as a functional category have been implicated in cardiac development, and large-scale genomic analyses have demonstrated enrichment of damaging de novo variants in chromatin regulators among individuals with CHD and neurodevelopmental disorders [8]. Disruption of chromatin remodeling complexes during embryonic development has been associated with multisystem developmental phenotypes [2,8], providing biological plausibility for cardiac involvement in CHD1-related disease. Although secundum ASD is among the most common CHDs in the general population [12,13], causality cannot be established from a single observation, and this finding raises the possibility that structural cardiac anomalies may represent an underrecognized component of the PILBOS phenotypic spectrum.

The clinical course in this case was markedly more severe than in previously reported PILBOS cases, which all survived into childhood or adolescence [4–6]. Early-onset refractory epilepsy, profound hypotonia, recurrent respiratory infections, and death in infancy collectively represent the most severe manifestation of CHD1-related disease documented to date. Whether this severity reflects the specific pathogenic effect of the c.797C>T variant, the contribution of co-identified carrier variants in NDUFAF6 and HERC1, or other genetic or environmental modifiers cannot be determined from a single case. Regardless, this case highlights the importance of early and comprehensive multidisciplinary surveillance in affected infants.

Management across all reported PILBOS cases has been supportive and symptom-directed, encompassing developmental therapies, ASM, and respiratory support where indicated [4–6]. No targeted molecular therapy has been reported, and the clinical course in this patient was marked by progressive deterioration despite maximal supportive care.

This report has several limitations. The CHD1 variant was not confirmed by Sanger sequencing due to the patient's death prior to validation, and echocardiographic images documenting the ASD were unavailable, as evaluation was performed at an external institution. Furthermore, the findings cannot be generalized, and additional cases are required to clarify the full phenotypic spectrum associated with CHD1 variants.

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Table 1. Previously Reported Cases of Pilarowski–Bjornsson Syndrome.

Author, Year	No of Cases, Gender, Age	CHD1 variant	Inheritance	Dysmorphic features	Developmental delay	Intellectual disability	Hypotonia	Respiratory complications	Seizures	Cardiac Findings	Therapeutic interventions	Outcome
Pilarowski et al., 2018 [4]	n = 6, All F, 7 mo – 10 yo	p.Arg618Gln; p.Arg1708Gln (2 patients); p.Arg460Lys; p.Arg141Gly; p.Asp857Gly	3/6 de novo; 3/6 unknown	Arched eyebrows, almond-shaped eyes, down-slanting palpebral fissures, pointed chin, and frontal bossing	Global developmental delay (6/6)	Confirmed in 2/6; absent in 1/6; not assessable in 3/6	Generalized hypotonia (6/6)	No respiratory complications reported	Seizures in 2/6	None reported	Developmental therapies; antiepileptic treatment in patients with seizures	All patients alive
Sunwoo et al., 2022 [5]	n = 1, M, 17 yo	c.862A>G (p.Thr288Ala)	De novo	Wide-set eyes, low nasal bridge, microtia	Severe global delay	Severe intellectual disability	Present in early life	No respiratory complications reported	None	None (echocardiogram normal)	Rehabilitation and speech therapy; no antiepileptic treatment was required	Alive at 17 years
Al-Aamri et al., 2023 [6]	n = 1, F, 3 yo	c.966G>A (p.Trp322Ter)	Unknown (parents not tested)	Depressed midface, almond-shaped eyes, flaring eyebrows, pointed chin	Severe global delay	Severe intellectual disability	Severe neonatal hypotonia	Neonatal respiratory distress and aspiration pneumonia reported	Febrile seizures	None reported	Neonatal respiratory support, treatment of aspiration pneumonia, and antiepileptic therapy for febrile seizures	Alive at last follow-up

F, female; M, male; mo, months; yo, years old; n, number of cases; CHD1, chromodomain helicase DNA-binding protein 1; c., coding DNA sequence; p., protein change; Arg, arginine; Gln, glutamine; Lys, lysine; Gly, glycine; Asp, aspartic acid; Thr, threonine; Pro, proline; Leu, leucine; Ter, termination codon; ASD, atrial septal defect.

4. Conclusion

Identification of a de novo CHD1 missense variant in an infant with severe early-onset NDI and a structural ASD suggests that CHD1-related disease may extend to involve CHD in addition to its established neurodevelopmental phenotype. This association raises the possibility that systemic evaluation, including cardiac assessment, may be warranted in affected individuals. Further case accumulation and functional studies will be essential to clarify the phenotypic spectrum and underlying mechanisms of CHD1-related disease.

Declarations

Conflicts of interest: The authors have no conflicts of interest to disclose.

Ethical approval: Not applicable

Patient consent (participation and publication)**:** Written informed consent was obtained from the parents of the deceased patient for the publication of this case report and any accompanying clinical details.

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Use of AI: ChatGPT-4.5 was used to assist with language refinement and improve the overall clarity of the manuscript. All content was thoroughly reviewed and approved by the authors, who bear full responsibility for the final version.

Data availability statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Alendar A, Berns A. Sentinels of chromatin: chromodomain helicase DNA-binding proteins in development and disease. Genes & development. 2021;35(21-22):1403-30. doi:10.1101/gad.348897.121
2. Gaspar-Maia A, Alajem A, Polesso F, Sridharan R, Mason MJ, Heidersbach A, et al. Chd1 regulates open chromatin and pluripotency of embryonic stem cells. nature. 2009;460(7257):863-8. doi:10.1038/nature08212
3. De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Ercument Cicek A, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature. 2014;515(7526):209-15. doi:10.1038/nature13772
4. Pilarowski GO, Vernon HJ, Applegate CD, Boukas L, Cho MT, Gurnett CA, et al. Missense variants in the chromatin remodeler CHD1 are associated with neurodevelopmental disability. Journal of medical genetics. 2018;55(8):561-6. doi:10.1136/jmedgenet-2017-104759
5. Sunwoo Y, Seo SH, Kim HJ, Park MS, Cho A. Variant of CHD1 gene resulting in a Korean case of Pilarowski-Bjornsson syndrome. Journal of Genetic Medicine. 2022;19(2):111-4. doi:10.5734/JGM.2022.19.2.111
6. Al-Aamri M, Alshaqaq M, Al-Abdi SY. A Saudi Girl With Co-occurring CHD1 (Pilarowski-Bjornsson Syndrome) and ASH1L Gene Variants. Cureus. 2023;15(12). doi:10.7759/cureus.49905
7. Ong LT. Genetics and Pathophysiology of Co-occurrence of Congenital Heart Disease and Autism Spectrum Disorder. EMJ. 2024. doi:10.33590/emj/MKPN4473
8. Ji W, Ferdman D, Copel J, Scheinost D, Shabanova V, Brueckner M, et al. De novo damaging variants associated with congenital heart diseases contribute to the connectome. Scientific reports. 2020;10(1):7046. doi:10.1038/s41598-020-63928-2
9. Prasad S, Nassar M, Azzam AY, García-Muro-San José F, Jamee M, et al. CaReL guidelines: a consensus-based guideline on case reports and literature review (CaReL). Barw Medical Journal. 2024;2(3):13-19. doi:10.58742/bmj.v2i2.89
10. Abdullah HO, Abdalla BA, Kakamad FH, Ahmed JO, Baba HO, Hassan MN, et al. Predatory Publishing Lists: A Review on the Ongoing Battle Against Fraudulent Actions. Barw Medical Journal. 2024;2(2):26-30. doi:10.58742/bmj.v2i2.91
11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine. 2015;17(5):405-23. doi:10.1038/gim.2015.30
12. Sarkozy A, Conti E, Neri C, d'Agostino R, Digilio MC, Esposito G, et al. Spectrum of atrial septal defects associated with mutations of NKX2. 5 and GATA4 transcription factors. Journal of medical genetics. 2005;42(2):e16-. doi:10.1136/jmg.2004.026740
13. Okubo A, Miyoshi O, Baba K, Takagi M, Tsukamoto K, Kinoshita A, et al. A novel GATA4 mutation completely segregated with atrial septal defect in a large Japanese family. Journal of Medical Genetics. 2004;41(7):e97-. doi:10.1136/jmg.2004.018895