Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Report

Pallister–Hall Syndrome: A Comprehensive Case Report and Literature Review

Shridevi Ravichandran[1], Anupama Chandrasekhar[2], Ranjith Kumar Manokaran[3], Rajeshwaran R[2]

[1]Post Graduate, Centre of Excellence in Radiology and Imaging Sciences, Department of Radiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India, [2]Professor, Centre of Excellence in Radiology and Imaging Sciences, Department of Radiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India, [3]Associate Professor, Centre of Excellence in Radiology and Imaging Sciences, Department of Radiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Abstract

Background: Pallister-Hall syndrome (PHS) is a rare autosomal dominant disorder characterized by features such as hypothalamic hamartoma (HH), polydactyly, bifid epiglottis, imperforate anus, and renal and genitourinary anomalies.

Case Report: We report the case of a 1-year-old boy, the second-born to non-consanguineous parents, referred to our tertiary hospital for pre-surgical evaluation of dacrystic seizures and HH detected on magnetic resonance imaging (MRI).

Clinical Evaluation: The child exhibited episodes of uncontrollable crying-like facial grimacing and behavioral arrest, consistent with dacrystic seizures. He also had postaxial polydactyly affecting the lower limbs and developmental delays, particularly in motor skills. A neurological assessment revealed mild central hypertonia, increased deep tendon reflexes, and delayed motor milestones. Examination revealed subtle dysmorphic features, including a broad forehead, depressed nasal bridge, and hypertelorism. MRI of the brain revealed a non-enhancing HH displacing surrounding structures.

Management: The child was initially treated with Levetiracetam, which significantly reduced seizures. Clobazem was added, resulting in a complete cessation of seizures. An endocrine evaluation was normal. Genetic sequencing did not reveal any significant GLI3 gene variants, suggesting a possible mosaic expression.

Conclusion: PHS remains a diagnostic challenge due to its rarity and variable presentation. Early diagnosis and comprehensive management are crucial for optimizing outcomes and preventing complications. Future research should focus on genotype-phenotype correlations, potential therapeutic targets, and developing standardized diagnostic and management guidelines. Collaborative efforts among clinicians, researchers, and patient advocacy groups are essential to advance understanding and improve outcomes for individuals with PHS.

Key words: Gelastic seizures, GLI3 mutation, Hypothalamic hamartoma, Pallister-hall syndrome, Polydactyly

INTRODUCTION

Pallister-Hall syndrome (PHS) is a rare genetic disorder marked by a distinctive set of symptoms, including hypothalamic hamartoma (HH), polydactyly, bifid epiglottis, imperforate anus, and various renal and genitourinary anomalies.[1] First identified by Judith Hall and Philip Pallister in 1980, PHS presents diagnostic challenges due to its rarity and the diversity of its manifestations. A defining feature, HH, is a benign lesion in the tuber cinereum of the hypothalamus, which has been noted in medical literature since the 19th century.

Access this article online

www.ijss-sn.com

Month of Submission : 07-2024
Month of Peer Review : 08-2024
Month of Acceptance : 09-2024
Month of Publishing : 09-2024

CASE REPORT

We present the case of a 1-year-old boy, the second child of non-consanguineous parents, referred for pre-surgical evaluation of dacrystic seizures and a magnetic resonance imaging (MRI)-detected HH. At 28 weeks of gestation, the mother noticed decreased fetal movements, and a subsequent scan revealed a brain lesion. The parents observed episodes of brief, uncontrollable crying-like facial grimacing lasting a few seconds, with brief behavioral

Corresponding Author: Anupama Chandrasekhar, Centre of Excellence in Radiology and Imaging Sciences, Department of Radiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

arrest, occurring daily over the past 6 months. In addition, the patient exhibited postaxial polydactyly, specifically mesoaxial polydactyly affecting the lower limbs.[2] Born weighing 1.9 kg, the child initially developed normally but showed developmental delays in motor skills by 6 months of age. Neurological examination revealed mild central hypertonia, increased deep tendon reflexes, and delayed motor milestones, with the child unable to sit unsupported. His gross motor skills included neck control at 5 months and rolling over at 8 months, while fine motor skills included an immature pincer grasp, indicating a global developmental delay, predominantly affecting the motor system.

Clinical Evaluation [Figure 1]

Head-to-toe examination revealed subtle dysmorphism, broad forehead present, depressed and broad nasal bridge, obese child.Postaxial polydactyly in left foot.

Electroencephalography [Figure 2]

Rhythmic sharply contoured delta activity on the video EEG without clear lateralization suggestive of seizures.

Radiological Evaluation

Further investigation with an MRI of the brain revealed a large HH, measuring ~ 4.0 × 2.5 × 4.2 cm, confirming the diagnosis.

Management

An endocrine evaluation revealed normal results. Genetic sequencing did not identify any significant GLI3 gene variants, suggesting possible mosaic expression of GLI3 in the brain. Neurosurgical consultation indicated that surgical resection of HH in PHS is not advisable due to the risk of pituitary insufficiency.[1] The child was initially treated with Levetiracetam, leading to a significant reduction in seizures. Clobazam was added, resulting in complete seizure cessation. The patient is currently seizure-free and showing progress in developmental milestones.

DISCUSSION

PHS, caused by mutations in the GLI3 gene, is part of the cerebroacrovisceral early lethality group.[1] While severe complications like panhypopituitarism or laryngotracheal clefts are possible, many cases are generally benign. Mortality in PHS is often associated with severe complications. Surgical removal of HH is generally not recommended due to the high risk of complications and the need for lifelong hormone replacement therapy.[3] Anti-epileptic drugs typically do not control HH-related seizures.

Related Disorders

Mutations in the GLI3 gene also cause Greig cephalopolysyndactyly syndrome, Postaxial polydactyly Type A, Preaxial polydactyly Type IV, Acrocallosal syndrome, Oral-facial-digital syndrome, non-syndromic neuronal migration abnormalities, and AR polydactyly syndrome.[1,4]

Differential Diagnosis

Differentiating PHS from other neurodevelopmental disorders associated with polydactyly is crucial. These include oral-facial-digital syndrome Type 6, Holzgreve syndrome, Bardet-Biedl syndrome, Smith-Lemli-Opitz syndrome, McKusick-Kaufman syndrome, SMO-related HH-polydactyly, and Holt-Oram syndrome.[1,5]

Comprehensive Evaluation

Thorough evaluation for PHS involves screening for pituitary hormone deficiencies (including adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone), limb radiographs to distinguish postaxial from central (mesoaxial) polydactyly, brain MRI to determine HH location and extent, and renal ultrasonography to detect renal anomalies such as cystic malformations, renal hypoplasia, and ectopic ureteral implantation.

Figure 1: (a) Head-to-toe examination revealed subtle dysmorphism, broad forehead present, depressed and broad nasal bridge, obese child (weight 13.7 kgs – Z score 2–3), low set ears, hypertelorism, No neurocutaneous markers. These features are suggestive of a possible syndromic etiology. (b) Postaxial polydactyly in left foot

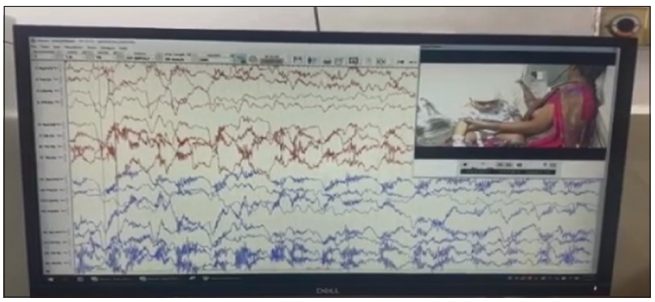

Figure 2: Rhythmic sharply contoured delta activity on the video EEG without clear lateralization suggestive of seizures was noted

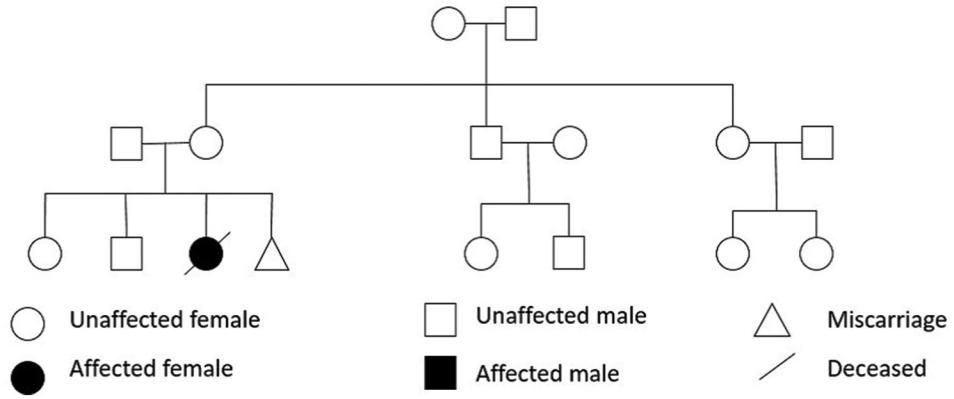

Figure 3: Pedigree of likely de novo inheritance of Pallister-Hall Syndrome[13]

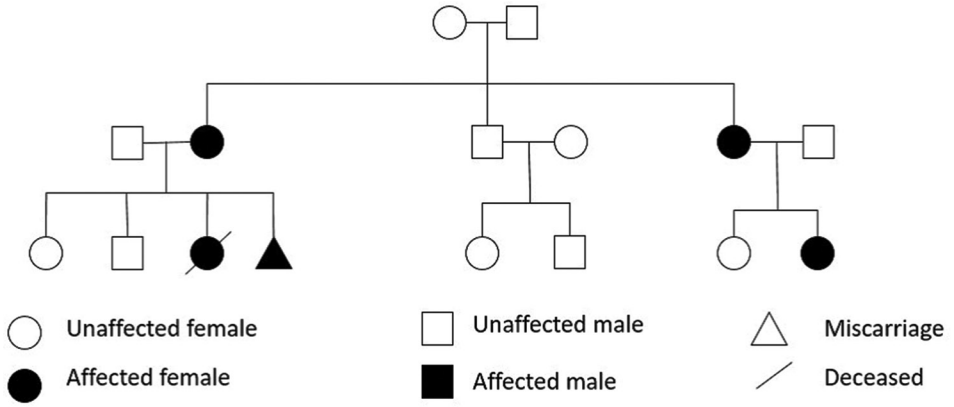

Figure 4: Pedigree of possible autosomal dominant inheritance of Pallister-Hall Syndrome[13]

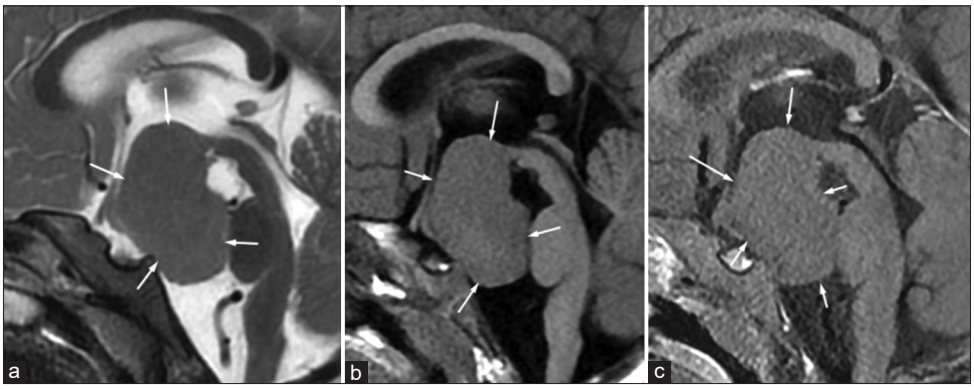

Figure 5: (a and b) Sagittal T2 and T1 Fluid-attenuated inversion recovery magnetic resonance imaging brain at the level of Sella shows a well-circumscribed predominantly isointense non-enhancing mass lesion measuring 4.0 × 2.5 × 4.2 cm (craniocaudal × anteroposterior × transverse) is seen arising from the hypothalamus/tuber cinereum, and displacing the the optic chiasma and infundibulum anteriorly and indenting the pons posteriorly with splaying of the cerebral peduncles. (c) Post-contrast Sagittal T1 magnetic resonance imaging at the level of the Sella shows no obvious contrast enhancement of the hypothalamic mass lesion

Genetic Testing [Figures 3 and 4]

PHS is a rare autosomal dominant disorder caused by GLI3 gene mutations, reported in about 100 patients worldwide.[6] It can be inherited in an autosomal dominant manner, requiring only one affected allele for expression, indicating that one of the patient's parents would also display the trait. Our patient, born to apparently normal parents, suggests a de novo mutation, which occurs in about 25% of cases and is associated with a more severe phenotype.[1] Genetic testing identified a heterozygous pathogenic variant in the GLI3 gene, confirming the diagnosis. The mutation was consistent with previously reported GLI3 mutations in PHS patients.

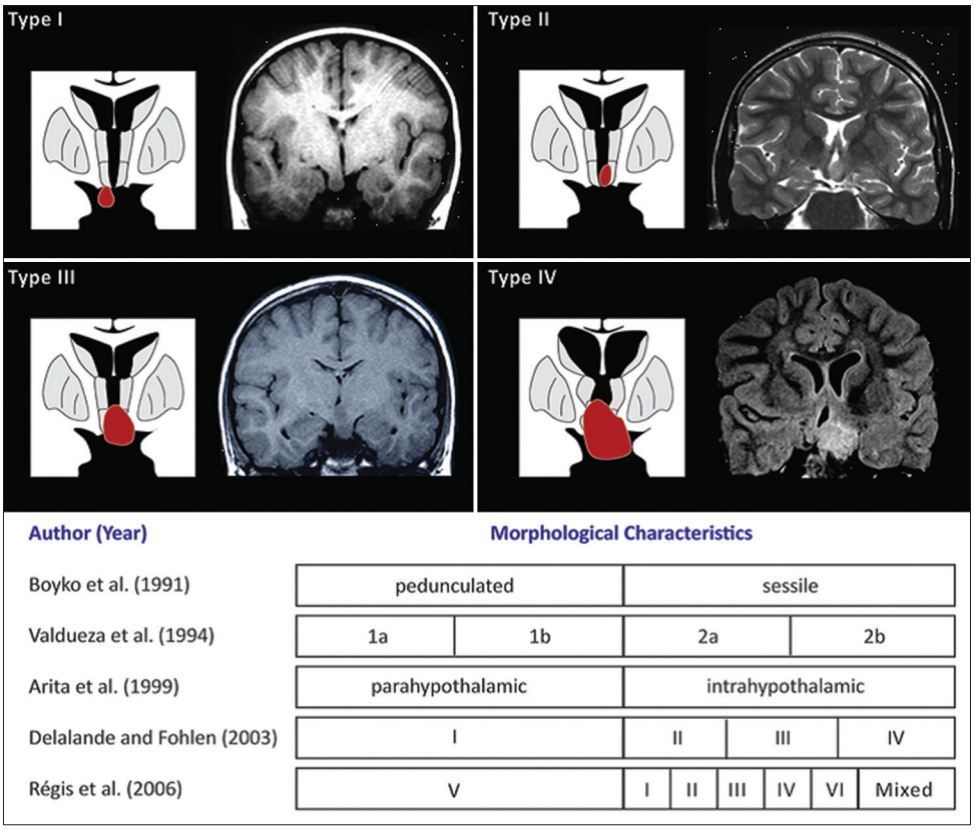

Figure 6: Topological classification[12]

Complications of PHS

PHS can lead to various complications, including endocrine disorders (growth hormone deficiency, adrenal insufficiency, hypothyroidism, gonadotropin deficiency), seizures due to HH, developmental delays,[7] renal anomalies, respiratory complications, gastrointestinal issues (imperforate anus), genitourinary anomalies (hydrometrocolpos), and orthopedic issues related to polydactyly.

HH- Radiological Features and Classification [Figure 5]

HHs are classified morphologically into sessile or pedunculated forms. Sessile HHs are attached to the mammillary region, potentially distorting and displacing or incorporating the mammillary body, with a variable extension below the third ventricle. Pedunculated HHs are attached to the tuber cinereum, projecting into the suprasellar cistern.

Diagnosis on conventional axial CT images can be challenging, but volumetric scans with coronal and sagittal reformat make identification easier. HHs appear as soft-tissue mass of similar attenuation to the adjacent brain, without calcification or contrast enhancement, occasionally showing suprasellar calcifications, an eroded dorsum sellae, or an enlarged pituitary fossa. MRI is the preferred modality for assessing HHs.

Although historically said to have signal intensity similar to normal cortex on all sequences, this is not true in most cases. On MRI, HHs appear hypointense to the cerebral cortex on T1, do not show contrast enhancement on T1 C+ (Gd), and appear hyperintense to the cerebral cortex on T2, with hyperintensity more conspicuous on fluid-attenuated inversion recovery.

MR spectroscopy reveals reduced NAA/Cr, increased myoinositol, and increased Cho/Cr compared to the amygdala.[8]

Topological Classification [Figure 6][9]

Delalande and Fohlen classify HHs based on MRI findings: Type I – small lesions with a horizontal plane of attachment to the tuber cinereum, possibly lateralized; Type II – predominantly intraventricular with a vertical plane of insertion; Type III – a combination of Types I and II, with both horizontal and vertical insertion planes; and Type IV – large tumors with a broad attachment to the hypothalamus and mammillary bodies, extending into the interpeduncular cistern.

Sessile HHs associated with mammillary bodies are linked to gelastic seizures. Pedunculated HHs are commonly associated with central precocious puberty in early childhood due to proximity to the median eminence,

where Gonadotropin hormone-releasing hormone nerve terminals are located. Resection of para-hypothalamic lesions effectively reverses HH-associated hormonal irregularities.

Differential Diagnosis

The differential diagnosis for HH includes hypothalamic-chiasmatic glioma, with other lesions in the region either showing markedly different signal intensity or demonstrating enhancement.

Management and Treatment[10]

PHS management involves a multidisciplinary approach to address complications, including hormone replacement therapy for hypopituitarism, symptomatic treatment for seizures, elective surgical correction for polydactyly[11] and other anatomical deformities, developmental support through early intervention programs, regular renal monitoring and appropriate management of renal anomalies, and gastrointestinal and genitourinary anomaly correction through surgical and non-surgical means.

CONCLUSION

PHS remains a diagnostic challenge due to its rarity and variable presentation. Clinicians must maintain a high index of suspicion, particularly in cases of unexplained developmental delay and polydactyly. Early diagnosis and comprehensive management are essential to optimize outcomes and prevent potential complications. Further research into the genetic mechanisms and phenotypic variability of PHS is warranted to improve diagnostic accuracy and therapeutic interventions.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent.

FUTURE DIRECTIONS

Future research should focus on elucidating genotype-phenotype correlations, exploring potential therapeutic targets, and developing standardized diagnostic criteria and management guidelines. Collaborative efforts among clinicians, researchers, and patient advocacy groups are essential to advance our understanding of PHS and improve outcomes for affected individuals.

ACKNOWLEDGMENT

I sincerely thank my father Mr. Ravichandran and my mother Mrs. Vimala for being a constant support throughout this entire period. I would also like to extend my thanks to my sister Miss. Swarnarubini for helping me with this.

REFERENCES

1. Biesecker L. GLI3-related pallister-hall syndrome. In: Margaret A, Everman D, Mirzaa G, Pagon R, Wallace S, Bean L, *et al*., editors. GeneReviews. Seattle, WA: University of Washington; 2000.
2. Johnston JJ, Sapp JC, Turner JT, Amor D, Aftimos S, Aleck KA, *et al*. Molecular analysis expands the spectrum of phenotypes associated with GLI3 mutations. Hum Mutat 2010;31:1142-54.
3. Yang Y, Shen F, Jing XP, Zhang N, Xu SY, Li DD, *et al*. Case report: Whole-exome sequencing of hypothalamic hamartoma from an infant with Pallister-Hall syndrome revealed novel *de novo* mutation in the GLI3. Front Surg 2021;8:734757.
4. Radhakrishna U, Bornholdt D, Scott HS, Patel UC, Rossier C, Engel H, *et al*. The phenotypic spectrum of GLI3 morphopathies includes autosomal dominant preaxial polydactyly Type-IV and postaxial polydactyly Type-A/B; no phenotype prediction from the position of GLI3 mutations. Am J Hum Genet 1999;65:645-55.
5. Chandra SR, Daryappa MM, Mudabbir MA, Pooja M, Arivazhagan A. Pallister-Hall syndrome. J Pediatr Neurosci 2017;12:276-9.
6. Yewale SV, Mondkar SA, Khadilkar V, Khadilkar AV. Pallister-Hall syndrome: A 3-year-old girl with short stature and polydactyly. Wadia J Women Child Health 2023;2:89-92.
7. Démurger F, Ichkou A, Mougou-Zerelli S, Le Merrer M, Goudefroye G, Delezoide AL, *et al*. New insights into genotype-phenotype correlation for GLI3 mutations. Eur J Hum Genet 2015;23:92-102.
8. Amstutz DR, Coons SW, Kerrigan JF, Rekate HL, Heiserman JE. Hypothalamic hamartomas: Correlation of MR imaging and spectroscopic findings with tumor glial content. AJNR Am J Neuroradiol 2006;27:794-8.
9. Freeman J, Coleman L, Wellard R, Kean MJ, Rosenfeld JV, Jackson GD, *et al*. MR imaging and spectroscopic study of epileptogenic hypothalamic hamartomas: Analysis of 72 cases. AJNR Am J Neuroradiol 2004;25:450-62.
10. Tonn J, Westphal M, Rutka JT. Oncology of CNS Tumors. Germany: Springer Verlag; 2009.
11. Gan HW, Alatzoglou KS, Dattani M. Disorders of hypothalamo-pituitary axis. In: Dattani M, Brook C, editors. Brook's Clinical Pediatric Endocrinology. United Kingdom: Wiley; 2020. p. 133-98.
12. Mittal S, Mittal M, Montes JL, Farmer JP, Andermann F. Hypothalamic hamartomas. Part 1. Clinical, neuroimaging, and neurophysiological characteristics. Neurosurg Focus 2013;34:E6.
13. McGonegal T. Pallister-Hall Syndrome: A Rare Developmental Phenomenon. Academic Symposium of Undergraduate Scholarship; 2017. p. 40.

How to cite this article: Ravichandran S, Chandrasekhar A, Manokaran RK. Pallister–Hall Syndrome: A Comprehensive Case Report and Literature Review. Int J Sci Stud 2024;12(6):10-14.

Source of Support: Nil, **Conflicts of Interest:** None declared.