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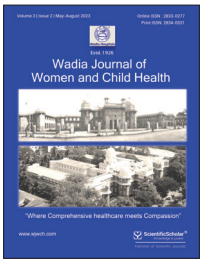

Case Report

Pallister-Hall syndrome: A 3-year-old girl with short stature and polydactyly

Sushil V. Yewale[1], Shruti A. Mondkar[1], Vaman Khadilkar[1], Anuradha V. Khadilkar[1]

[1]Department of Growth and Pediatric Endocrinology, Hirabai Cowasji Jehangir Medical Research Institute, Block V Lower Basement Jehangir Hospital, Pune, Maharashtra, India.

***Corresponding author:**
Anuradha V. Khadilkar, Department of Growth and Pediatric Endocrinology, Hirabai Cowasji Jehangir Medical Research Institute, Block V Lower Basement Jehangir Hospital, Pune, Maharashtra, India.

anuradhavkhadilkar@gmail.com

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ABSTRACT

A 3.1-year-old girl presented with short stature and developmental delay. She had a high-pitched voice, broad forehead, midfacial hypoplasia, hypoplastic labia, and bilateral mesoaxial polydactyly involving upper limbs. Biochemical reports were suggestive of isolated growth hormone deficiency (GHD) and magnetic resonance imaging revealed a large hypothalamic hamartoma (HH). The presence of auxological, clinical, and biochemical findings of GHD together with polydactyly and HH clinched the diagnosis of Pallister-Hall Syndrome. There are approximately 100 cases reported worldwide, which points toward the rarity of this disorder. Moreover, in contrast to most cases, our case had significant developmental delay.

Keywords: Pallister-Hall syndrome, Polydactyly, Hypothalamic hamartoma, Growth hormone

INTRODUCTION

Short stature in children has multiple etiologies, a rare but important one being syndromic short stature; diagnosis of syndromic short stature requires a high index of suspicion. Clinically evident features such as polydactyly or facial dysmorphism often serve as markers of underlying disease and such cases should be investigated in depth to avoid misdiagnosis.

Pallister-Hall syndrome (PHS) is a rare autosomal dominant disorder characterized by a constellation of features of hypothalamic hamartoma (HH), polydactyly, bifid epiglottis, imperforate anus, and renal and genitourinary anomalies. It results due to mutations in the GLI3 gene located on short arm of chromosome 7.[1] There are approximately 100 cases reported worldwide, which points toward the rarity of this disorder. Moreover, most cases reported in the literature so far were developmentally normal, unlike our case who presented with significant developmental delay.[2]

We report a 3.1-year-old girl, who presented with short stature and HH on magnetic resonance imaging (MRI). The child also had mesoaxial (central) polydactyly, which, in conjunction with HH is diagnostic of PHS.

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CASE REPORT

A 3.1-year-old girl, born to non-consanguineous parents, was referred to our tertiary level pediatric endocrinology centre for short stature compared to her younger sibling. She was delivered vaginally at term and weighed 2.4 kg at birth. She developed neonatal jaundice lasting for 11 days and required phototherapy for the same. She grew normally till 6 months of age as per her mother, but was noticed to have progressive growth faltering (affecting both, weight and height) subsequently. She was developmentally delayed particularly in the motor and speech domains, wherein she started walking at 2.6 years of age and could speak only 2–3 meaningful words at the time of presentation. She had no history suggestive of any chronic medical illness.

Examination revealed severe but proportionate short stature, with a height of 64.2 cm (−8.5 Z-score) for a mid-parental height of 157 cm (−0.4 Z-score) and an upper: lower segment ratio of 1.2:1 (within normal limits for her age). She weighed 5 kg (−10.2 Z-score). She had a high pitched voice, broad forehead, midfacial hypoplasia, hypoplastic labia, and bilateral mesoaxial polydactyly with left side postaxial polydactyly Type B (rudimentary digit on ulnar aspect of limb) involving the upper limbs. [Figure 1a] Lower limbs were spared. [Figure 1b] Biochemical investigations were suggestive of low serum insulin like growth Factor-1 (<7.0 ng/mL; reference range: 17–248 ng/mL) and low basal and stimulated (after 60 min of administration of Clonidine 25 mg orally) growth hormone concentrations (0.112 and 0.204 ng/mL, respectively; reference range: >7 ng/mL). Serum free T4 (1.20 ng/dL; reference range: 0.93–1.70 ng/dL) and serum cortisol assessed at 8AM (192.20 ng/mL; reference range: 62–194 ng/mL) were within reference range. Above mentioned reports were suggestive of isolated growth hormone deficiency (GHD). Radiograph of the hand confirmed the finding of mesoaxial polydactyly with Y-shaped metacarpal [Figure 1c]. An MRI advised to examine for pituitary abnormalities revealed a large 3.1 * 2.5 * 3.4 cm HH [Figure 2]. The presence of auxological, clinical, and biochemical findings of GHD together with polydactyly, developmental delay, and the presence of a HH clinched the diagnosis of PHS. Due to monetary constraints, genetic testing was deferred by the parents. She was started on recombinant human growth hormone at a dose of 25 mcg/kg/day and is slated for a follow-up.

DISCUSSION

We report a case of clinically diagnosed PHS, with GHD, and HH on MRI, who presented with short stature, developmental delay, and bilateral mesoaxial polydactyly with left side post-axial polydactyly Type B.

PHS is an extremely rare autosomal dominant disorder that results from GLI3 gene mutation.[1] So far, it has been reported in only around 100 patients worldwide.[1,2]

Features such as a HH; mesoaxial (insertional or central) or postaxial polydactyly; bifid epiglottis; imperforate anus; renal anomalies including cystic malformations, renal hypoplasia and ectopic ureteral implantation; genitourinary anomalies including hydrometrocolpos; bilateral bilobed lungs; and short limbs, with a strong family history with multiple generations affected should raise the suspicion of PHS. Clinical diagnosis can be made in the presence of HH and mesoaxial polydactyly in a child.[1] Molecular genetic testing suggestive of a heterozygous pathogenic variant in GLI3 confirms the diagnosis.[3]

Contrary to the commonly reported finding of postaxial polydactyly in other Indian Case reports [Table 1], our patient had both HH and mesoaxial polydactyly which were diagnostic of PHS, eliminating the need for genetics. Post-axial polydactyly, although more common than mesoaxial

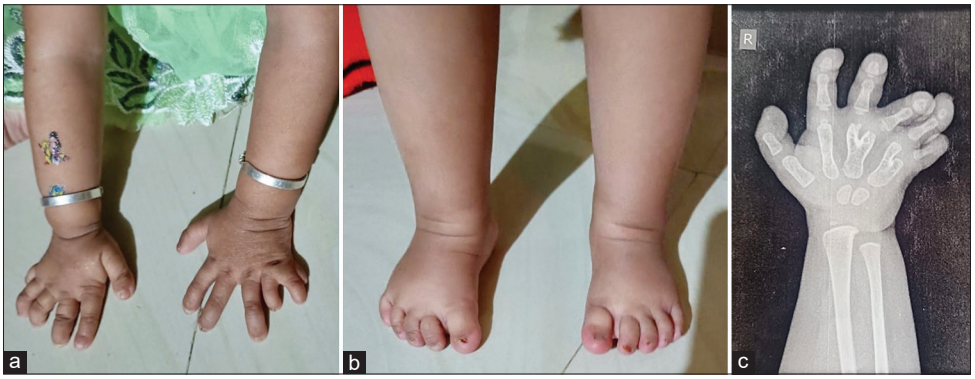

Figure 1: A 3-year-old girl with Pallister-Hall Syndrome who presented with short stature. (a) Upper limbs showing bilateral mesoaxial polydactyly with left side postaxial polydactyly Type B. (b) Lower limbs are normal. (c) Radiograph of right hand P-A view showing mesoaxial polydactyly and Y-shaped 3rd and 4th metacarpals.

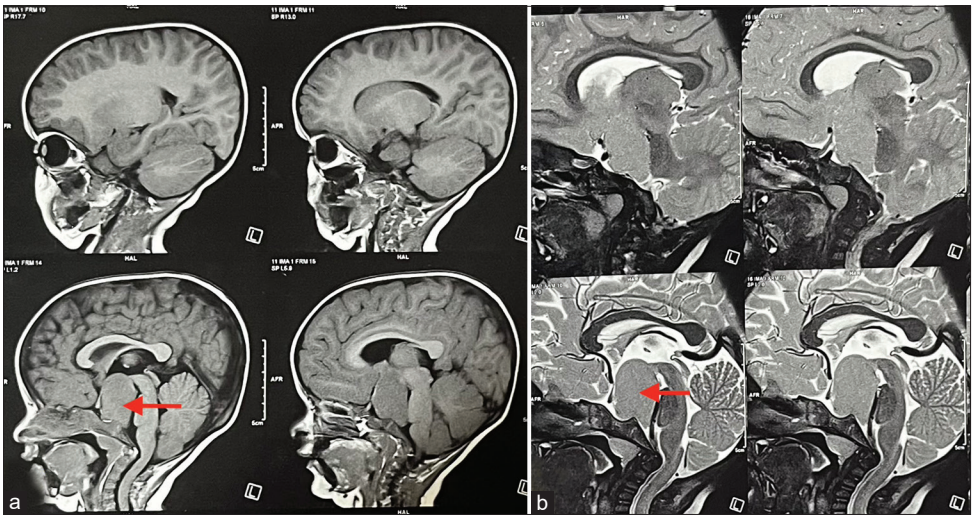

Figure 2: A 3-year-old girl with Pallister-hall syndrome who presented with short stature. (a) Magnetic resonance imaging brain T1-weighted images show a large hypothalamic hamartoma (arrow) isointense to gray matter. (b) T2-weighted images show the same mass (arrow) which is isointense to gray matter and measures 3.1 * 2.5 * 3.4 cm.

Table 1: Review of cases of Pallister-Hall syndrome reported from India.

Author(s)	Age at presentation/Gender	Clinical, biochemical and radiological findings	Genetic diagnosis
Chandra *et al*., 2017[9]	10 months/Male	Developmental delay, microcephaly, hypertelorism, cleft lip and palate, postaxial polydactyly type A with syndactyly, hypothalamic hamartoma	Not available
Jaiman *et al*., 2012[6]	Antenatal (39 weeks)	Intrauterine fetal death, hydrometrocolpos, Postaxial polydactyly Type A with syndactyly, anteriorly placed anus, atrial septal defect, bifid epiglottis, hypothalamic hamartoma, absent corticotrophs, adrenal and thyroid gland hypoplasia.	Not available

polydactyly in PHS, is non-specific with high incidence in persons of Central African descent and therefore should not be used as a diagnostic feature. Similarly, the presence of oligodactyly, such as that reported in a 2-year-old female child from Poland, is not characteristic of the condition and mandates a genetic diagnosis.[4]

Our patient was born to apparently normal parents, suggestive of a de novo mutation. It has been reported that only 25% of cases occur due to a *de novo* mutation and they have a more severe phenotype than inherited cases.[1] Although over 95% of cases of PHS are due to small intragenic deletions, insertions or missense, non-sense, and splice site variants, 5% of cases with no pathogenic variant in GLI3 have been reported, thus highlighting the importance of a clinical diagnosis.[2,5]

Polydactyly in a newborn should be thoroughly investigated, as it can aid in early diagnosis of this condition. Our case presented in early childhood, and the finding of HH was established after investigating the etiology of GHD. HH, although, the most commonly seen feature of PHS is asymptomatic in most cases and thus can be missed. Misdiagnosis of cases as non-syndromic isolated polydactyly is thought to be one of the reasons for the strikingly low prevalence of PHS.

If symptomatic, HH usually manifests with either isolated GHD, isolated precocious puberty or panhypopituitarism. Cortisol deficiency is more commonly seen in non-familial cases and is one of the causes of mortality in PHS, as described in a case of intrauterine fetal death with absent adrenocorticotrophs on immunohistochemistry of the pituitary gland, in Hyderabad, India.[6] Most cases of isolated GHD reported in the literature have a preserved intellect. In contrast, PHS may be associated with significant developmental delay, as seen in our case.[2]

PHS belongs to the cerebroacrovisceral early lethality group of disorders, largely owing to mortality related to panhypopituitarism or laryngotracheal clefts. However, most cases are benign and such categorization should be discouraged.[1]

Although previously reported in a case report on an infant with PHS in China, surgical removal of HH is contraindicated as it may result in complications and a lifelong need for hormone replacement.[7]

GLI3 gene mutations are known to cause a variety of other disorders such as Greig cephalopolysyndactyly syndrome, postaxial polydactyly Type A, pre-axial polydactyly Type IV, Acrocallosal syndrome, oral-facial-digital syndrome, non-syndromic neuronal migration abnormalities, and AR polydactyly syndrome, all having distinct phenotypes.[1,8]

There are numerous neurodevelopmental disorders associated with polydactyly such as Oral-facial-digital syndrome Type 6 and Holzgreve syndrome, both characterized by central polydactyly. Bardet-Biedl syndrome, Smith-Lemli-Opitz syndrome, McKusick-Kaufman syndrome, SMO-related HH-polydactyly, and Holt-Oram syndrome exhibit postaxial polydactyly in addition to other features and should be considered in the differential diagnosis of PHS.[1,9]

Evaluation should be thorough, wherein other pituitary hormone deficiencies (adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone) should be investigated as they can manifest later. Postaxial polydactyly can be distinguished from central polydactyly on a limb radiograph, wherein Y-shaped metacarpal or metatarsal will be seen in the latter, as in our case. MRI of the brain helps establish location and extent of the hamartoma. Renal ultrasonography should be performed to rule out renal anomalies. Genetic testing is performed for confirmation of diagnosis.[1]

Management primarily revolves around hormone replacement in hypopituitarism. In our case, the child was started on a standard dose of recombinant human growth hormone, administered routinely in GHD. Symptomatic treatment should be offered in case of seizures due to HH. Surgical correction of anatomical deformities such as polydactyly can be carried out on elective basis.[10] Since PHS is characterized by near complete penetrance, genetic counseling plays a key role in the management of this condition.

CONCLUSION

Diagnosed cases of PHS should undergo evaluation for deficiencies of all pituitary hormonal axes, as cortisol deficiency, if missed, can lead to critical consequences. Furthermore, such patients may later go on to develop precocious puberty, thus highlighting the importance of serial anthropometry and regular follow-up.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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