

## Pallister-Hall syndrome in a 2-years-old girl

### Zespół Pallistera-Hall u dwuletniej dziewczynki

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#### Abstract

**Introduction:** Pallister-Hall syndrome (PHS) is a rare autosomal dominant syndrome characterized by polydactyly, bifid or shortened epiglottis, visceral anomalies, hypothalamic hamartoma often combined with hypopituitarism. PHS is characterized by significant variability in the expression of clinical symptoms. The clinical course ranges from mild with a good prognosis to severe and which can lead to death during the neonatal period.

**Case report:** Two-years-old girl with facial dysmorphism, skeletal malformations of hand and feet and growth hormone deficiency. PHS was diagnosed on the basis of the presented symptoms and genetic tests.

**Summary:** Skeletal malformations, such as polydactyly or oligodactyly, are a markers which can be associated with endocrinological disorders. Quick and correct diagnosis would help in planning treatment during childhood and giving family counseling, including prenatal advice regarding the next pregnancy of the child's mother.

#### Key words:

Pallister-Hall syndrome, hypopituitarism, hamartoma, polydactyly.

#### Streszczenie

**Wprowadzenie:** Zespół Pallistera-Hall (PHS) jest rzadko występującym zespołem genetycznym, dziedziczonym autosomalnie dominująco. Objawami charakterystycznymi dla tego zespołu są: polidaktylia, podwójna lub skrócona nagłośnia, wady narządów wewnętrznych, częste występowanie zmian typu hamartoma w podwzgórzcu, niejednokrotnie połączone z niedoczynnością przysadki mózgowej. Zespół Pallistera-Hall charakteryzuje się znaczną zmiennością ekspresji objawów klinicznych. Opisywane są postacię łagodne, dobrze rokujące odnośnie do czasu przeżycia, jak i ciężkie, prowadzące do śmierci w okresie noworodkowym.

**Opis przypadku:** Dwuletnia dziewczynka z zaznaczonymi cechami dysmorficznymi twarzy, malformacjami kończyn oraz niedoborem hormonu wzrostu. Na podstawie prezentowanych objawów oraz badania genetycznego rozpoznano PHS.

**Podsumowanie:** Wady rozwojowe szkieletu, takie jak polidaktylia lub oligodaktylia, mogą być związane z zaburzeniami endokrynologicznymi. Szybka i prawidłowa diagnoza pomogłaby w planowaniu leczenia w dzieciństwie i udzielenie porady rodzinnej, w tym prenatalnej dotyczącej kolejnej ciąży matki dziecka.

#### Słowa kluczowe:

zespół Pallistera-Hall, niedoczynność przysadki, hamartoma, polidaktylia.

## Introduction

Pallister-Hall syndrome (PHS) is a rare, autosomal dominant disease first described in 1980 by Philip Pallister and Judith Hall [1]. To date, only 100 cases have been reported in the literature. Pallister-Hall syndrome is characterised by varying combinations of a spectrum of abnormalities: polydactyly, bifid epiglottis, cleft palate, high-arched palate, cleft palate, external ear anomalies, dysmorphic face with small retroverted nose with flat nasal bridge, vertical groove in the middle of the upper lip philtrum, and small tongue. Hypothalamic hamartomas are associated with hypopituitarism, growth hormone deficiency, and neurological disorders. Patients with PHS may have natal teeth, multiple frenula in the cheek, short limbs, dislocated hips, imperforate anus, renal and adrenal abnormalities, or cardiac defects. They may present micropenis or cryptorchidism [1–4] (Table I). This complex syndrome involves in 95% a mutation in the *GLI3* gene, which is located on the short arm of chromosome 7. This gene encodes zinc finger protein *GLI3*, a transcription repressor that is a mediator of sonic hedgehog signaling. The diagnosis should be confirmed by molecular testing of the *GLI3* zinc finger transcription factor gene on 7p13. Pathogenic variants in the *GLI3* gene are responsible for several conditions in addition to PHS, including postaxial polydactyly (PAP) type A and B. In 5% of people with clinical features, PHS has not been confirmed in *GLI3*. That suggests the existence other type of mutation. It is suspected that there may be many PHS cases that remain unidentified, either due to misdiagnosis and underdiagnosis with another polydactyly condition or because of a lack of awareness [5].

## Case report

Our patient is a two-year-old girl born from non-consanguineous, healthy parents after normal pregnancy. Based on medical history, it was the fifth gestation for the patient's mother and third labour, resolved via c-section at 40 weeks of gestation. The patient was born in general average condition (7/6/8/9 points in Apgar scale), body mass 3780 g, body length 54 cm. Because of respiratory problems, the patient was transferred to an Intensive Care Unit.

Due to congenital malformations, the patient was transferred to the Department of Neonatology in Wrocław in order to perform further diagnostics. The ultrasound of the central nervous system, heart, abdominal cavity and chest X-ray revealed no disorders. Whole exome sequencing (WES) identified the variant c.3454G>T, pGlu1152 in gene *GLI3*. On the basis of the WES results, PHS was diagnosed. Because of recurrent urinary tract infections, ultrasound of the urinary tract and cystography were performed. The results revealed vesicoureteral reflux (VUR) grade III/IV. The patient was transferred to the Department and Clinic of Endocrinology and Diabetology for Children and Adolescents to assess the severity of hormonal disorders. Physical examination revealed symptoms typical for PHS: retardation of psychomotor development, decreased muscle

tension, craniofacial dysmorphic features: prominent forehead, low-set ears, micrognathia, "gothic" palate, and tooth and nail malformations; oligodactyly of the right hand (lack of the one finger), dysmorphic features of left hand (brachydactyly, short phalanges, short hand, wrong palmar crease), proximal shortening of upper and lower limbs, dysmorphia of feet (short metatarsus, brachydactyly, wide toe position, forefoot adduction, and laryngomalacia. Auxological examination: height 63.5 cm – below third percentile (SDS –4.6), and body mass 8 kg (3<sup>rd</sup>–10<sup>th</sup> percentile for sex and age). Laboratory results, performed during hospitalisation in the clinic, revealed decreased concentration of IGF-1, decreased concentration of IGFBP3 protein, and total growth hormone deficiency (assessed on the basis of nocturnal release of growth hormone; Table II). The MRI scan of the brain and brainstem revealed a solid mass in the area of the sella turcica, well separated from the surrounding tissue, of dimensions 3 × 2 × 4 cm, not susceptible to contrast enhancement, modulating the pituitary funnel, the intersection of optic nerves, midbrain, and pons varoli, and protruding into the third ventricle. The MRI scan also revealed small pituitary gland (2 mm in diameter), misplaced with pituitary funnel anteriorly through the tumour.

Based on MRI scan, hamartoma within tuber cinereum was diagnosed. The gynaecologist who consulted the patient stated normal external urogenital organs adequate to age and sex, narrowed vestibule of the vagina, retracted urethral meatus, a lineal rupture of the mucosa from vagina to the anus and anal fissure. The patient is currently under multidisciplinary care (endocrinologist, nephrologist, neurologist, laryngologist, orthopaedist, speech therapist) and is undergoing intensive

**Table I.** Major manifestations of PHS

Major manifestations of PHS	Frequency
CNS:	
<b>Hypothalamic hamartoma</b>	+++
Other malformations	+
Limb:	
<b>Polydactyly</b>	+++
<b>A. central with metacarpal bones</b>	
<b>3<sup>rd</sup> and 4<sup>th</sup> fingers are Y-shaped</b>	
<b>B. postaxial</b>	
<b>Dysplastic nails</b>	+++
Syndactyly	++
Craniofacial dysmorphic:	
<b>Bifid epiglottis</b>	++
Ear anomalies	++
Broad or flat nasal bridge	+
Short or anteverted nose	+

**Table II.** Laboratory results

GH ng/dl	GH ng/dl	GH ng/dl	GH ng/dl	GH ng/dl	GH ng/dl	150'	180'
	0.14		0.13	0.16	0.23	0.12	0.3
GH after glucagon ng/dl	0.10	–	–	0.07	0.12	0.27	0.14
GH after clonidine ng/dl	0.15	0.38	0.24	0.27	0.17	–	–
IGF-1 <15 ng/ml N: 55–327	IGFBP-3 <0.5 µg/ml N: 0.7–3.6	TSH 4.3 µIU/ml N: 0.33–6.3	ft4 15.3 pmol/l N: 8.36–29.6	ACTH 8.02 pg/ml N: do 46	Cortisol 11.4 µg/ml N: 3.7–19.4	Fasting glycemia 76 mg/dl N: 70–99	Total cholesterol 228 mg/dl N: do 190

rehabilitation. At the age of 17<sup>th</sup> months the patient underwent a cystoscopy of misplaced ureteric orifice with concomitant injections with Deflux solution. To date, except for growth hormone deficiency, no other disorders of endocrine secretion have been diagnosed. Currently she is two years old with height 70.5 cm (below the third percentile [SDS –6.0]) and body mass 9.1 kg (3<sup>rd</sup>–10<sup>th</sup> percentile for sex and age). We have completed the endocrinological diagnostics pertaining to growth hormone release after stimulation tests and bone age (Table II). The patient is currently being prepared for treatment with growth hormone. The patient requires further careful endocrinological observation. Special attention should be paid to further functioning of pituitary and adrenal glands.

### Discussion

Pallister-Hall syndrome is a developmental disorder inherited in an autosomal dominant pattern. PHS is caused by mutation in the *GLI3* gene located in the short arm of chromosome 7, locus 7p13, encoding the transcription factor between zinc finger-binding domain and the place of proteolytic breakdown. The *GLI3* gene consists of 15 exons and encodes the protein comprised of 1580 amino acids. Over 36 mutations of the gene have been found in PHS patients. As a result of the mutation, the stop codon occurs precociously. Many cases of PHS are the result of de novo mutation, as in the case of our patient. Usually, patients with de novo mutation express more severe clinical symptoms. The risk of passing the mutation to offspring is estimated at 50%. Every child of a patient with PHS has a 50% chance of inheriting the mutation in the *GLI3* gene. It has been observed that the offspring often present similar clinical symptoms to those presented in their parents. The risk for the offspring of isolated hypothalamus hamartoma

caused by mutation in *GLI3* gene is unclear [5, 6]. There was one case of germinal mosaicism reported in the literature (presence of the mutation in some reproductive cells of one of the parents) [7]. To diagnose PHS, there must be co-occurrence of phenotypic symptoms, polydactyly, and hamartoma-type lesions in hypothalamus. Clinical diagnosis of sub-PHS can be made based on the presence of oligodactyly/polydactyly/hypothalamic hamartoma and at least one of following disorders: double epiglottis, hypoplastic pituitary gland, growth hormone deficiency, hypoplastic nails, genital organs disorders, and anal atresia. The main manifestation of PHS in our patient was hypothalamic hamartoma. On the other hand, the oligodactyly of her right hand and craniofacial dysmorphism were the initial manifestations that led to the genetic investigation. An MRI of the brain demonstrated the presence of hypothalamic hamartoma, which is a benign tumour that does not need surgical treatment. Other problems are associated with its localisation, which can cause epilepsy, endocrine disorders with hypopituitarism, and most commonly central precocious puberty [7–9]. It is often a cause of neurological symptoms including epilepsy. Contrary to patients with isolated HH, seizures are usually well controlled with anticonvulsant medication [10]. We have not observed any neurological, ophthalmic, or laryngological disorders, but deletion of the *GLI3* gene may lead to hearing impairment [11]. The mentioned case of PHS was not associated with bifid epiglottis. According to the literature, this symptom is observed in 40% of patients with PHS. In most cases it is asymptomatic but can occur concomitantly with dysphagia and dyspnoea [3, 12]. Limb malformations may range from dysplastic nails to post-axial polydactyly. We observed in our patient hypoplastic nails, oligodactyly of the right hand, dysmorphism of the left hand and feet, and proximal shortening of the limbs. The patient started to walk shortly before two years of age; to date there has been no need for surgical intervention, only continued rehabilitation. In

limb malformations many syndromes may overlap. It is mandatory to go beyond skeletal abnormalities to search for associated manifestations because the co-occurrence of hypothalamic hamartoma is always a signature of PHS, as in our case [13]. According to Roscioli *et al.*, the specific mutation of the *GLI3* gene determines the presence of severe skeletal abnormalities in patients with PHS. The authors conclude that examination toward PHS should be included in differential diagnosis before surgical procedures performed because of acromesomelic shortening of the limbs or hypoplasia of fibula, especially with polydactyly [14]. Our patient suffers from short stature, and we have confirmed growth hormone deficiency. Severe hypoglycaemia was not noted, but we plan to introduce treatment with growth hormone as quickly as possible. The studies provide no evidence that GH treatment increases the tumour progression. There was no change in tumour size and no tumour progression [15]. Other symptoms associated with PHS observed in our patient were: misplaced ureters with bilateral vesicoureteral reflux, suspected proximal placement of the anus, and narrowing of the vagina. Some authors suggest that micropenis and cryptorchidism in boys with PHS are caused by diminished secretion of gonadotropins during foetal development. It is also possible that hypopituitarism caused by disruption of the relationship between the pituitary gland and hypothalamus due to

hypothalamic hamartoma, can be also a cause of malformations in vaginal structure in girls with PHS [16]. On the other hand, according to Narumi *et al.*, malformations in urogenital organs in patients with PHS are caused by mutation of the *GLI3* gene, and not by hormonal disorders. The authors suggest performing the examination towards malformations of urogenital organs in patients with PHS, even without hypopituitarism [17]. A significant factor associated with PHS is retardation of psychomotor development, which was also present in our patient. Improved knowledge of PHS symptoms may allow better diagnosis and management of this condition in the future, including prenatal care of the mothers of children with PHS and mothers with PHS. Families are offered prenatal examination and genetic diagnostics of the foetus.

## Summary

Polydactyly is a marker associated with endocrinological disorders, and it can be the first manifestation of PHS. An early genetic diagnostic process is necessary to identify the genetic syndrome. A quick and accurate diagnosis will help in planning treatment during childhood and for family counselling, including prenatal advice regarding the mother's subsequent pregnancy.

## References

1. Biesecker L, Graham Jr J. Pallister-Hall syndrome. *J Med Genet* 1996; 33: 585–589.
2. Chandra S, Daryappa M, Mudabbir M, et al. Pallister-Hall syndrome. *J Pediatr Neurosci*. 2017; 12: 276–279. doi: 10.4103/jpn.JPN\_101\_17
3. Kraus M, Diu M. Bifid epiglottis in a patient with Pallister-Hall syndrome. *Can J Anesth* 2016; 63: 1197–1198. doi: 10.1007/s12630-016-0686-y
4. Al-Qattan MM, Shamseldin HE, Salih MA, Alkuraya FS. *GLI3*-related polydactyly: a review. *Clinical Genetics* 2017; 92: 457–466.
5. Démurger F, Ichkou A, Mougou-Zerelli S. New insights into genotype-phenotype correlation for *GLI3* mutations. *Eur J Hum Genet* 2015; 23: 92–102. doi: 10.1038/ejhg.2014.62
6. Ng D, Johnston JJ, Turner JT, et al. Gonadal mosaicism in severe Pallister-Hall syndrome. *Am J Med Genet A* 2004; 30: 124A: 296–302.
7. Mundlos S, Horn D. Pallister-Hall Syndrome. *Limb Malformations* 2014; 61–62.
8. Courtney E, Swee D, Shak D, et al. A delayed diagnosis of Palmister-Hall syndrome in an adult male following the incidental detection of a hypothalamic hamartoma. *Human Genome Variation* 2018; 5: 31.
9. Dunham C, McFadden D, Dahlgren L, et al. Congenital Hypothalamic “Hamartoblastoma” Versus “Hamartoma”. *Pediatr Dev Pathol* 2018; 21: 324–331. doi: 10.1177/1093526617701338
10. Boudreau E, Liow K, Frattali C et al. Hypopyhalamic hamartomas and seizures: distinct natural history of isolated and Pallister-Hall syndrome cases. *Epilepsia* 2005; 46: 42–47. doi: 10.1111/j.0013-9580.2005.68303.x
11. Avula S, Alam N, Roberts E. Cochlear abnormality in a case of Pallister-Hall syndrome. *Pediatr Radiol* 2012; 42: 1502–1505. doi: 10.1007/s00247-012-2458-3.
12. Stevens CA, Ledbetter JC. Significance of bifid epiglottis. *Am J Med Genet A* 2005; 134: 447–449. doi: 10.1002/ajmg.a.30659
13. Lacerda L, Alves UD, Zanier JF, et al. Differential diagnoses of overgrowth syndrome: the most important clinical and radiological disease manifestations. *Radiol Res Pract* 2014; 947451.
14. Roscioli T, Kennedy D, Cui J, et al. Pallister-Hall syndrome: unreported skeletal features of a *GLI3* mutation. *Am J Med Genet A* 2005; 136A: 390–394. doi: 10.1002/ajmg.a.30818
15. Van Varsseveld NC, Van Bunderen CC, Franken AA et al. Tumor recurrence of regrowth in adults with nonfunctioning pituitary adenomas using GH replacement therapy. *J Clin Endocrine Metab* 2015; 100: 3132–3139. doi: 10.1210/jc.2015-1764
16. Hayek F. Pallister-Hall syndrome with orofacial narrowing and tethered cord: a case report. *J Med Case Rep* 2018; 12: 354. doi: 10.1186/s13256-018-1868-8.
17. Narumi Y, Kosho T, Tsuruta G, et al. Genital abnormalities in Pallister-Hall syndrome: Report of two patients and review of the literature. *Am J Med Genet A* 2010; 152A: 3143–3147. doi: 10.1002/ajmg.a.33720.