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 dysmorphia, 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.
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 characterized by varying combinations of a spectrum of abnormalities: polydactyly, bifid epiglottis, cleft palate, high-arched palate, cleft lip, 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 microenpes 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 signalling. 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 Wroclaw 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; oligodonty 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, dysmorphism 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 (3rd–10th 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 $3 \times 2 \times 4$ 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 treatment.

Table I. Major manifestations of PHS

| Major manifestations of PHS                  | Frequency |
|---------------------------------------------|-----------|
| CNS: Hypothalamic hamartoma                 | +++       |
| Other malformations                         | +         |
| Limb: Polydactyly                           | +++       |
| A. central with metacarpal bones            |           |
| 3rd and 4th fingers are Y-shaped            |           |
| B. postaxial                               |           |
| Dysplastic nails                            | +++       |
| Syndactyly                                  | +         |
| Craniofacial dysmorphic:                    |           |
| Bifid epiglottis                            | ++        |
| Ear anomalies                               | ++        |
| Broad or flat nasal bridge                  | +         |
| Short or anteverted nose                    | +         |
rehabilitation. At the age of 17th 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 (3rd–10th 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 hypothalamic 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 dysmorphia 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, dysmorphia 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.

**Table II. Laboratory results**

|               | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | 150’ GH  | 180’ GH |
|---------------|----------|----------|----------|----------|----------|----------|----------|----------|
| GH after glucagon | 0.10     | –        | –        | 0.07     | 0.12     | 0.27     | 0.14     |
| GH after clonidine | 0.15     | 0.38     | 0.24     | 0.27     | 0.17     | –        | –        |
| IGF-1         | <15 ng/ml| <0.5 µg/ml| 4.3 µU/ml| 15.3 pmol/l| ACTH | 8.02 pg/ml | Cortisol | 11.4 µg/ml |
| N: 55–327     | N: 0.7–3.6| N: 0.33–6.3| N: 8.36–29.6| | Fasting glycemia | N: 3.7–19.4 | 76 mg/dl | 228 mg/dl |
|               | IGF-1    | TSH      | ft4      | ACTH     | Cortisol | Fasting glycemia | Total cholesterol | |
|               | <15 ng/ml| <0.5 µg/ml| 4.3 µU/ml| 15.3 pmol/l| ACTH | 8.02 pg/ml | Cortisol | 11.4 µg/ml |
| N: 55–327     | N: 0.7–3.6| N: 0.33–6.3| N: 8.36–29.6| | Fasting glycemia | N: 3.7–19.4 | 76 mg/dl | 228 mg/dl |

|               | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | 150’ | 180’ |
|---------------|----------|----------|----------|----------|----------|----------|------|------|
| GH after glucagon | 0.10     | –        | –        | 0.07     | 0.12     | 0.27     | 0.14     |
| GH after clonidine | 0.15     | 0.38     | 0.24     | 0.27     | 0.17     | –        | –        |
| IGF-1         | <15 ng/ml| <0.5 µg/ml| 4.3 µU/ml| 15.3 pmol/l| ACTH | 8.02 pg/ml | Cortisol | 11.4 µg/ml |
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| N: 55–327     | N: 0.7–3.6| N: 0.33–6.3| N: 8.36–29.6| | Fasting glycemia | N: 3.7–19.4 | 76 mg/dl | 228 mg/dl |

|               | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | GH ng/dl | 150’ | 180’ |
|---------------|----------|----------|----------|----------|----------|----------|------|------|
| GH after glucagon | 0.10     | –        | –        | 0.07     | 0.12     | 0.27     | 0.14     |
| GH after clonidine | 0.15     | 0.38     | 0.24     | 0.27     | 0.17     | –        | –        |
| IGF-1         | <15 ng/ml| <0.5 µg/ml| 4.3 µU/ml| 15.3 pmol/l| ACTH | 8.02 pg/ml | Cortisol | 11.4 µg/ml |
| N: 55–327     | N: 0.7–3.6| N: 0.33–6.3| N: 8.36–29.6| | Fasting glycemia | N: 3.7–19.4 | 76 mg/dl | 228 mg/dl |
|               | IGF-1    | TSH      | ft4      | ACTH     | Cortisol | Fasting glycemia | Total cholesterol | |
|               | <15 ng/ml| <0.5 µg/ml| 4.3 µU/ml| 15.3 pmol/l| ACTH | 8.02 pg/ml | Cortisol | 11.4 µg/ml |
| N: 55–327     | N: 0.7–3.6| N: 0.33–6.3| N: 8.36–29.6| | Fasting glycemia | N: 3.7–19.4 | 76 mg/dl | 228 mg/dl |
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 [3]. 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.

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