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Panhypopituitary insufficiency in a patient with clinical diagnosis of Chitayat-Hall syndrome

Wielohormonalna niedoczynność przysadki u pacjenta z klinicznym rozpoznaniem zespołu Chitayat-Hall

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Abstract

We report an 8-year-old proband with severe motor and intellectual disability presenting a variety of dysmorphic features such as microcephaly, prominent glabella (ridged metopic suture) and congenital distal limb contractures. As well as panhypopituitary insufficiency, brain defects, *e.g.* agenesis of corpus callosum, colpocephaly, and pachygyria as well as strabismus and tracheo-laryngeal hypoplasia, were diagnosed. Genetic examination revealed a normal karyotype and excluded Wolf-Hirschhorn syndrome and subtelomeric deletions. Chitayat-Hall syndrome was diagnosed based on clinical traits. **(Pol J Endocrinol 2010; 61 (3): 318–321)**

Key words: *Chitayat-Hall syndrome, congenital distal limb contractures, panhypopituitarism, facial dysmorphism*

Streszczenie

W pracy przedstawiono opis przypadku chorobowego 8-letniej dziewczynki z głębokim opóźnieniem rozwoju psychoruchowego i intelektualnego, prezentującego szereg różnych cech dysmorficznych, takich jak: małogłowie, wydatna gładzizna oraz wrodzone przykurcze dystalnych części kończyn. Ponadto u dziecka rozpoznano wielohormonalną niedoczynność przysadki, wady mózgowia, takie jak: agenezja ciała modzelowatego, nadmiernie szerokie zakręty mózgu oraz kolpocefalia, a także zez, wiotkość krtani i tchawicy. W wykonanych badaniach genetycznych wykazano prawidłowy kariotyp żeński, wykluczono zespół Wolfa-Hirschhorna oraz delecje subtelomerowe, ponadto w porównawczej hybrydyzacji genomowej (CGH) nie wykazano nieprawidłowości. Na podstawie całości obrazu klinicznego postawiono u pacjentki rozpoznanie zespołu Chitayat-Hall. **(Endokrynol Pol 2010; 61 (3): 318–321)**

Słowa kluczowe: *zespół Chitayat-Hall, wrodzone przykurcze dystalnych części kończyn, panhipopituitaryzm, dysmorfia twarzy*

Introduction

Chitayat–Hall syndrome (OMIM #208080) is a rare, severe disorder with autosomal recessive inheritance. The clinical traits are very heterogeneous. The most important symptoms include neurological anomalies and intellectual disability, distal joint contractures and characteristic dysmorphic features, as well as respiratory system and skeletal anomalies and endocrine abnormalities concerning the pituitary gland.

We present an 8-year-old female proband with severe intellectual disability, distinctive facial dysmorphism: contractures and panhypopituitarism clinically diagnosed as Chitayat-Hall syndrome.

Case report

An 8-year-old girl born to a G4P3 was referred to the Genetics Department for genetic counselling because of psychomotor delay followed by mental and physical retardation as well as dysmorphic features. The propositа was born to unrelated parents, her family and prenatal history was unremarkable. Mother excluded known teratogen exposure during pregnancy. The parameters at birth were as follows: birth weight — 2850 g, OFC (occipitofrontal circumference) — 32 cm, 7 Apgar points. The newborn was hospitalized on the neonatal ward because of an apnoea episode, hypoglycaemia respiratory insufficiency and bradycardia. Toxoplasmosis,

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cytomegaly infection, and internal defects were excluded. Hearing test results was normal.

The hypotonia and retardation of growth development and distal arthrogryposis were observed in infanthood. The milestones in psychomotor development were delayed (she started to sit at 2 years of age, walking at 4 years), and her crying was high pitched.

Many hospitalizations occurred during early childhood. The girl was admitted to the Department of Endocrinology for Children and Adolescents for the first time at the age of four because of the recurrent hypoglycaemic episodes. A hormone examination revealed regular tropic hormone levels. Stimulating tests with Synacthen and TSH were performed and in both cases the results were normal. An excessive insulin projection on the blood glucose curve was not found, although a low growth hormone (GH) level was observed (the nocturnal profile of GH, dynamic tests with clonidine and glucagon). The hypoglycaemic episodes were not observed for two years. Subesquently, neuroglycopenia during an infection of the respiratory tract was the reason for a second, sudden hospitalization. Lower ACTH and TSH levels with adrenocortical insufficiency and hypothyroidism as well as low GH projection (in the nocturnal profile and the dynamic tests — below 1 ng/ml) were diagnosed. The above results confirmed panhypopituitary insufficiency. L-thyroxine, hydrocortisone, and growth hormone were introduced into therapy. MRI of the brain revealed a small pituitary gland, agenesis of the corpus callosum, mild deformation of the brain ventricles (colpocephaly), pachygyria, septum pellucidum absence, and the anterior part of cerebral falx hypoplasia. Additional examinations revealed strabismus, tracheo-laryngeal hypoplasia, and abnormal EEG. Metabolic disorders were excluded in GC-MS and tandem MS tests. Normal levels of 7-dehydrocholesterol in blood serum were revealed.

Clinical evaluation at the 8-year-old showed intellectual disability and delayed speech development as well as severe microsomia: body weight 13 kg (7 kg below third percentile, –4.3 SDS), height 86 cm (30 cm below third percentile, –8.4 SDS), and head circumstance 43 cm (7 cm below third percentile, –7.2 SDS). The patient presented a variety of facial dysmorphic features including microcephaly, bitemporal narrowing, prominent glabella (ridged metopic suture), epicanthic fold, ptosis, strabismus, expressionless face, small tipped nose, anteverted nares, hypoplastic, low-set ears, high palate, long philtrum, down-turned corners of the mouth, thin upper lip, micrognathia and a short, wide neck (Fig. 1). Moreover, she had small hands and feet, camptodactyly, clinodactyly, distal arthrogryposis, deformation of the thorax, wide-spaced nipples, scoliosis, and hypoplastic external genitalia.

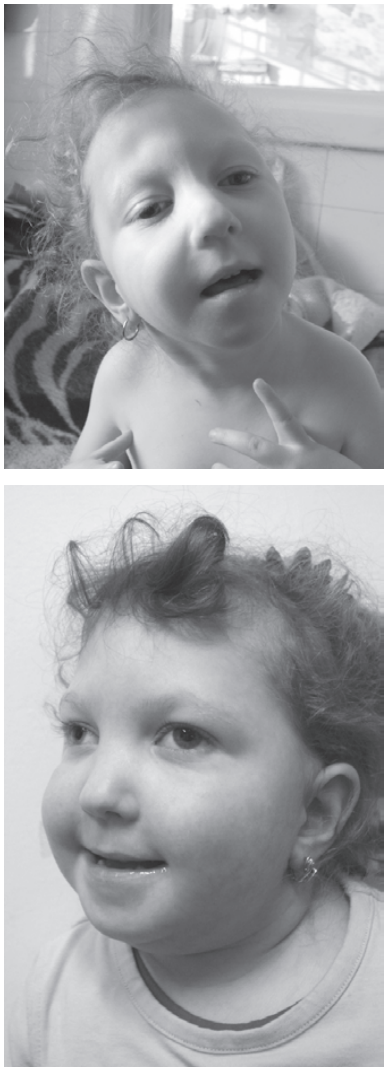

Figure 1A, B. The phenotype of Chitayat-Hall syndrome in a patient with panhypopituitarism

Rycina 1A, B. Fenotyp pacjenta z zespołem Chitayat-Hall oraz z wielohormonalną niedoczynnością przysadki

Genetic analysis

A venous blood sample was taken from the patient to perform karyotyping and fluorescence *in situ* hybridization studies. Chromosomal analysis was performed according to standard procedures and G-banding at 550-band level revealed a normal, female karyotype. FISH studies excluded subtelomeric deletions and Wolf––Hirschhorn syndrome (4p microdeletion). The patient's DNA was investigated by comparative genomic hybridization (Vysis, Abbott Molecular, USA) carried out

Table I. *A comparison clinical features of Chitayat-Hall syndrome patients with previously described cases and ours*
Tabela I. *Dane kliniczne pacjentów z zespołem Chitayat-Hall opisanych w literaturze*

Clinical traits and other disorders	Chitayat et al. 1990		Chitayat et al. 1991		Wortmann et al. 2007	Smigiel et al. 2009
	Pat. 1	Pat. 2	Pat. 1	Pat. 2		
Square shaped head	+	+	+	–	+	+
Narrow forehead	+	+	+	–	+	+
Ridges over sutures	+	+	+	–	+	+
Small anterior fontanelle	+	–	+	–	–	–
Hypertelorism	–	–	–	–	–	–
Ptosis	–	–	+	–	–	–
Nystagmus	–	+	–	–	–	–
Strabismus	–	–	–	–	+	+
Myopathic face	–	–	+	–	+	+
Depressed nasal bridge	+	+	+	–	+	+
Hypoplastic malar areas	+	+	+	–	+	+
Highly arched palate	+	+	+	–	+	+
Chubby cheeks	+	+	+	–	+	+
Retrognathia	+	+	+	–	+	+
Ear deformation	+	+	+	–	+	+
Posteriorly angulated ears	+	–	+	–	–	+
Short neck	–	+	+	–	+	+
Increased fatty tissue and decreased muscle mass	+	+	+	+	+	+
Ulnar deviation	+	–	+	–	–	–
Radio-ulnar synostosis	+	–	–	–	–	–
Distal arthrogryposis	+	+	+	+	+	+
Adducted thumbs	+	+	+	–	+	+
Subluxation of proximal radius	+	–	–	–	–	–
Dimples over the knuckles	+	+	+	–	–	–
Fingers overlapping (2^{th}, 5^{th}/3^{rd}, 4^{th})	+	+	+	–	+	+
Palmar creases	+	+	+	–	+	–
Hypoplasia of thenar and hypothenar	+	–	+	–	+	+
Chest deformations	+	+	+	–	+	+
Scoliosis	+	–	+	–	–	–
Dislocated hips	+	–	+	–	–	–
Hallux valgus	–	–	+	–	–	–
Hammer toes	+	–	+	–	–	–
Respiratory system defects	+	+	+	+	+	+
Enlarged thymus	–	+	–	–	–	–
Apneic episodes	+	+	+	–	–	+
Bradycardia	+	+	+	–	–	+
Hypoglycaemia	+	–	–	–	–	+
Hypopituitarism	+	+	–	–	–	+
Secondary hypothyroidism	+	–	–	–	–	–
Hypoplasia of labia minora	–	–	+	–	–	–
Cryptorchismus	–	+	–	–	–	–
Hydronephrosis	–		–	+	–	–
Cystic dysplastic foci in kidneys	–	+	–	–	–	–
Bilateral pelviectasis	+	–	–	–	–	–
Dilatation of ureters	–	–	–	+	–	–
Physical and mental development delay	+	+	+	–	+	+
Seizures	+	–	–	–	+	–
Pachygyria	+	–	–	–	+	+
Decreased cerebral tissue	+	–	–	–	–	–
Enlarged ventricles	+	–	+	+	–	+
Subgaleal haemorrhage	–	–	–	+	–	–
Epidural haemorrhage	–	–	–	+	–	–
Agenesis/hypogenesis of corpus callosum	–	–	–	–	–	+
Septum pellucidum absence	–	–	–	–	–	+

according to the manufacturer's protocol. Normal female reference DNA was used as a control. No ratio profile imbalances were detected in the proband.

Discussion

In 1990 David Chitayat reported two siblings — a brother and a sister with distal arthropathy, hypopituitarism, mental retardation, and characteristic pattern of facial dysmorphism [1]. The brother died at the age of three months for unknown reasons. The sister developed deficiency of growth hormone and responded to hormonotherapy. The occurrence in two sibs of different sex suggests autosomal recessive inheritance, although the affected gene was not described. One year later Chitayat presented two other siblings with similar symptoms such as characteristic facial dysmorphic features and distal arthrogryposis [2]. One of them died shortly after delivery because of respiratory failure due to lung hypoplasia. The second sibling developed severe mental retardation.

Chitayat-Hall syndrome includes a variety of skull and face dysmorphisms such as brachycephaly, microcephaly, or trigonocephaly. Cranial sutures are often ridged and fontanelles begin to close early. The face has a round shape with full cheeks. Facial features include also a prominent forehead, low-set, prominent and posteriorly rotated ears with absent or hypoplastic ear lobules, short, up-slanting palpebral fissures, telecanthus, and sparse or decreased eyebrows with lateral hypoplasia. Small, short, and upturned nose with depressed nasal bridge or anteverted nares is a common finding in Chitayat-Hall syndrome [2, 3]. The clinical features found in our patient overlap with those reported by Chitayat and other authors (Fig. 1, Table I).

The most significant features for diagnosis of Chitayat-Hall syndrome are congenital distal limb contractures. Bamshad and co-workers defined this anomaly as a consequence of foetal hypokinesis due to congenital myopathies, neuropathies, central nervous system disorders, or connective tissue abnormalities [4]. On the other hand, distal arthrogryposis is defined as an inherited primary limb malformation, characterized by congenital contractures of at least two areas without primary neurologic and/or muscle disease affecting limb function [5, 6]. Chitayat and co-workers used the term distal arthrogryposis. It is suggested that central nervous system anomalies are responsible for the congenital contractures in Chitayat-Hall syndrome. In our case with Chitayat-Hall syndrome we confirm the hypothesis that the congenital limb contractures are due to brain anomalies.

The cases described in literature by Chitayat et al. are linked by panhypopituitarism, which was diagnosed at the age of six in our patient. Pituitary gland abnormalities were confirmed by brain imaging [7, 8]. What is interesting is that endocrine tests performed during the first hospitalization on the endocrinology ward showed normal hormone concentrations. After that, a severe neurohypoglycaemic episode revealed panhypopituitarism. Substitution treatment was successful and prevented hypoglycaemic attacks.

In the presented case, the girl has clinical traits overlapping with those observed in Chitayat-Hall syndrome. The phenotype is highly variable and the gene responsible for it is still unknown. Hence clinical diagnosis is difficult. We hope that additional reported cases will contribute to establishing the diagnostic and treatment criteria for this rare dysmorphic syndrome and will help to find the affected gene.

References

1. Chitayat D, Hall JG, Couch RM et al. Syndrome of mental retardation, facial anomalies, hypopituitarism, and distal arthrogryposis in sibs. Am J Med Genet 1990; 37: 65–70.
2. Chitayat D, Hodgkinson KA, Blaichman S et al. Syndrome of mental retardation and distal arthrogryposis in sibs. Am J Med Genet 1991; 41: 49–51.
3. Wortmann SB, Rodenburg R, Schwahn B et al. Distal joint contractures, mental retardation, characteristic face and growth retardation: Chitayat syndrome revisited. Genet Couns 2007; 18: 119–123.
4. Bamshad M, Jorde LB, Carey JC. A revised and extended classification of distal arthrogryposes. Am J Med Genet 1991; 65: 277–281.
5. Boles RG. Cleft palate, ptosis, digital anomalies and mental retardation: a new syndrome or a distal arthrogryposis variant? Clin Dysmorphol 1999; 8: 63–65.
6. Schrander-Stumpel CT, Fryns JP, Schrander JJ et al. Distal arthrogryposis, specific facial dysmorphism and psychomotor retardation: a recognizable entity in surviving patients with the fetal akinesia deformation sequence. Genet Couns 1991; 2: 69–75.
7. Pisarek H, Pawlikowski M, Kunert-Radek J et al. Expression of somatostatin receptor subtypes in human pituitary adenomas – immunohistochemical studies. Endokrynol Pol 2009, 60: 240–251.
8. Gut P, Kosowicz J, Ziemnicka K et al. The incidence of the pituitary autoantibodies in Addison disease. Endokrynol Pol 2008, 59: 490–494.