CONGENITAL HYPOPITUITARISM WITH MONOSOMY OF CHROMOSOME 18

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Congenital hypopituitarism is a rare disease. It can be caused by isolated inborn defects of the pituitary, gene mutations (*PROP1, PIT1*), and chromosomal abnormalities.
Deletions of chromosome 18 (De Grouchy syndrome types 1 and 2) are a group of rare genetic diseases with a frequency of 1:50,000. Hypopituitarism in these syndromes is detected in from 13 to 56% of cases and depends on the size and location of the deleted segment.
We have described a series of clinical cases of patients with congenital hypopituitarism due to deletions in chromosome 18. All children had a characteristic dysmorphic features and delayed mental and speech development. Within first months of life, patients developed muscular hypotension, dysphagia, and respiratory disorders. The patients had various congenital malformations in combination with hypopituitarism (isolated growth hormone deficiency and multiple pituitary-hormone deficiencies). In the neonatal period, there were the presence of hypoglycemia in combination with cholestasis. Hormone replacement therapy led to rapid relief of symptoms.
Chromosomal microarray analysis in 2 patients allowed us to identify exact location of deleted area and deleted genes and optimize further management for them.

KEYWORDS: congenital hypopituitarism; De Grouchy syndrome; monosomy 18p-; monosomy 18q-; hypoglycemia; cholestasis.

ВРОЖДЕННЫЙ ГИПОПИТУИТАРИЗМ ПРИ ДЕЛЕЦИЯХ 18 ХРОМОСОМЫ

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Врожденный гипопитуитаризм — редкое заболевание, причиной которого могут быть изолированные пороки развития хиазмально-селлярной области, мутации генов, участвующих в развитии гипофиза (например, *PROP1, PIT1*), и хромосомные нарушения.
Делеции 18 хромосомы (синдром De Grouchy 1 и 2 типов) — группа редких генетических заболеваний с частотой встречаемости 1:50 000. Гипопитуитаризм при данном синдроме выявляется в 13–56% случаев и зависит от размера и локализации делеции.
В статье описана серия клинических случаев врожденного гипопитуитаризма при делециях короткого и длинного плеч 18 хромосомы.
Все дети имели характерные стигмы дизэмбриогенеза и задержку психоречевого развития различной степени выраженности. Обращало на себя внимание наличие мышечной гипотонии, дисфагии, дыхательных нарушений в раннем неонатальном периоде. У пациентов отмечалось наличие различных врожденных пороков развития в сочетании с гипопитуитаризмом, проявления которого варьировали от изолированного СТГ-дефицита до множественных тропных недостаточностей аденогипофиза. Особенностью течения гипопитуитаризма в период новорожденности являлось наличие рецидивирующих гипогликемий в сочетании с синдромом холестаза, которые быстро купировались на фоне заместительной гормональной терапии.
Двум пациентам проводился хромосомный микроматричный анализ, при помощи которого были определены точная локализация области делеции и гены, выпавшие при данном дефекте, что позволило оптимизировать тактику дальнейшего ведения.

КЛЮЧЕВЫЕ СЛОВА: врожденный гипопитуитаризм; синдром De Grouchy; моносомия 18p-; моносомия 18q-; гипогликемия, холестаз.

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RELEVANCE

Deletions of chromosome 18 (18p monosomy, 18p- syndrome, partial 18p monosomy, 18q monosomy, 18q- syndrome) are a group of rare genetic diseases with a frequency around 1:50,000. The phenotype of patients with deletion of the short arm was first described by Jean de Grouchy in 1963 [1]. De Grouchy syndrome types 1 (deletion of the short arm of chromosome 18) and 2 (deletion of the long arm of chromosome 18) were subsequently identified. In either type, the syndrome may involve congenital hypopituitarism (14% to 56% of cases), which is often associated with other congenital anomalies and concomitant conditions [2, 3].

With 18p- monosomy (OMIM #146390), deletions most often occur de novo (89%) and are more frequent in girls (2/3). Short arm monosomy most often occurs in the mother's chromosome and in 50% cases takes place in the centromeric side [4]. Phenotypical manifestations in patients include delayed mental development (average IQ = 69), delayed growth, delayed speech development, holoprosencephaly-related anomalies, ptosis and specific phenotypical characteristics (flat nasal dorsum, wide mouth with short upper lip, micrognathia, protruding ears, short neck with pterygoid folds, kyphoscoliosis). Hypopituitarism is found in 13% of 18p- syndrome cases and is considered a rare manifestation of the syndrome. Other rare manifestations include autoimmune abnormalities, alopecia, and muscular dystonia. Patients with micro-deletions display varied phenotypes depending on the deleted segment's size and location. If an entire arm is lost, and the deletion affects the centromeric side, the phenotypes are less mixed and include the fullest range of defects [5].

With 18q- monosomy (OMIM #601808), phenotypes are extremely varied. Two types of deletions may be distinguished here: the proximal (18q11.2-q21.1) and the distal (18q21.1-q23) one.

Typical for distal deletions are delays in speech and mental development, congenital heart disorders, central nervous system pathology, orthopaedic pathology, ophthalmological disorders (strabismus, nystagmus, myopia), IgA deficiency, hypothyreosis, auditory deficiency, and kidney pathology. Hypopituitarism (isolated growth hormone deficiency) is a relatively frequent condition for this type of chromosome disorders [6–9].

Besides delayed mental and speech development, typical for proximal deletions are corpus callosum hypoplasia, kidney hydronephrosis, cardiac anomalies, frequent sinusitis, strabismus, eczema, obstructive apnoea, and conductive hearing loss. In patients with proximal deletion, growth hormone deficiency occurs less frequently (up to 14% of cases).

Since phenotypical manifestations of 18q- monosomy are highly varied and depend on the deleted segment's size and location and on the dosage dependence of genes in the deleted area, no definite phenotype may be described: manifestations will vary from one patient to another [9].

Some common features can be present: midface hypoplasia, upward or downward-inclined short palpebral fissures, epicanthus, and low-seated auricles with prominent antihelical fold.

Typical for all children with short and long-arm monosomy in chromosome 18 are muscular hypotonia, dysphagia, and respiratory disorders (respiratory distress syndrome) in the first months of life. Neonatal hypoglycaemia and cholestasis may be among the symptoms of congenital hypopituitarism and could be life-threatening if timely diagnosis and treatment are not available.

CASE

We examined four children with chromosome 18 disorders (three children with 18p- monosomy and one child with 18q- monosomy) which manifested, *inter alia*, as congenital hypopituitarism.

In all these children, the diagnosis was confirmed by a genetic analysis/testing (two patients underwent karyotyping only, and two other patients underwent a microarray analysis).

Congenital hypopituitarism was diagnosed based on hormonal tests and typical clinical manifestations. All children received hormone replacement therapy and were supervised by an endocrinologist and other medical professionals depending on their concomitant pathology.

Data on the children's speech development and skill acquisition were obtained by surveying their legal representatives.

Findings of Physical and Laboratory Examinations and Investigations

Patient 1.

Full-term female baby born to unrelated parents, fifth pregnancy (pregnancies 1 and 2 ended with healthy children pregnancy 3 was terminated with a therapeutic abortion; pregnancy 4 ended with a healthy child . Anthropometrics at birth corresponded to the term of gestation (see Table 1); Apgar score was 6/8. At birth, the baby had the following phenotypical characteristics: wide mouth, low-seated auricles, and flat nose bridge (see Figure 1a). At the end of day 1, an apnoea occurred with simultaneous hypoglycaemia (0.7 mmol/L), which were relieved after intravenous infusion of glucose solution. During the first 10 days of life, direct fraction-driven hyperbilirubinemia rise (total bilirubin at 360 μmol/L; direct bilirubin at 46 μmol/L), moderate cytolysis syndrome (aspartate aminotransferase (AST) at 55/L; alanine aminotransferase (ALT) at 35/L), and hyperlipoidemia were observed, as well as faecal hypocholia with negative inflammatory markers and lack of evidence of any infection pathology. Some hereditary metabolism disorders (tyrosinaemia and galactosaemia) were ruled out. The baby was suspected to have biliary atresia and underwent a liver edge biopsy test which found symptoms of chronic periportal hepatitis with low histological grade. No evidence of biliary atresia was found. Hepatobiliary radionuclide scanning identified lower hepatocyte expression but, again, no evidence of biliary atresia. Further examinations revealed a congenital cardiac anomaly (defect of interventricular septum) and congenital cataract. Considering the specifics of this phenotype and the multiple developmental defects, a karyotyping test was performed, which identified a short arm monosomy in chromosome 18 (46XX,del (18) (p11.1; p11.32)). It was observed that hypoglycaemia episodes up to 2.6 mmol/L did occur even after intervals between meals were prolonged.

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Table 1. The patients' clinical and laboratory data

Indicator	Patient 1	Patient 2	Patient 3	Patient 4
Sex	female	male	male	Female
Age at the time of writing	9 years 4 months	5 years 3 months	2 years 10 months	3 years 7 months
Karyotype	46 XX, del (18)(p 11.1; p 11.32)	46 XY, del (18)(p11.32-p11.21)	46XY,del(18)(p11.2)	46XX,del(18q22-q23)
Microarray analysis	N/A	N/A	Molecular karyotype: arr[hg38] 18p11.31p11.21(3067756_14489102)x1 Genes located in the imbalanced region: *AFG3L2, APCDD1 GNAL, LAMA1, MC2R, NDUFV2, PIEZO2, TGIF1, TUBB6*	Molecular karyotype: arr[hg19]18q22. 3q23(69283126_78014123)x1 Genes located in the imbalanced region: *CBLN2, NETO1, FBXO15, TIMM21, CYB5A, FAM69C, CNDP1, CNDP2, NF407, TSHZ1, ZNF516, ZNF236, MBP, GALR1, SALL3, ATP9B, NFATC1, CTD1, KCNG2, TXNL4A, PARD6G*
Birth weight (g)	3,210	2,700	2,300	3,240
Weight SDS	-0.18	-1.69	-1.68	0.34
Birth length (cm)	50	48	44	50
Length SDS	0.37	-1.09	-2.22	0.68
Apgar score	6/8	7/8	6/7	8/9
Muscular hypotonia	+	+	+	+
Neonatal cholestasis	+	-	+	hyperbilirubinemia
Hypoglycaemia	+	+	-	-
Early neonatal respiratory disorders	+	-	+	+
Feeding problems	+	+	-	+
Delays in motor development	+	+	+	+
Delays in speech development	+	+	+	+
Delays in mental development	+	+	+	+
Growth hormone deficiency	+	*	+	*
Secondary hypothyroidism	+	+	-	-
Secondary adrenal insufficiency	+	+	-	-
MRI data	MR image: partial empty sella	Corpus callosum agenesis and posterior pituitary ectopia	Anterior pituitary hypoplasia, infundibulum hypoplasia and posterior pituitary ectopia	N/A
Congenital cardiac anomaly	Defect of interventricular septum	-	-	-
Congenital cataract	+	-	-	-
Auditory deficiency (conductive)	-	-	-	+
Ptosis/semi ptosis	+	+	+	-
Solitary median maxillary central incisor	-	-	+	-
Gait disorders (ataxia)	+	-	-	-
Optic nerve hypoplasia	-	+	-	-

*Growth hormone deficiency was not proven as per 2018 Russian National Consensus on Hypopituitarism Diagnostic and Treatment in Children. The diagnosis was deemed highly probable. A case conference decided to assign a growth hormone therapy.

Table 2. Hormone examination data prior to hormone treatment

Indicator	Patient 1	Patient 2	Patient 3	Patient 4
Age when examined (months)	3.5	3	24	8 /36
ACTH (pg/mL) Reference: 7.2 to 63.3	6.05	8	25.03	N/A
Cortisol (nmol/L) Reference: 77 to 630	<11	28.9	435.2	277
TSH (mU/L) Reference: 0.64 to 5.76	1.6	3.28	1.42	1.9
Free T4 (pmol/L) Reference: 11.5 to 20.4	7.37	8.4	12.56	13.28
IGF-1 (ng/mL)	32*	48	13.43	59.9/49.8
SDS IGF-1 Reference: +/-2	-3.2	-0.94	-5.37	-0.41/-1.46

*was examined at the age of 24 months

Table 3. The patients' psychic and motor development. Age of key skills acquisition (based on a survey)

Indicator	Patient 1	Patient 2	Patient 3	Patient 4
Age at the time of survey	9 years 4 months	5 years 3 months	2 years 10 months	3 years 7 months
Holds their head up	12 months	3 months	8 months	4 months
Turns around	3 years	6 months	5 months	5.5 months
Crawls	Never	10 months	11 months	Never
Stands unsupported	4 years	12 months	18 months	19 months
Walks unsupported	5 years	22 months	18 months	21 months
Pronounces individual words	3 years	3.5 years	No speech	3 years
Performs simple tasks (understands the speaker)	2 years	3 years	2 years	12 months
Pronounces sentences	6 years	4 years (chanted speech, pre-memorised sentences)	No speech	3 years 5 months
Uses the potty/toilet at daytime	5 years	Not always	Does not	2 years 7 months
Uses the potty/toilet at nighttime	Does not	Does not	Does not	2 years 7 months
Attends a kindergarten	Correctional daycare facility, since the age of 6 (with their mother)	Does not. Is provided with individual training and introduced into small groups of children	Does not	Does not. Attends speech therapist classes and sensory integration classes
Attends a school (regular or correctional: please specify)	Since the age of 8 (home schooling)	Does not	Does not	Does not

Figure 1a. Patient 1 at the age of 3.5 years

Figure 1b. Patient 1 at the age of 9

At 3.5 months, the child was first seen by an endocrinologist. The examination revealed a moderate hepatomegalia, direct hyperbilirubinemia (total bilirubin at 76.32 pmol/L; direct bilirubin at 23.18 μmol/L), cytolysis syndrome (AST at 214.4/L; ALT at 83.5/L), and hypoglycaemia up to 1.1 mmol/L with prolonged intervals between meals (4.5 hours).

Hormone examination confirmed hypopituitarism, secondary hypothyroidism, and secondary adrenal insufficiency (see Table 2). Hormone replacement therapy with levothyroxine (12.5 μg/day) and hydrocortisone (1 mg/kg/day) was assigned. Brain MRI revealed evidence of partial empty sella. Cholestasis and cytolysis syndrome, as well as hypoglycaemia episodes were relieved by hormone replacement therapy within a few weeks. At the age of 2, due to a manifest delay of growth (SDS = -8.2), the child was examined again: her bone age corresponded to that of 8 months; IGF-1 was at 32 ng/mL, that confirmed a growth hormone deficiency. Through hormone replacement therapy with growth hormone (0.033 mg/kg/day), clear positive changes were observed (see Figure 2). At present, the patient is 9 years old (see Figure 1b). The girl receives hormone replacement therapy (hydrocortisone: 12.5 mg/day = 15.2 mg/m^2/day; levothyroxine: 50 μg/day; recombinant growth hormone: 0.033 mg/kg/day). Growth delay persists. The child shows a notable delay in her psychic and motor development. She started walking at the age of 5; she has a gross delay in speech development (she started speaking at the age of 6 and uses short sentences, helping herself with gestures) (see Table 3 and Figure 2). She still has feeding problems (choking over solid food, chews with difficulty). The child has had a number of rehab courses and is observed by a speech therapist and special-needs expert.

Patient 2.

A full-term baby boy born to a mother who had neurofibromatosis type 2. When born, his weight and length were at the lower end of the normal range, Apgar score was 7/8 (see Table 1). Examination found dysembryogenic stigma: protruding and low-seated ears, wide mouth, nipple hypertelorism, and congenital semi ptosis (see Figure 3). From day 1, he had recurrent hypoglycaemia up to 0.9 mmol/L and was therefore treated with infusions of glucose solution. At the age of 3 weeks, he was examined; hyperinsulinism was ruled out, and a diagnosis was confirmed: hypopituitarism, secondary hypothyroidism and secondary adrenal insufficiency (see Table 2). Hydrocortisone therapy was initiated (1 mg/kg/day), through which hypoglycaemia episodes were relieved. Thereafter he received levothyroxine (12.5 μg/day). His IGF-1 was measured twice: at the age of 2 and 3 months. The readings were within the normal range (49 to 54 ng/mL).

At the age of 3 months, the child was seen by an ophthalmologist who found optic nerve hypoplasia. Brain magnetic resonance imaging revealed corpus callosum agenesis and posterior pituitary ectopia. Septo-optic dysplasia was suspected. A molecular genetic test (hypopituitarism gene panel) was performed which found no mutations. Following that, the boy was regularly seen by an endocrinologist; despite a higher dosage of glucocorticoids (hydrocortisone dosage was 17.7 mg/m^2/day), hypoglycaemia persisted with prolonged intervals between meals.

At the age of 6 months, due to hypopituitarism and recurrent hypoglycaemia persisting even when higher dosages of hydrocortisone were administered, and despite a normal growth rate, a medical comission decided to give this

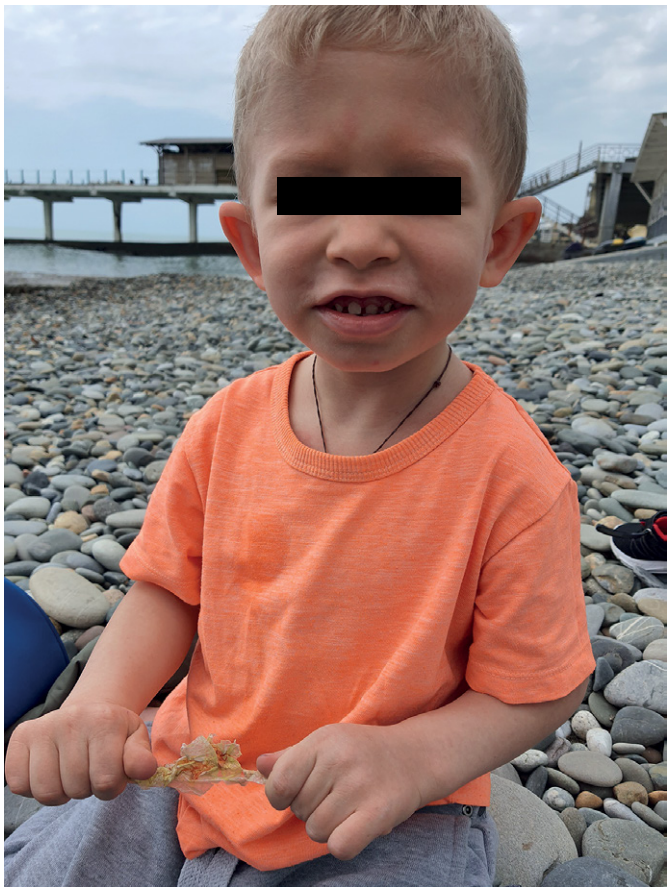

Figure 3. Patient 2 at the age of 4.5

child hormone replacement therapy with 0.028 mg/kg/day recombinant growth hormone (see Figure 4) as growth hormone deficiency was deemed highly probable. It ought to be noted that in the first three years of life this boy had frequent adrenal deficiency periods with simultaneous respiratory diseases accompanied by vomiting and hypoglycaemia.

Because of/due to the dysembryogenic stigma, a karyotyping test was performed, which identified a deletion in the short arm of chromosome 18 (46XY,del (18) p11.32-p11.21). Notable delays in psychic and motor development (started walking at 22 months) and speech development (at the age of 3.5 he could repeat individual words and understood the speaker only partially) were observed. A series of brain MRIs was conducted which found multiple foci in both hemispheres' white matter; presumably, these were schwannomas/ demyeliniation loci. Due to a difficult hereditary history, a molecular genetic test was conducted which found a mutation in *NF2* gene, thus confirming neurofibromatosis type 2. Considering the risk of large lumps in the cerebrospinal axis, the growth hormone dosage was reduced from 0.028 to 0.005 mg/kg/day. At the time of writing, this child is 5 years old. He demonstrates a notable progress in speech, psychic and motor development as he attends speech therapist classes and is seen by a special-needs expert (see Table 3). Satisfactory growth rate is observed as hormone replacement therapy with growth hormone is provided (see Figure 4).

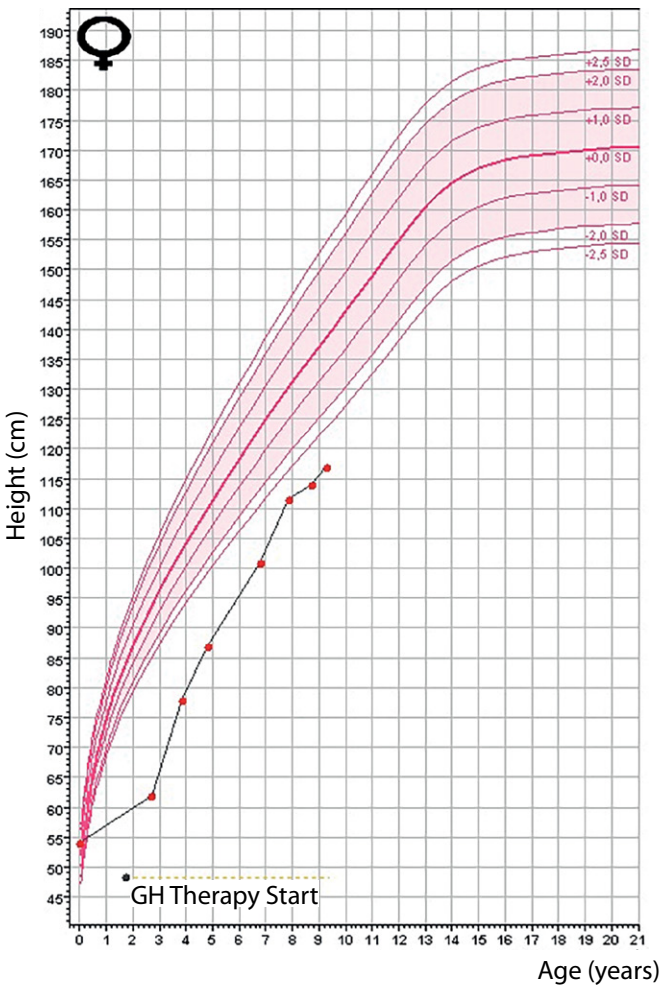

Figure 2. Patient 1

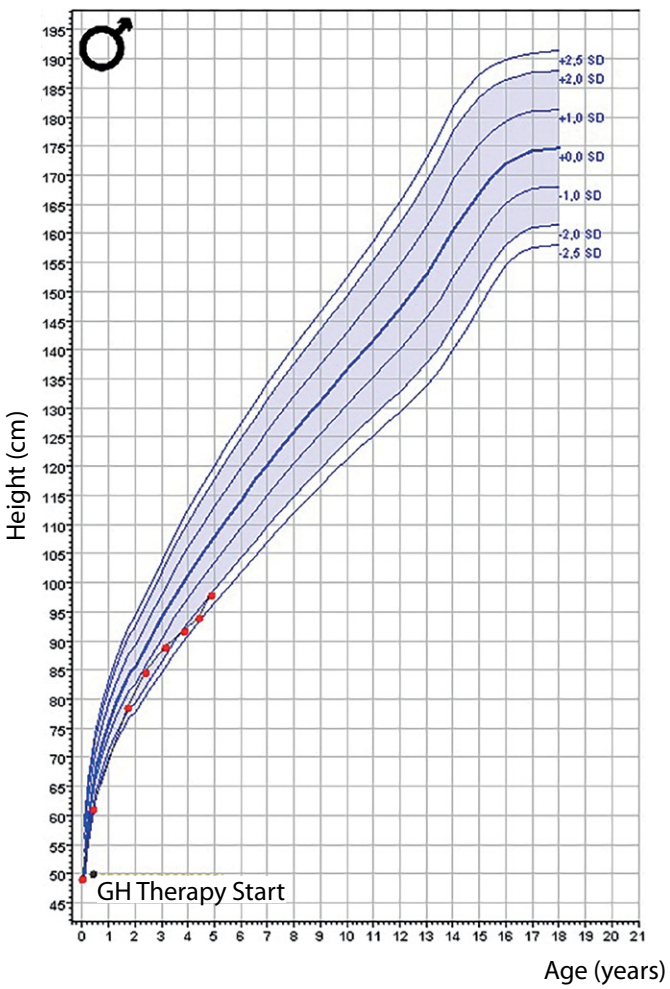

Figure 4. Patient 2

Patient 3

This boy was born from first pregnancy through surgical delivery (due to breech presentation). His weight and length at birth were low and Apgar scope was 6/7 (see Table 1). Dysembryogenic stigma (low-seated auricles, long philtrum, and wide mouth) and semi ptosis were identified at birth (see Figure 5a). After birth this child was regularly seen by a neurologist and was diagnosed with muscular hypotonia syndrome and ventriculomegalia. Since early age, this child had low growth rate and delays in psychic and motor development. At the age of 1, a karyotyping test was conducted, which identified a deletion in the short arm of chromosome 18 (46 XY.del(18)(p11.2)). No hypoglycaemia was observed.

He was first seen by an endocrinologist at the age of 2. By then, he had a notable growth delay (height 72.5 cm; growth SDS -4.17). In terms of hormonal profile, he had low IGF-1. No deficiency in other anterior pituitary tropic hormones was identified (see Table 2). Bone age at the age of 2 was on 3 months. Examination revealed a supermaxilla development anomaly (solitary median maxillary central incisor).

An MRI investigation was conducted at the age of 2 which found a typical hypopituitarism-related "triad" of symptoms: anterior pituitary hypoplasia, infundibulum hypoplasia, and posterior pituitary ectopia, as well as periventricular leukomalacia and ventriculomegalia. The child was diagnosed with an isolated growth hormone deficiency. A treatment with 0.025 mg/kg/day recombinant growth hormone was initiated. At the time this child was visited last, he was 2 years and 10 months old (see Figure 5b). He still has a delay in speech development and is seen by a speech therapist and a neurologist (see Table 3). Due to treatment, a growth rate improvement has been observed (see Figure 6).

Patient 4.

A girl born from the first pregnancy ended with delivery at term. Her weight and length at birth corresponded to the term of gestation (see Table 1), and Apgar scope was 8/9. 16 hours after birth she was moved to emergency and intensive therapy ward due to respiratory disorders (congenital pneumonia). At neonatal period, hyperbilirubinemia was observed, but no hypoglycaemia episodes occurred. Specific phenotypical features were notable: brachycephalic shape of the skull, wide nose bridge, short nose, midface hypoplasia, narrow upper lip, downturned mouth, low-seated dysplastic auricles, short neck, nipple hypertelorism, umbilical hernia, 2–3 partially webbed toes, and clinodactyly on 5 toes. From the first months of life she demonstrated muscular hypotonia and delays in psychic and motor development (started holding her head up at 4 months, started turning around at 6 months), due to which was seen by a neurologist and a geneticist. At the age of 8 months, microarray analysis of DNA revealed partial monosomy in the long arm of chromosome 18 (distal deletion 18q22-q23); for this

Figure 5a. Patient 3 at the age of 2 years and 3 months

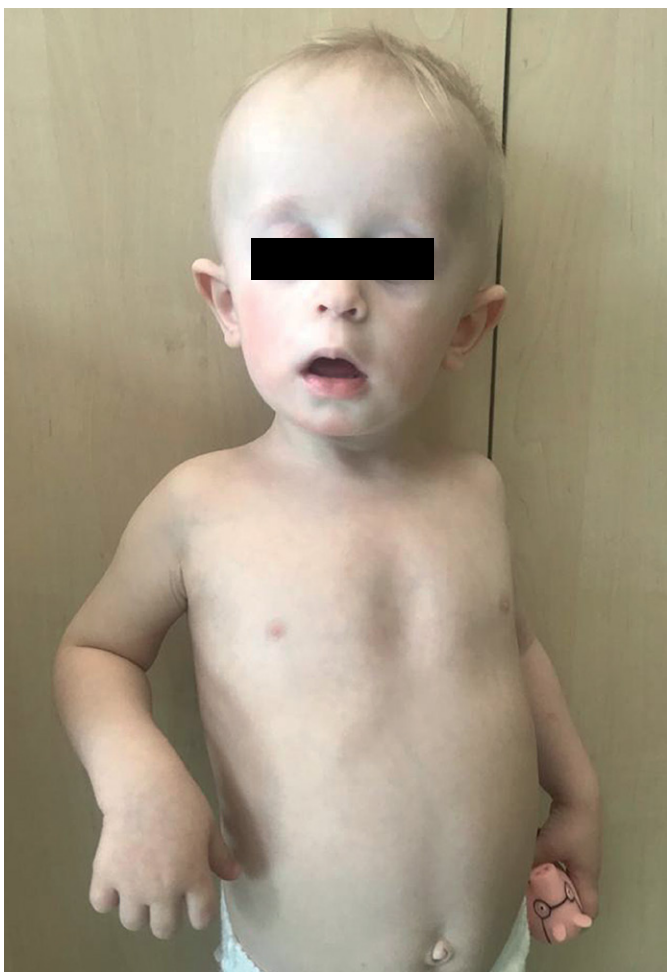

Figure 5b. Patient 3 at the age of 2 years and 8 months

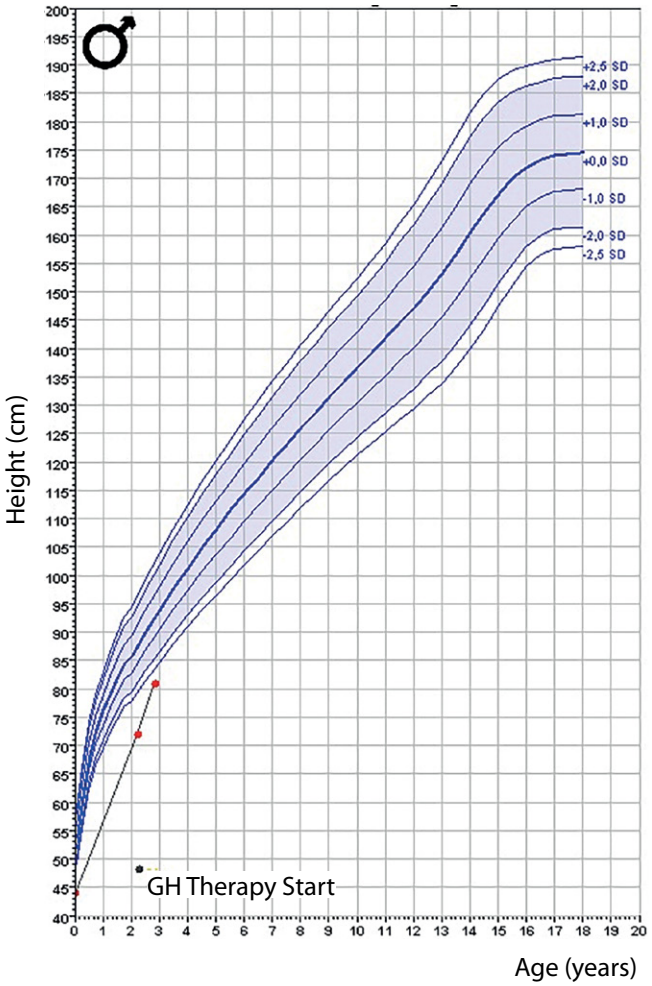

Figure 6. Patient 3 GH

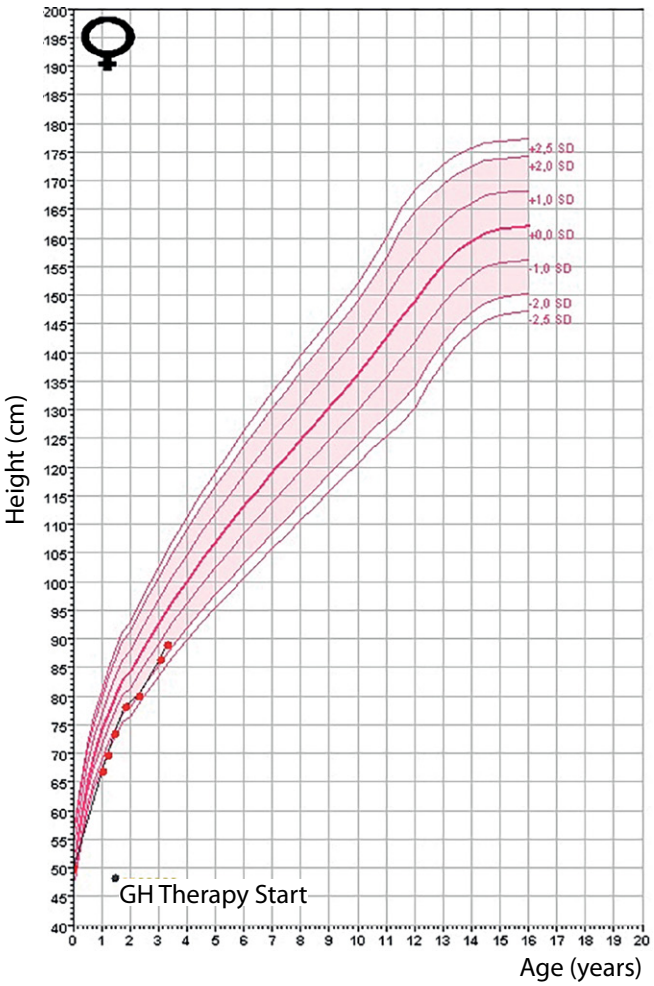

Figure 7. Patient 4 GH

reason, she was referred to an endocrinologist. Examination of her hormonal profile found no abnormalities; a moderate low IGF-1 was observed (see Table 2). Bone age corresponded to chronological one.

At 16 months, despite the rehabilitation efforts, muscular hypotonia persisted and medical comission decided to initiate growth hormone therapy to improve metabolism (first, 0.01 and then 0.025 mg/kg/day). Stimulation tests were not conducted due to the child's very low age. During the growth hormone therapy, laboured breathing intensified and the therapy was suspended for 3 months. Once the growth hormone therapy stopped, symptoms of respiratory disorders disappeared. The child was seen by a thoracic surgeon who made a chest radiography and identified wrong position of a hemidiaphragm. The child was regularly examined; at the age of 3, her growth rate decreased (growth SDS = –2.13). IGF-1 went down to 49.8 ng/ml, and growth hormone therapy was resumed in a metabolism-recommended dosage that was gradually increased to 0.033 mg/kg/day, given a high probability of growth hormone deficiency. The child's growth rate was analysed, and positive changes were seen at the period of the therapy. No further side effects of growth hormone therapy were observed.

At the age of 3 years 7 months, conductive hearing loss was identified. Active rehabilitation efforts and speech therapist classes resulted in an improvement of the child's psychic and motor development (see Table 3).

DISCUSSION

We examined four patients with deletions in chromosome 18. Three of them had different degrees of congenital hypopituitarism. In one of the patients, this diagnosis was highly probable (Patient 4). Similar phenotypical features are notable: low-seated dysplastic auricles, short neck, narrow upper lip, downturned mouth, and ptosis. In early neonatal period, all these children had muscular hypotonia and respiratory disorders; two of the patients had hypoglycaemia (Patients 1 and 2). All of the patients demonstrate delays in psychic and motor development.

In three of the patients, (Patients 1, 2, and 3), a deletion in the short arm of chromosome 18 was identified. Among them, Patient 1 had the largest deletion (46 XX, del (18) (p 11.1; p 11.32)), which led to a whole range in congenital abnormalities (congenital heart disorders, congenital cataract, ptosis, multiple anterior pituitary tropic hormone deficiency). This child's severe delay in psychic and motor development was be due to the syndrome itself, as well as the consequences of acute hypoglycaemia and ischemic injury of cerebrospinal axis during neonatal period. Patient 2 had a large deletion, too. This patient had progressing hypopituitarism (see Table 1); however, he had no congenital visceral abnormalities, but had optic nerve hypoplasia. As per the current diagnostic criteria, growth hormone deficiency was not confirmed in this patient [10]. However, since the baby had recurrent hypoglycaemia and compensated secondary adrenal insufficiency, a medical comission

decided to initiate hormone replacement therapy with growth hormone, given a high probability of growth hormone deficiency. Neurofibromatosis type 2 in this patient is an independent disease caused by a mutation in *NF-2* gene located on the long arm of chromosome 22.

Patient 3 has a deletion in the short arm of chromosome 18. This patient has isolated growth hormone deficiency and supermaxilla development anomaly (solitary median maxillary central incisor).

All of our patients who had deletions in the short arm (Patients 1, 2, and 3) had structural anomalies in sella turcica area, which are found in people with congenital hypopituitarism (see Table 1).

The short arm of chromosome 18 has 66 genes, out of which 12 are believed to be dosage dependent [5].

Studies (Cody *et al.*, 2009) identified short arm regions whose deletions cause the following abnormalities: perceptive and conductive hearing loss (8% and 22%, respectively), strabismus (38%), ptosis (47%), orthopaedic pathologies (47%), nystagmus (9%), MRI-identified structural defects of cerebrospinal axis (66%), holoprosencephaly (13%), kidney anomalies (14%), congenital heart disorders (56%), convulsions (13%), congenital cataract (6%), and delays in speech development (100%) [7].

Moreover, individual genes have been identified whose hemizygosity may cause various disorders. Among them, *TGIF1, AFG3L2, LAMA1, GNAL, DLGAP1, LCCR30, ANKRD12,* and *IMPA2* have been relatively well studied.

TGIF1 codes the homeodomain protein TWSG, which has a key role in TGF signal transduction. Mutations of this gene cause holoprosencephaly and maxillofacial area anomalies. Scholars report that 11% of children with 18p- have holoprosencephaly defects of cerebrospinal axis development, including anomalies in sella turcica area. Moreover, data suggest that solitary median maxillary central incisor and conductive hearing loss are also linked to a missing *TGIF1* [11].

AFG3L2 codes a subunit of mitochondrial proteases involved in proteolysis of misfolded proteins. Point mutations in this gene are known to cause spinocerebellar ataxia type 28, which typically manifests through ataxia development in childhood, dysarthria, nystagmus, and ptosis. This gene is believed to have incomplete penetrability, since its duplications and deletions exist in general population. However, this group of patients requires monitoring, since this disease may manifest in at a later age and there have been a report that complete deletion of this gene causes phenotypical manifestations, just as point mutations do [12].

LAMA1 codes the protein involved in basement membrane formation. Point homozygous mutations and compound heterozygous mutations in this gene have been described in a case of PORETTI-BOLTSHAUSER SYNDROME, typical for which are cerebellum defects, myopia, retinal degeneration, oculomotor activity disorders, and delays in speech and motor development.

GNAL codes G-alpha, a subunit of G-protein receptor. Mutations in this gene cause various forms of hereditary dystonia. Studies report that 3% of patients with 18p- deletions that cover this gene's region have been diagnosed with torsion dystonia.

The short arm region also contains several genes that are considered candidates for an association with autism (*DLGAP1, LCCR30, ANKRD12, IMPA2*). Their deletions are probably linked to our patients' delays in speech development [5].

Patient 3 underwent a microarray analysis that identified genes located in the deletion area. Among them, *AFG3L2, GNAL, LAMA1, TGIF1* can be singled out. Their deletion determines the child's phenotypical manifestations (see Table 1; Figure 5). This patient required closer monitoring with regard to potential development of dystonia in the future.

Thus, the clinical range of 18p- syndrome manifestations is highly varied and depends on the deletion size. In our case, none of the patients lacked an entire arm with centromeric side; their deletions were partial and their sizes varied, which is why clinical manifestations varied, too.

One patient (Patient 4) had a distal deletion in the long arm of chromosome 18 causing conductive hearing loss and delay in psychic and motor development.

Cody *et al.* single out two regions in the long arm of chromosome 18: the proximal one (between the positions 19 667 062 and 45 578 734) and the distal one (between the position 46 739 965 and the telomere), which may have clinically significant variations. Out of the 196 genes located on the long arm of chromosome 18, to date 15 have been described as having clinically significant hemizygosity; however, their penetrability varies and thus the phenotypical manifestations may may be variable [9].

Microarray analysis identified the precise region in which Patient 4 had a deletion, and this enabled us to determine the genes identify the genes within the deletion (see Table 1). Among them, one may single out *ZNF236, SALL3, TXNL4A*, which are involved in the maxillofacial area and auditory pathway embryogenesis, and thus may account for this specific phenotype.

At present, no specific gene in the distal region of the long arm of chromosome 18 has been identified to be responsible for growth hormone deficiency; however, the literature suggests that it is growth hormone deficiency that is a pathognomonic symptom of distal-type 18q deletions, as it occurs in up to 56% of patients who have this genetic disorder [9, 13].

Due to a very small age, no stimulation tests were conducted in Patient 4 to diagnose growth hormone deficiency. Initially, hormone replacement therapy was initiated to stimulate her metabolism, and subsequently to stimulate growth, as her growth SDS and IGF-1 decreased. Thus, growth hormone deficiency was not fully confirmed by laboratory investigations; however, distal deletion in the long arm of chromosome 18 combined with a reduced growth rate suggests that the deficiency is in fact the case.

Within the distal region of the long arm of chromosome 18, critical areas have been identified which are responsible for congenital heart disorders (29%), orthopaedic pathologies (29%), autoimmune diseases of thyroid gland (15%), strabismus (40%), IgA deficiency (18%), and myelination disorders (97%), which do not cause degenerative diseases of cerebrospinal axis [9, 14].

All children with this pathology display delays in mental, psychic and motor development. Studies have found that deletions covering the region that hosts *TCF4* gene account for severe delays in psychic and motor development. If *TCF4* is not lost, mental development in this group of patients varies from normal to moderately delayed [15]. The deletion

in our patient does not cover *TCF4*, and that patient's delay in development is believed to be moderate; the child is advancing in psychic and motor development as a result of rehabilitation activities.

CONCLUSION

We described clinical cases that demonstrate phenotypical variety of 18p- and 18q- syndrome. Symptoms common for all our patients were growth hormone deficiency, facial deformity, and delay in speech development.

Congenital hypopituitarism is a rserious disorder, especially in neonatal period, as cortisol deficiency and, likewise, growth hormone deficiency may cause children to develop severe recurrent hypoglycaemia in their first days and months of life. Hypoglycaemia syndrome with simultaneous cholestasis in neonatal period is an absolute indication to conduct hormonal examination, so that the diagnosis may be verified as early as possible and hormone replacement therapy may be initiated.

Aetiology of congenital hypopituitarism may vary. When children with partial or complete loss of pituitary tropic hormones display dysmorphic features, this ought to alert the specialists to conduct karyotyping or microarray analysis in order to rule out a chromosome 18 pathology.

Despite such variety of clinical manifestations and their degrees in patients with chromosome 18 deletions, more precise identification of area of the defect will enable foreseeing the range of potential disorders, optimising the examination plan and monitoring such children more efficiently.

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Patients' consent. Informed and unconstrained written consent was obtained from the patients who agreed to have their personal medical data published in anonymised form.

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