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Growth hormone treatment in a patient with deletion of the long arm of chromosome 18: An 8-year observation

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Abstract

BACKGROUND: Deletion of the long (q) arm of chromosome 18 causes a rare genetic disease termed 18q- syndrome. This syndrome has varying clinical presentation, depending on the extent of the deletion and the percentage of cells with abnormal chromosomes. One of the most common disorders in children affected by the disease is short stature, usually associated with growth hormone deficiency. Numerous reports on patients with 18q- syndrome show growth hormone treatment has significant therapeutic benefits, not only in terms of final body height but also cognitive functions and psychosocial development.
CASE PRESENTATION: Here we describe the case of a 10-year-old girl with 18q- syndrome treated with recombinant human growth hormone from the age of 2. This is the first report of such a patient in Poland. After 8 years of observation, the child showed a clear benefit from recombinant human growth hormone treatment in terms of height and possibly mental development. The girl remains under cardiac care due to congenital heart disease and under neurological care for epilepsy.
CONCLUSIONS: This case indicates the need for early diagnosis and multidisciplinary action to achieve satisfactory quality of life in patients with 18q- syndrome.

Abbreviations:
ASD - atrial septal defect
GH - growth hormone
rh GH - recombinant human growth hormone

BACKGROUND

Chromosome 18q- syndrome (del[18q] syndrome, de Grouchy syndrome type 2, OMIM# 601808) is a rare genetic disease caused by a deletion of the long (q) arm of chromosome 18, with the breakpoint usually in bands 18q21–23. In most cases, the defect extends from the deletion site to the end of the chromosome (18qter). The vast major-

CASE REPORT

ity (about 75%) of the mutations arises de novo on the paternal chromosome; in other cases, it is a hereditary aberration. The incidence of the syndrome is estimated at 1:40,000 births worldwide (Ghidoni *et al.* 1997; Cody *et al.* 2015).

The clinical picture of 18q- syndrome is variable, depending on the extent of the deletion and the percentage of cells with abnormal chromosomes. Studies in larger patient groups suggest a relationship between the occurrence of phenotypic abnormalities and the breakpoint on the chromosome. So far, several critical regions have been identified on the long arm of chromosome 18 that encode genes whose absence is responsible for the characteristic features of 18q- syndrome (Cody *et al.* 2014; www.rarechromo.org).

Because of the lack of homogeneity in the genotype of affected patients (molecular studies indicate no common breakpoints in chromosome 18 in unrelated patients), it is difficult to talk about the 18q- syndrome as a disease syndrome in the classic sense of the word. Indeed, each phenotypic feature of the syndrome may also occur in a person who has a hemizygous deletion of a critical chromosome region encoding a gene responsible for that particular feature. Therefore, any report comparing the pathologies present in the syndrome should be treated with some reserve and in strict respect of the patient's genotype. However, several genes responsible for specific disorders have been identified. For example, *TSHZ1* gene hemizygosity has been shown to be responsible for ear canal atresia and the *ZNF407* and *NETO1* genes are suspected to be responsible for cognitive dysfunction (Cody *et al.* 2014; Cody *et al.* 2005; Cody *et al.* 1999).

In the described cases of 18q-, the most common disorders are short stature associated with growth hormone (GH) deficiency, failure to thrive, gait disorders, mental disorders of varying degrees, delays in speech development, structural hand and foot anomalies, hypotony, heart defects, central nervous system demyelination, epilepsy, sensorineural and conductive hearing loss, spinal disorders, and proximally placed thumbs. In children affected by the syndrome, there may also be dysmorphic features and abnormalities of the skull, including microcephaly, narrow eyelids, epicanthic fold hypertelorism, depressed nasal bridge, short philtrum, thin upper lip, high-arched palate, short lingual frenulum, and hypoplasia of auricle. Eye disorders are also often noted, such as optic nerve hypoplasia, strabismus, nystagmus, and visual defects. About 40% of newborns with 18q- syndrome have cleft lip and palate. IgA deficiency is also commonly described in ~24% of patients. In addition to the abovementioned GH deficiency, other endocrinopathies present in patients include thyroid dysfunction and hypogonadism. Many children are also diagnosed with abnormal genital structure (i.e., hypoplasia of the labia majora, hypospadias, and cryptorchidism) (Cody *et al.* 2014; www.rarechromo.org; Hale *et al.* 2000; Cody *et al.* 1997).

Due to the complex nature of the disorders, patients afflicted with 18q- syndrome require multi-specialist care (i.e. from a cardiologist, endocrinologist, neurologist, orthopedist, speech therapist, and psychologist), as well as early stimulation and development support. Prognosis is good and patient life expectancy is not divergent from the wider population, indicating the importance of efforts to improve the patients' quality of life.

Here we describe the case of a 10-year-old girl with terminal deletion of the long arm of chromosome 18, who was treated from the age of 2 with recombinant human GH (rhGH). To the best of our knowledge, this is the first report of a patient with 18q- syndrome in Poland who was treated with rhGH.

CASE PRESENTATION

A second child (G.J.) from a second pregnancy (from unrelated parents) was born with a body weight of 2640 g (SDS -0,97) and in good general condition (Apgar 9/10) in the 37th week of gestation. The adaptive period was complicated by hyperbilirubinemia requiring phototherapy. Prenatally, interventricular septal defect was suspected. In the echocardiographic study performed in the neonatal ward, atrial septal defect (ASD) II was found, and the presence of a chorda tendinea in the left ventricle. Brain and abdominal ultrasonography were without significant deviations. There was evidence of a foot defect (talipes calcaneovalgus) and the presence of a dermal sinus in the sacral area.

Due to delayed psychomotor development, reduced muscle tension and feeding difficulty, the girl was rehabilitated from her first months of life onwards by the Vojta method. A neuropsychologist was consulted many times regarding the child's psychomotor development. Development was assessed as delayed but with normal course dynamics: she rotated around the axis of the body only in one direction, did not crawl, learned to sit up when she was 12 months old, and learned to walk at age 3. Speech development was also delayed: her first words were at the age of 4 years. In addition, the girl occasionally showed aggressive behavior, and a tendency to quickly get upset. During school activities, she sometimes found it difficult to focus attention, was easily distracted, and became bored with some tasks. At age 6, the girl was diagnosed with autism spectrum disorder, and remained under constant psychological care. Due to her speech impediment, she was also placed under the care of a speech therapist.

At 8 months of age, the girl was diagnosed cardiosurgically. An echocardiographic study showed ASD II with significant left-to-right shunt, right ventricular enlargement, and septal dyskinesia. Laboratory tests were without significant deviations. Correction of the defect was performed in the extracorporeal circulation. Postoperative examination showed tightness of the atrial septum and reduction of the cardiac silhouette in

relation to preoperative examination. The girl remained under constant cardiac care. In the most recent echocardiographic study, an extra superior vena cava, paradoxical movement of the interventricular septum, and impaired flow through the valves were described.

At the age of 16 months, the girl was placed under orthopedic care due to an incorrect left foot structure. During hospitalization, complete subtalar release was performed by the Cincinnati incision, with repositioning of the talonavicular joint, calcaneocuboid joint and talocalcaneal joint, as well as elongation of the tendons. The rearfoot was fixed with Kirschner's wires. A month later, the same surgery was performed on the right foot.

At 14 months of age, a genetic study was performed and the 46XX, del (18) (q21.32).ish22q11.2 (D22S75x2) karyotype was observed. This corresponds to a terminal deletion of the long arm of chromosome 18, which arose de novo. The parents' karyotype was assessed as normal, with a 1qh+ variant in the mother that was also present in the patient. The risk of defect in subsequent children was assessed as low but higher than in the wider population.

At the age of 19 months, the girl had left-sided seizures with open eyes during sleep, accompanied by mild salivation. The entire episode lasted about 10 minutes, during which time the girl was not responsive. Left hand paresis was observed after symptoms resolved. Epilepsy was diagnosed following neurological examination, and Depakine Chronosphere was included as treatment. Despite treatment, an episode of left-sided seizure occurred again nine months later. The dose of Depakine Chronosphere was increased, and since then, seizures have not been observed.

In the fifth year of life, the girl was hospitalized in a neurological ward. The video EEG examination confirmed epilepsy with seizures with focal beginnings, valproinic acid remained the main treatment. Basic laboratory tests showed no significant deviation from the standard based on her age. Valproate concentration was also in the therapeutic range.

At 7 years of age, EEG showed localized lesions. At 8 years of age, EEG showed abnormal activity with focal epileptiform abnormalities with right-sided lateralization, as well as poorly expressed sleep characteristics without seizures. In neuroimaging studies (MRI of the brain) in 2009 (at the age of 2), there was small cortical and subcortical atrophy. In the 2011 examination (at the age of 4), minor cortical and subcortical atrophy was observed, as well as significantly delayed myelination of the brain and cerebellum, which is characteristic of 18q-. A minor improvement in myelination is described in the 2014 examination (at the age of 7).

At the age of 20 months, the girl was hospitalized in the Clinic of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age, due to significantly short stature and considerable slowing of growth. Physical examination demonstrated features of facial dysmorphia including: depressed nasal bridge, prominent frontal eminences, and high-arched palate. In addition, hypoplasia of the labia majora, dermal sinus in the sacral area, as well as postoperative scars on the skin of the chest and feet were observed. Assessment of psychomotor development revealed that the girl sits on her own but cannot walk and moves by sliding on her buttocks. She speaks in single words, plays, and likes to make contact with her carers and the environment. Her body height was 73 cm (<3rd percentile, -4.36 SDS) and body weight was 7 kg (<3rd percentile, -5SDS). The growth rate was estimated at 10.8 cm/year. Bone age was delayed by 8 months in relation to the nominal age of the child. MRI scan of the brain showed no abnormalities in the hypothalamus and pituitary area.

No deviations in blood count, hepatic cell function or kidney function were observed in laboratory studies. Urinalysis was normal and correct values were observed in the daily glycemic profile. Measurement of nighttime GH secretion showed concentrations up to 3.9 ng/ml. An L-DOPA stimulation test was performed in which the maximum GH level was 8.5 ng/ml. IGF-1 concentration was too low to measure. Due to the young age and low weight of the child, a second pharmacological GH secretion stimulation test was not performed. Partial GH deficiency was identified. Based on the results of the study, the girl was qualified for a short stature treatment program in children with somatotropin hypopituitarism. In accordance with the guidelines of the therapeutic program, a GH dose of 0.031 mg/kg/day was administered in subcutaneous injections once daily in the evening.

Initially follow-up visits at the clinic were every 3 months, then every 6 months. During the follow-up visits, the response to treatment, treatment tolerance, and laboratory results (with special attention given to carbohydrate metabolism and bone age progression) were assessed.

During a follow-up visit at 30 months, subclinical hypothyroidism was diagnosed and L-thyroxine was included in her treatment (based on TSH concentration 6,55 μIU/ml, FT4 1,16 ng/dl).

In the initial period of treatment the 9.18 cm/year; during the first 18 months of treatment, her body height increased by 13.7 cm. In subsequent years, the growth rate was lower, but the tendency to improve in terms of deviation from the population average for the age is maintained. The child's current growth rate is 5.03 cm/year. Her target height calculated from mean parental height is 166.5 cm. Her predicted adult height calculated using the Bayley-Pinneau method started at 147.56 cm when first calculated at the age of 7 and reached 153.96 cm in the last measurement at the age of 10. The growth pattern is shown on the Figure 1 and Figure 2, and in Table 1.

At present, the patient's body height is just below the 3rd percentile (-2.09 SD), which is an improvement of 2.25 SD over the 8 years. No serious side effects of

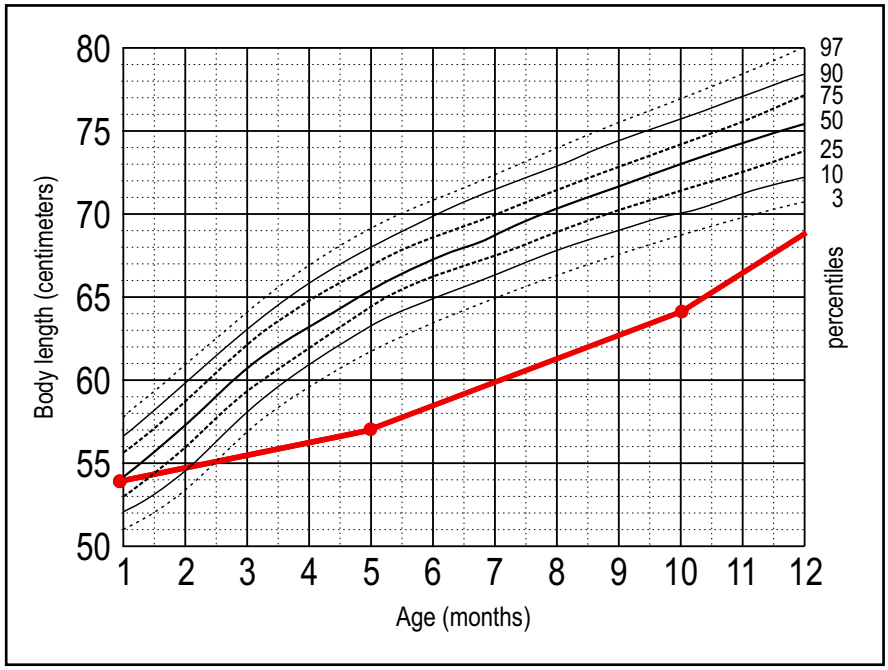

Fig. 1. Patient's body lengths in the first 12 months of life

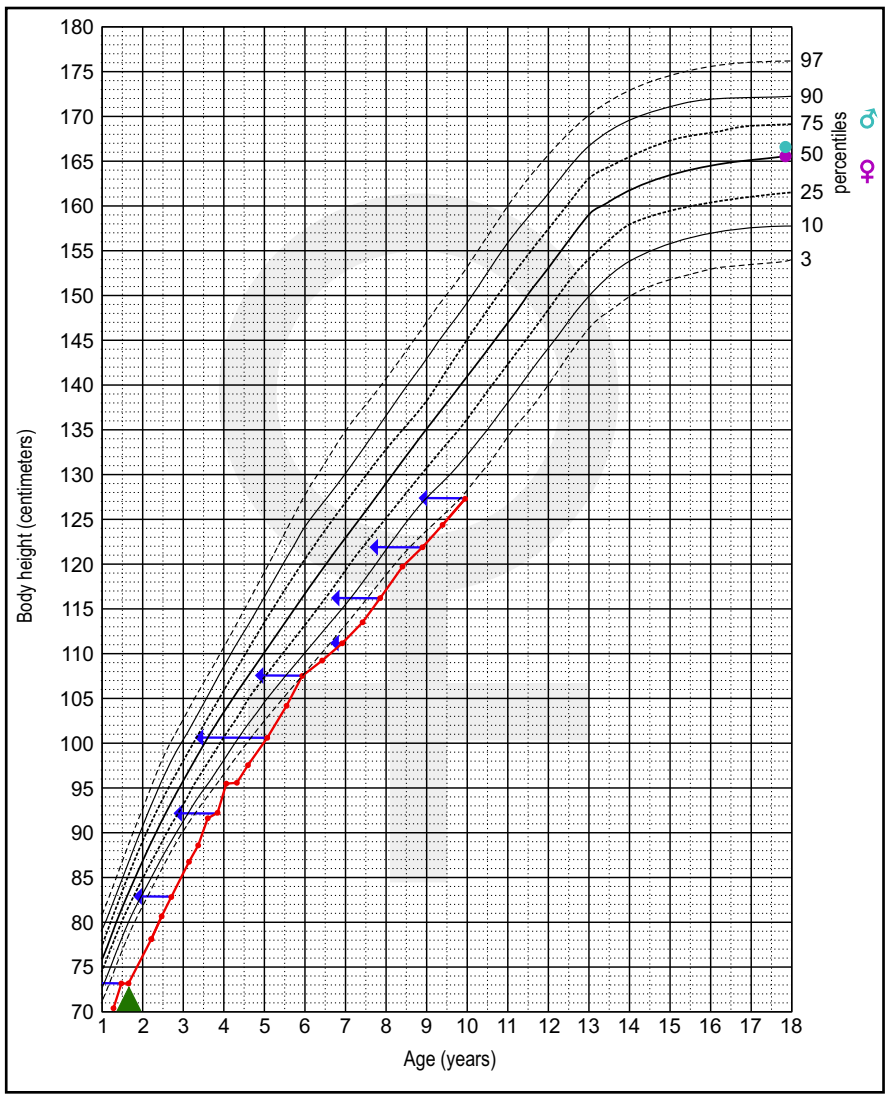

Fig. 2. Patient's body height

the therapy have been reported. The patient tolerates her daily GH injections well. Her IGF-1 levels monitored throughout the treatment are within the normal range for her age. She began normal puberty in the 9th year of life. She is covered by comprehensive logopedic, cardiological, neurological, and rehabilitation care.

Her parents have observed significant improvements in the girl's psychomotor development. Her intellectual development is at a level appropriate to her age. At present, she does not require special education; she attends the integration class at a common school with a tutor, with good learning outcomes. She undergoes yearly psychological evaluation with assessment of intellectual abilities, which have come with satisfactory results.

DISCUSSION

18q- syndrome was first described in 1964 by de Grouchy and co-workers, hence its historical name, de Grouchy syndrome type 2. Currently, the largest group of patients described and reports on progress in diagnosis and therapy come from the United States. There is an association and a registry of patients with disorders of chromosome 18 (The Chromosome 18 Research & Registry Society). Based on American literature, we are able to estimate the proportion of patients suffering from individual symptoms of the syndrome. In this regard the studies of Cody *et al.* (1999; 2014) seem to be the most important, evaluating largest groups of patients described by one study group thus far and estabilishing the reference group of 18q- patients. It is estimated that the most common disorders in the group include delayed myelination of the central nervous system (>90% of patients),

Tab. 1. Growth (change in height) of the girl from birth to 10 years of age

Age	Body height [cm]	SDS
At birth	54	1.7
5 months	57	-4.85
10 months	64	-4.00
16 months	70	-3.85
18 months	72	-3.40
20 months	73	-4.36
2 years 3 months	78	-4.06
2 years 6 months	80.5	-3.84
2 years 8 months	82.7	-3.77
3 years 2 months	86.7	-3.50
3 years 5 months	88.5	-3.32
3 years 8 months	91.6	-2.78
3 years 11 months	92.1	-3.06
4 years 1 months	95.4	-2.46
4 years 3 months	95.5	-2.85
4 years 6 months	97.5	-2.7
5 years 1 months	100.5	-2.59
5 years 6 months	104.1	-2.26
6 years	107.5	-1.94
6 years 4 months	109.2	-2.15
6 years 11 months	111.1	-2.29
7 years 4 months	113.5	-2.41
7 years 11 months	116.2	-2.37
8 years 4 months	119.8	-2.21
8 years 11 months	121.9	-2.27
9 years 4 months	124.4	-2.21
10 years	127.3	-2.09

SDS-Standard Deviation Score

delayed speech development (91%), hand and foot malformations (81%), hypotony (79%), gait disturbances (68%), ear canal atresia/stenosis (64%) microcephaly (51%), proximal position of the thumbs (45%), cleft palate (43%), IgA deficiency (24%), hypoplasia of the optic nerve (23%), and heart failure (10%) (Cody *et al.* 2014).

GH deficiency in patients with 18q-syndrome has been reported since the mid-1990s (Ghidoni *et al.* 1997). It is estimated that up to 80% of del18q patients will not reach normal height and weight, and GH deficiency is observed in approximately 68% of them. However, there are numerous benefits of rhGH therapy in children with proven deficiency, not only in improving the growth rate, but also in terms of increasing IQ and cognitive improvement. Improvement of neurological features has also been described, mainly changes in T1 relaxation time and in the white matter of the frontal lobe (Cody *et al.* 2005). Despite the above-mentioned results, Budisteanu *et al.* (2010) described a case of a del18q patient who did not benefit from treatment with GH. In this case, three weeks after the onset of treatment, there was an episode of high fever with eyelid edema and psychomotor regress: the child ceased to sit down, was weakened, and had a reduced reactivity. After a week of persistent complaints, despite treatment with antibiotics and antipyretics, the child's parents demanded the completion of therapy. The child underwent intensive rehabilitation and cognitive stimulation to improve the state after a month. Since then, no recurrence has been reported, the treatment was however discontinued definitely (Budisteanu *et al.* 2010). This case may be unrelated to growth hormone treatment, as such reports have never been seen before.

Our patient seemed to benefit from treatment with rhGH. There was a noticeable improvement in growth rate (and approximation of the growth curve to -2SD), and the predicted adult height changed from 147,56 cm to 153,96 cm, indicating therapeutic success, however mild. The growth rate may seem to have dropped in the initial period of treatment, but one has to take into account the natural growth rate decrease in children after the age of 1 – the pre-treatment growth rate was calculated including the first year of life, during which the growth rate is generally higher than later in life. However, it is also important to note, that our patient was only diagnosed with partial growth hormone deficiency, which may have resulted in the response to treatment not being as spectacular as in children with severe hypopituitarism. One can't also forget about other positive effects of growth hormone treatment on 18q-patients, as mentioned in the publications mentioned above. Consequent MRI scans have proven improvement in the myelination of the brain. The treatment influenced the psychomotor, cognitive and intellectual development of our patient, which are currently at a satisfactory level for a child aged 10 years. The patient undergoes yearly evaluations of her intellectual and cognitive functions, which place her within the normal range for children her age. One cannot underestimate the great contribution of the work put into the stimulation of the development of the child by her mother, who was very much involved in the progress of her daughter.

Therefore, it seems that for the development of patients with 18q-syndrome, it is important to quickly undertake multi-specialty care and start rehabilitation and cognitive stimulation early. It should be kept in mind that the expected life expectancy of del18q patients is not different from the wider population, which further emphasizes the importance of achieving adequate quality of life. Most of these patients are still fertile, and although many of them remain socially withdrawn and describe their family and carers as their closest friends, some of them will develop emotional ties and create happy relationships. Most patients enjoy

their social life, going out for a meal or to a pub. Some of them will attend college. One patient even undertook studies in genetics and now plans to work in the genetic laboratory (www.rarechromo.org).

CONCLUSIONS

1. 18q-chromosome patients require multi-specialty care to improve their quality of life.
2. Early diagnosis and multidirectional therapies can help patients achieve their full potential.
3. Patients who have been diagnosed with growth hormone deficiency significantly benefit from rhGH treatment, both in terms of improved growth rate and intellectual development. There are also several other areas in which such treatment might be helpful, such as psychointellectual development.

DECLARATIONS

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

The inform consent was taken from the patient's parents for publication.

Availability of data and material:

Please contact authors for data requests.

Competing interests:

The authors declare that they have no competing interests.

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