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EFFICACY OF RECOMBINANT GROWTH HORMONE THERAPY IN TWO PATIENTS WITH THE FAMILIAL FORM OF SCHAAF-YANG SYNDROME*

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Introduction. As of May 2022, approximately 250 cases of Schaaf-Yang syndrome (SYS) have been reported worldwide. SYS is an autosomal dominant multisystem disorder that occurs with equal frequency in both sexes and across all ethnic groups. Only a few familial cases have been described to date [1]. The first report of clinical features resembling SYS was published by D. Chitayat et al. (1990) [2], although the term *Schaaf-Yang syndrome* was later proposed by Christian P. Schaaf and Yaping Yang, who in 2013 characterized SYS as a distinct imprinting disorder with phenotypic overlap with Prader-Willi syndrome (PWS) [3]. In the same year, the first four individuals with truncating mutations in the paternal copy of the *MAGEL2* gene were identified [3].

SYS clinically overlaps with Prader-Willi syndrome (PWS) during early life; however, the phenotypic distinctions become increasingly apparent throughout childhood and adolescence [4]. The most prominent features of the syndrome include hypotonia (reduced muscle tone), joint contractures, and global developmental delay, which may progress to intellectual disability and autism spectrum disorder [5].

Typically, the condition manifests at birth with muscular hypotonia and distal joint contractures in the majority of affected individuals [6]. Gastrointestinal (GI) and feeding difficulties are particularly pronounced during the neonatal period and infancy; later in life, these may evolve into hyperphagia and obesity in adulthood, although generally less severe than in PWS [7]. Respiratory distress syndrome is present in many neonates, with approximately half requiring intubation and mechanical ventilation, and around 20 % undergoing tracheostomy [8]. Additional skeletal manifestations, such as scoliosis and decreased bone mineral

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density, are frequently observed. Other reported features include short stature, seizures, ophthalmologic abnormalities, and hypogonadism [9].

The adult phenotype of SYS is variable [7]. Based on data from a cohort of seven adult patients, the following clinical features have been described: cognitive functioning ranges from complete dependence on external assistance to mild intellectual disability or borderline cognitive functioning; most adults reported to date possess verbal communication skills and basic reading abilities, and some are capable of employment in structured environments. Common behavioral issues include reduced initiative and motivation, stubbornness, and social withdrawal. Features of autism spectrum disorder (ASD) are present in the majority of cases, and heightened anxiety is observed in nearly all individuals. Hyperphagia and obesity characterize most adults with SYS. Although these manifestations are variable, the onset of obesity appears to occur later than in PWS, where it typically develops during childhood [10]. In adulthood, obesity may lead to features of metabolic syndrome, including hyperlipidemia and insulin resistance [7]. Chronic constipation and gastroesophageal reflux are present in the majority of affected adults. Hypogonadism has been reported in 15–65 % of cases (15–25 % in females and 55–65 % in males), depending on the phenotype of the external genitalia.

The diagnosis of SYS is established in a proband by the identification of a heterozygous pathogenic or likely pathogenic variant in the *MAGE Family Member L2* (*MAGEL2*) gene (OMIM 605283), located on chromosome 15 within the critical PWS region (15q11-15q13) [11]. This gene is subject to maternal imprinting (i.e., the maternal allele is epigenetically silenced) and is expressed exclusively from the paternal chromosome. *MAGEL2* is part of a cluster of imprinted genes essential for normal neurodevelopment; therefore, pathogenic variants affecting the paternal allele result in disease due to maternal imprinting [12, 13]. *MAGEL2* has long been recognized as one of the critical imprinted protein-coding genes implicated in the phenotype of Prader-Willi syndrome (PWS; OMIM #176270), and the absence of *MAGEL2* expression has been shown to play a crucial role in the pathogenesis of PWS. As the clinical cohort of individuals with truncating pathogenic variants in *MAGEL2* expanded, a distinct phenotypic profile became increasingly evident, ultimately leading to the recognition and designation of Schaaf-Yang syndrome (SYS; OMIM #615447) as a separate clinical entity.

Approximately 50 % of individuals diagnosed with SYS have inherited a pathogenic *MAGEL2* variant from a clinically unaffected father, while the remaining cases arise de novo. If the proband's father is heterozygous for the pathogenic *MAGEL2* variant identified in the proband, the recurrence risk for siblings, both male and female, is 50 %. The recurrence risk for relatives on the maternal side is equivalent to that of the general population. Once a pathogenic *MAGEL2* variant has been identified in an affected family member, prenatal testing in high-risk pregnancies and preimplantation genetic testing are available options [14].

The diagnosis of SYS may be supported by the presence of any of the following hormonal or metabolic abnormalities: low levels of insulin-like growth factor 1 (IGF-1) despite normal body weight and adequate nutritional status in the child; elevated glucose levels during an oral glucose tolerance test (OGTT); and increased fasting ghrelin concentrations [14].

When SYS is suspected, definitive diagnosis relies on molecular genetic testing through the identification of a heterozygous pathogenic (or likely pathogenic) variant in the paternal allele of *MAGEL2* [15]. According to the ACMG/AMP guidelines for variant interpretation, the terms *pathogenic variant* and *likely pathogenic variant* are considered clinically equivalent, meaning that both are regarded as diagnostic and may be used to guide clinical decision-making [16]. In this GeneReview, references to «pathogenic variants» are understood to include likely pathogenic variants as well [10]. The identification of a heterozygous *MAGEL2* variant of uncertain significance (VUS) in the paternal allele neither confirms nor excludes the diagnosis of SYS and requires further reclassification and segregation analysis.

Management of patients with SYS includes correction of congenital anomalies (musculoskeletal, ophthalmologic, and neurological) in accordance with established standards of care.

In cases of confirmed hypothyroidism, thyroid hormone replacement therapy with levothyroxine should be initiated at age-appropriate optimal doses.

In the presence of cryptorchidism, treatment is conducted according to current clinical guidelines, including administration of human chorionic gonadotropin (hCG) or surgical intervention when indicated.

Currently, the indication, safety, and efficacy of recombinant human growth hormone (rhGH) therapy in patients with SYS are widely discussed in the literature [17]. Given that SYS and PWS share several phenotypic features-including short stature, muscular hypotonia, and developmental delay/intellectual disability-and considering evidence suggesting that, similar to PWS, growth hormone (GH) deficiency may also be a feature of SYS, the use of rhGH therapy appears pathogenetically justified. Although rhGH therapy has been approved for the treatment of PWS, its effects in individuals with SYS have not yet been fully documented. Patients with SYS are frequently treated with rhGH; however, evidence regarding its efficacy remains limited. Nevertheless, despite the relatively small number of reported cases, positive outcomes have already been observed. A retrospective analysis of rhGH treatment in children with SYS, including 14 treated individuals and 12 untreated controls, demonstrated a significant increase in linear growth in the treated group over six months, with improvement in the mean height z-score from −2.6 to −1.7 following therapy [18]. Parental satisfaction with rhGH therapy was high, and subjective improvement or marked improvement in muscle strength was reported in 13 of 14 treated individuals. Similarly, Juriaans A.F., Hokken-Koelega A.C., and colleagues [19] reported favorable outcomes. The mean (95 % CI) height standard deviation score (SDS) significantly increased from −1.74 (−3.55; 0.07) at baseline to −0.05 (−1.87; 1.77) after four years of rhGH therapy in seven patients. Treatment was associated with significant improvement in height SDS, absolute height, and body mass index (BMI).

This study **aimed** to evaluate the clinical and laboratory efficacy of recombinant human growth hormone therapy in 2 siblings with Schaaf-Yang syndrome.

Own Data, clinical cases.

Patient S., male, aged 11 years and 10 months. The parents report concerns regarding delayed cognitive development and short stature, muscular weakness, and atopic dermatitis. According to the medical history, the patient was born from the mother's third uncomplicated pregnancy at 40 weeks of gestation, with a birth weight of 3,450 g and a length of 49 cm. Delivery was performed by cesarean section. The mother's first pregnancy was spontaneous and uneventful, resulting in the birth of a child (see below). The second pregnancy had a normal course; delivery was also by cesarean section. The infant died on the third day of life due to birth trauma and asphyxia.

Since birth, the boy has exhibited contractures of all fingers on both hands. By the third year of life, following intensive therapy (physiotherapy and therapeutic massage), residual contractures persisted in the distal phalanges of the fourth and fifth fingers of both hands.

During the neonatal period and up to two years of age, significant feeding difficulties were observed, including absence of the sucking reflex. The patient began consuming solid foods and chewing at the age of three years. Persistent complaints include abdominal bloating, chronic constipation, and gastroesophageal reflux (GER).

Psychomotor developmental delay has been evident since early childhood, accompanied by marked muscular hypotonia. The patient achieved independent sitting at 2.5 years of age and independent walking at 3.8 years. At present, he speaks only single words, with no coherent sentence formation, and demonstrates significant intellectual disability, although he is able to establish social contact. Growth delay has been present since birth. Manifestations of atopic dermatitis were observed from the age of two years. Scoliosis was diagnosed at five years of age.

Physical examination at initial presentation: height 116 cm (height SDS −4.1); body weight 21 kg (weight SDS −1.9) [20]. Linear growth velocity was below the 3rd percentile (see Photo 1). Dysmorphic features included hy-

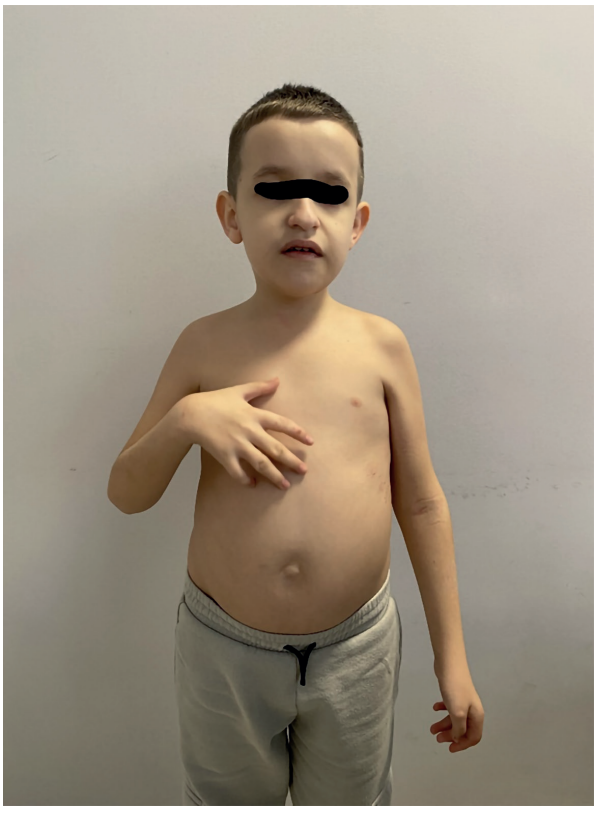

Photo 1. External appearance of Patient S., aged 11 years 10 months; height 116 cm (height SDS = – 4.8).
Note: Written informed consent for publication of the photographs was obtained from the patient's parents.

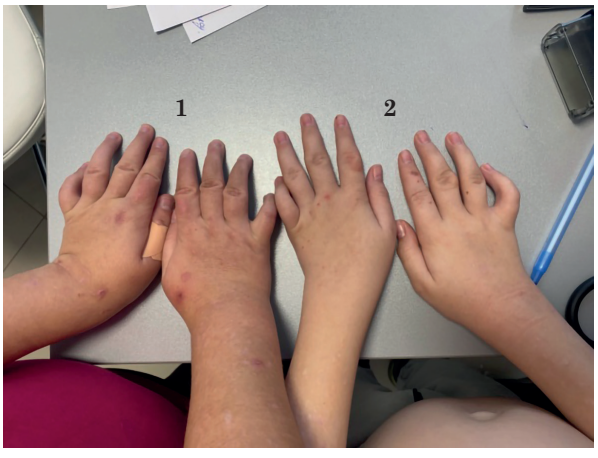

Photo 2. Patients T. (1) and S. (2): joint contractures and atopic dermatitis.

pertelorism, downslanting palpebral fissures, a pointed nasal tip, and large ears (see Photo 1). Musculoskeletal examination revealed thoracic kyphosis, clinodactyly, and contractures of the fifth fingers on both hands (identical findings were observed in the patient's sister and mother) (Photo 2).

The thyroid gland was not enlarged. Permanent dentition was present, with enamel defects and malocclusion, maxillary hypoplasia, and multiple dental caries; the patient was wearing fixed metal orthodontic applian-

Table 1

Dynamics of anthropometric and hormonal parameters in patient S. during recombinant human growth hormone (rhGH) therapy

Parameter	Before initiation of rhGH therapy	Seven months after initiation of rhGH therapy	Fifteen months after initiation of rhGH therapy
Age, years, months	12 yrs 2 mo	12 yrs 9 mo	13 yrs 3 mo
Height, cm	116	122	128
SD_{height}	~	~	~
SDS_{height}	—	-	—
Change in height from baseline, cm		+ 8	+ 12
Body weight, kg	21	25	26.5
Change in body weight from baseline, kg		+ 4	+ 5.5
SDS_{weight}	—	—	—
IGF-1, ng/mL	20	106	280
SDS_{IGF}	—	—	—
rhGH dose, mg/day		0.6	0.9
Growth velocity, cm/mo		+ 1.1	+ 0.9
Bone age, years	7		11

ces. The skin was dry and pale with a yellowish hue; mild pastosity was noted without peripheral edema. Hair was brittle. Signs of atopic dermatitis were present (see Photo 2). Abdominal distension and constipation were noted. The liver was palpable 3 cm below the right costal margin. Sexual development corresponded to Tanner stage I; cryptorchidism was absent. The child wore diapers and lacked self-care skills.

Molecular genetic testing identified a heterozygous variant in the *MAGEL2* gene: c.2873G > A (p.Trp958*), inherited from the father. The same variant was detected in the patient's biological sister. This variant represents a nonsense mutation resulting in a premature stop codon and subsequent protein truncation and is classified as pathogenic. Its identification fully confirms the clinical diagnosis of Schaaf-Yang syndrome (SYS).

Laboratory evaluation: IGF-1 20.1 ng/mL, (reference range 143–506 ng/mL); IGF-1 SDS –5.28 (markedly decreased) [21], basal GH 0.84 ng/mL; prolactin (PRL) 522 mIU/L (reference range up to 320 mIU/L); thyroid-stimulating hormone (TSH) — 0.88 mIU/L; free thyroxine (fT4) — 1.12 ng/mL; anti-thyroid peroxidase antibodies (anti-TPO) — 10 IU/mL, within reference values. Hand radiograph: bone age corresponded to seven years, with disruption of the normal sequence of ossification [18, 22].

Given the markedly reduced IGF-1 levels and delayed bone age, the child exhibited clear clinical and biochemical features consistent with GH deficiency. The confirmed molecular genetic diagnosis further supported the indication for initiating rhGH replacement therapy at a dose of 0.025 mg/kg/day. The dynamics of anthropometric and hormonal parameters are presented in Table 1.

As early as the first seven months of rhGH therapy, positive dynamics were observed in the emotional, physical, and cognitive domains. Improvements included increased muscle strength and enhanced physical activity (the patient began playing football). The boy started speaking fluently, engaging in communication, and attending a mainstream school with individualized instruction. Self-care skills emerged: he began eating independently, was able to hold a spoon and fork, used the toilet independently, and diapers were discontinued. Gastrointestinal symptoms also improved, with resolution of constipation and abdominal distension, normalization of bowel movements, and improved appetite. A complete clinical remission of atopic dermatitis was achieved. After 15 months of rhGH therapy at a dose of 0.9 mg/day, the positive trend persisted, with gradual further improvement in psycho-emotional functioning, self-care abilities, speech, learning capacity, linear growth, and bone age advancement (+4 years). rhGH therapy was continued at an increased dose of 1.0 mg/day.

Patient T., female, aged 18 years and 10 months, the biological sister of Patient S. The parents reported delayed cognitive development, impaired social adaptation, short stature, muscular weakness, atopic dermatitis, obesity, hyperphagia, and irregular menstrual cycles. According to the medical history, she was born from the mother's first uncomplicated pregnancy at 41–42 weeks of gestation, with a birth weight of 3,850 g and a length of 52 cm. Delivery was performed by cesarean section. Since birth, contractures of all fingers on both hands were noted. By the fifth year of life, following intensive therapy (physiotherapy and therapeutic massage), residual contractures persisted in the distal phalanges of the fourth and fifth fingers of both hands. During the neonatal period and up to two years of age, feeding difficulties were present, including absence of the sucking reflex. She began consuming solid foods and chewing at the age of eight years. Persistent gastrointestinal complaints included abdominal bloating and chronic diarrhea. In early childhood, she frequently suffered from obstructive bronchitis and pneumonia, averaging 2–3 episodes per year. From the age of 1.5 years, she received prolonged glucocorticoid therapy. Due to glucocorticoid overexposure, she developed Cushingoid features, followed by progressive weight gain beginning at five years of age.

Psychomotor developmental delay was evident from early childhood. Until the age of seven years, the patient demonstrated minimal response to external stimuli and speech. Marked muscular hypotonia was present. She achieved independent sitting at four years of age and

Table 2

Dynamics of clinical and laboratory parameters during rhGH therapy in patient T.

Parameter	Before initiation of rhGH therapy	Fifteen months after initiation of rhGH therapy
Age, years, months	18 yrs 6 mo	19 yrs 8 mo
Height, cm	134	134
SD_{height}	~	~
SDS_{height}	—	—
Body weight, kg	68.5	60.0
Change in body weight from baseline, kg		—
Body fat percentage, %	51	45
Fat mass, kg	30.6	27.4
Visceral fat percentage, %	9	7
Muscle mass percentage, %	52.1	56.0
Muscle mass, kg	28	31.7
SDS_{weigt}	+ 1.5	+ 1.2
IGF-1, ng/mL	80	130
SDS_{IGF}	—	– 1.2
rhGH dose, mg/day		0.3

independent walking at 6.5 years. Hypothermia was observed until the age of five years, with persistently low body temperature ranging from 34.5 to 35.5 °C. At present, she speaks in simple sentences, possesses basic self-care skills, and is socially interactive and friendly. Growth delay has been present since birth. Manifestations of atopic dermatitis have been noted since the age of two years. Scoliosis was diagnosed at seven years of age.

Physical examination at initial presentation: height 134 cm (height SDS −4.5); body weight 68 kg (weight SDS +1.5) [20]. Bioimpedance analysis revealed a fat mass of 30.6 kg (51 %), visceral fat mass of 9 kg, muscle mass of 28 kg (52.1 %), and bone mass of 1.7 kg [21]. Dysmorphic features included hypertelorism, moderately downslanting palpebral fissures, a pointed nasal tip, a wide mouth, and large ears (see Photo 3). Musculoskeletal examination demonstrated thoracic kyphosis, clinodactyly, and contractures of the fifth fingers on both hands (identical findings were observed in the brother and mother) (Photo 2). The thyroid gland was not enlarged. Permanent dentition was present, with enamel defects, malocclusion, and maxillary hypoplasia. The skin was dry with mild pastosity and no peripheral edema. Hair was brittle. Signs of atopic dermatitis were present (see Photo 2). Abdominal distension and constipation were noted. The liver was palpable 3 cm below the right costal margin. Abdominal ultrasound demonstrated features consistent with hepatic steatosis. Sexual development corresponded to Tanner stage V. Menarche occurred at the age of 16 years. Since menarche, the menstrual cycle has been irregular, with menses occurring 2-3 times per year.

Molecular genetic testing identified a heterozygous variant in the *MAGEL2* gene: c.2873G > A (p.Trp958*), inherited from the father, which fully confirms the clinical diagnosis of Schaaf-Yang syndrome (SYS). The same variant was also detected in the patient's biological brother (see above).

Laboratory evaluation: IGF-1 80 ng/mL, IGF-1 SDS −2.8 (decreased) [21] (reference range 155–480 ng/mL); basal GH 0.9 ng/mL; PRL 320 mIU/L (reference range up to 320 mIU/L); TSH 1.2 mIU/L; fT4 1.15 ng/mL; anti-TPO 9 IU/mL, within reference values. Lipid profile demonstrated dyslipoproteinemia, with elevated total cholesterol (6.1 mmol/L) and low-density lipoprotein cholesterol (LDL-C)

Photo 3. External appearance of Patient T., aged 18 years 6 months; height 134 cm (height SDS = – 4.5).
Note: Written informed consent for publication of the photographs was obtained from the patient's parents.

(2.5 mmol/L). Fasting insulin was 45.6 μIU/mL, and fasting glucose was 5.6 mmol/L.

Pelvic ultrasound (transabdominal): uterine hypoplasia; ovaries with a follicular pattern; endometrial thickness 3 mm. Conclusion: Primary oligomenorrhea. Hand radiograph: bone age corresponded to 18 years, with complete closure of the epiphyseal growth plates [18, 22].

Given the intellectual and physical impairments, as well as the decreased IGF-1 levels, rhGH therapy was initiated at a low dose of 0.3 mg/day with the aim of correcting metabolic abnormalities. The dynamics of clinical and laboratory parameters during therapy are presented in Table 2.

After 15 months of rhGH therapy, positive dynamics were observed in both clinical and laboratory parameters, as well as in the emotional, physical, and cognitive domains. Improvements included increased muscle strength, enhanced physical activity, favorable changes in psycho-emotional status, improved social adaptation, and a reduction in behavioral disturbances. From the gastrointestinal perspective, clinical improvement was also noted, including resolution of constipation and abdominal distension, normalization of bowel movements, and a reduction in appetite. Favorable changes in anthropometric parameters were documented, with a decrease in fat mass and an increase in muscle mass (Photo 3). The menstrual cycle remains irregular. Given the presence of oligomenorrhea, uterine and endometrial hypoplasia, and clinical and laboratory signs of insulin resistance, rhGH therapy was continued at a low dose of 0.3 mg/day in combination with hormone replacement therapy (estradiol 1 mg/dydrogesterone 10 mg) and metformin at a dose of 500 mg/day.

CONCLUSIONS

1. In both patients with the familial form of Schaaf-Yang syndrome, growth hormone deficiency was confirmed based on low basal growth hormone levels, decreased IGF-1 standard deviation score, delayed bone age, and molecular genetic sequencing, in the context of the typical clinical phenotype of Schaaf-Yang syndrome (hypotonia, joint contractures, and developmental delay).
2. In the 11-year-old boy, 15 months of recombinant human growth hormone therapy resulted in a marked acceleration of linear growth (+12 cm over 15 months), significant advancement of bone age (+4 years), improvement in cognitive and social functioning, and normalization of muscle tone and motor activity.
3. In the female patient (aged >18 years), 15 months of recombinant human growth hormone therapy were associated with improvement in body composition, including a 6 % reduction in fat mass and a 3.9 % increase in muscle mass. Positive changes in metabolic control were observed, along with a marked decrease in appetite and a reduction in body weight of 10.8 kg. Psycho-emotional stabilization was also noted, manifested by improved social adaptation and a reduction in behavioral disturbances.
4. Recombinant human growth hormone therapy demonstrated a favorable safety profile and high efficacy in patients with Schaaf-Yang syndrome, both in childhood and in adolescence/adulthood.

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EFFICACY OF RECOMBINANT GROWTH HORMONE THERAPY IN TWO PATIENTS WITH THE FAMILIAL FORM OF SCHAAF-YANG SYNDROME

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Schaaf-Yang syndrome (SYS) is an autosomal dominant multisystem disorder with early clinical overlap with Prader–Willi syndrome. Key features include hypotonia, joint contractures, autism spectrum disorders, intellectual disability, and growth retardation. The feasibility and efficacy of recombinant human growth hormone (rhGH) therapy in SYS remain under discussion. This study **aimed** to evaluate the clinical and laboratory efficacy of recombinant human growth hormone therapy in 2 siblings with Schaaf-Yang syndrome.

Materials and methods. Two siblings with SYS were examined: an 11.10-year-old boy and his 18.2-year-old sister. Serum GH, IGF-1, TSH, free T4, and prolactin levels were measured by ELISA. Bone age was assessed using the Greulich–Pyle method. Anthropometric parameters were evaluated according to WHO standards. Molecular genetic testing identified a heterozygous nonsense variant in the *MAGEL2* gene (c.2873G > A, p.Trp958*), inherited from the father, confirming the diagnosis of SYS in both patients. Both received rhGH in pediatric and adult dosage and the efficacy was assessed.

Results. The boy presented with congenital finger contractures, persistent hypotonia, feeding difficulties in infancy, chronic constipation, gastroesophageal reflux, and severe psychomotor delay (independent sitting at 2.5 years, walking at 3.8 years). Baseline GH was 0.84 ng/mL. rhGH therapy was initiated at 0.035 mg/kg/day. After 15 months, height increased from 116 to 128 cm (SDS −4.8 to −4.2), weight from 21.1 to 26.5 kg, and growth velocity reached +12 cm. IGF-1 increased from 20.0 to 126.0 ng/mL (SDS −5.28 to −2.40), and bone age progressed from 7 to 11 years. Marked improvements were noted in muscle strength, physical activity, speech development, communication, and self-care skills. The sister exhibited intellectual disability, social maladaptation, short stature, muscle weakness, obesity with hyperphagia, atopic dermatitis, and secondary amenorrhea. Baseline height was 134 cm (SDS −4.5), bone age 18 years, IGF-1 80 ng/mL (SDS −2.8), and GH 0.9 ng/mL, with normal thyroid and prolactin levels. She received rhGH 0.3 mg/day combined with estradiol and dydrogesterone. After 15 months, fat mass decreased from 51 % to 45 %, muscle mass increased from 28 to 31.7 kg, and body weight decreased from 68.8 to 58.0 kg. Clinical improvements included reduced appetite, increased physical activity, better social adaptation, reduced behavioral disturbances, and normalization of the menstrual cycle.

Conclusions. Patients with Schaaf-Yang syndrome demonstrate clinical and laboratory signs consistent with growth hormone deficiency. Recombinant human growth hormone therapy appears safe and effective in both pediatric and adult patients, significantly improving growth parameters, body composition, and psychoemotional functioning.

Keywords: Schaaf-Yang syndrome, recombinant human growth hormone, therapy.

ЕФЕКТИВНІСТЬ ТЕРАПІЇ РЕКОМБІНАНТНИМ ГОРМОНОМ РОСТУ У ДВОХ ПАЦІЄНТІВ ІЗ СІМЕЙНОЮ ФОРМОЮ СИНДРОМУ ШААФА-ЯНГА

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Синдром Шаафа-Янга (SYS) — це аутосомно-домінантне мультисистемне захворювання, яке на ранніх етапах клінічно схоже на синдром Прадера-Віллі. Ключові ознаки включають гіпотонію, контрактури суглобів, розлади аутистичного спектра, інтелектуальну недостатність та затримку росту. Доцільність та ефективність терапії рекомбінантним гормоном росту людини (рГР) при SYS залишаються предметом обговорення. Це дослідження мало на **меті** оцінити клінічну та лабораторну ефективність терапії рекомбінантним гормоном росту людини у брата та сестри із синдромом Шаафа-Янга.

Матеріали та методи. Обстежено двох сибсів із SYS: хлопчика (пацієнт С.) віком 11 років 10 місяців та його сестру (пацієнтка Т.) віком 18 років 2 місяці. Рівні ГР, ІФР-1, ТТГ, вільного Т4 та пролактину в сироватці крові визначали методом ІФА. Кістковий вік оцінювали за методом Грейліха-Пайла. Антропометричні параметри оцінювали відповідно до стандартів ВООЗ. Молекулярно-генетичне тестування виявило гетерозиготний нонсенс-варіант у гені *MAGEL2* (c.2873G > A, p.Trp958*), успадкований від батька, що підтвердило діагноз SYS у обох пацієнтів. Обидва отримували рГР у дитячому та дорослому дозуванні, після чого було проведено оцінку ефективності.

Результати. Пацієнт С.: спостерігалися вроджені контрактури пальців, стійка гіпотонія, труднощі з годуванням у грудному віці, хронічні запори, гастроезофагеальний рефлюкс та виражена затримка психомоторного розвитку (самостійно сів у 2,5 роки, почав ходити у 3,8 роки). Базальний рівень ГР 0,84 нг/мл, ІФР-1 20 нг/мл. Терапію рГР розпочато в дозі 0,035 мг/кг/добу. Через 15 місяців зріст збільшився зі 116 до 128 см (SDS від −4,8 до −4,2), вага — з 21,1 до 26,5 кг, а швидкість росту сягнула +12 см. Рівень ІФР-1 підвищився до 126,0 нг/мл (SDS від −5,28 до −2,40), а кістковий вік прогресував із 7 до 11 років. Відмічено значне покращення м'язової сили, фізичної активності, розвитку мовлення, комунікації та навичок самообслуговування. Сестра, пацієнтка Т.: мала інтелектуальну недостатність, соціальну дезадаптацію, низький зріст, м'язову слабкість, ожиріння з гіперфагією (надмірним апетитом), атопічний дерматит та вторинну аменорею. Початковий зріст становив 134 см (SDS −4,5), кістковий вік 18 років, ІФР-1 80 нг/мл (SDS −2,8), ГР — 0,9 нг/мл при нормальних рівнях гормонів щитоподібної залози та пролактину. Вона отримувала рГР у дозі 0,3 мг/добу у поєднанні з естрадіолом та дидрогестероном. Через 15 місяців вміст жирової маси знизився з 51 % до 45 %, м'язова маса зросла з 28 до 31,7 кг, а маса тіла зменшилася з 68,8 до 58,0 кг. Клінічні покращення включали зниження апетиту, підвищення фізичної активності, кращу соціальну адаптацію, зменшення поведінкових порушень та нормалізацію менструального циклу.

Висновки. Пацієнти із синдромом Шаафа-Янга демонструють клінічні та лабораторні ознаки, що відповідають дефіциту гормону росту. Терапія рекомбінантним гормоном росту людини є безпечною та ефективною як для дітей, так і для дорослих пацієнтів і значно покращує параметри росту, склад тіла та психічні й когнітивні функції.

Ключові слова: синдром Шаафа-Янга, рекомбінантний гормон росту людини, терапія.