PRIKAZ SLUČAJA

UDK BROJEVI:
616-008.9-056.1:615.357
615.357.015.3:577.175.3
DOI: http://doi.org/10.5937/zdravzast50-30794

PRVI PRIKAZ UČINKA TERAPIJE HORMONOM RASTA KOD PACIJENTA SA SPONDILODISPLASTIČNIM TIPOM EHLERS-DANLOSOVOG SINDROMA I NORMALNOM SEKRECIJOM HORMONA RASTA

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SAŽETAK

Uvod/Cilj: Spondilodisplastični tip Ehlers-Danlosovog sindroma (sdEDS) je redak genetski poremećaj sinteze kolagena, uzrokovan mutacijama u B4GALT7, B3GALT6 ili u SLC39A13 genu. Karakteristike ovog veoma retkog poremećaja su nizak rast, hipotonija, hiperfleksibilni zglobovi, meka, tanka i preterano rastegljiva koža, retka kosa i obrve, stariji izgled lica, široko čelo i sporo zarastanje rana. Molekularna genetska analiza je neophodna za definitivnu potvrdu dijagnoze. Do sada su objavljena samo tri prikaza, koja opisuju odgovor na lečenje hormonom rasta (HR) kod pacijenata sdEDS. Svi ovi pacijenti su imali nedostatak HR. Predstavljamo prvi prikaz primene HR kod pacijenta sa sdEDS i normalnom sekrecijom HR.
Prikaz slučaja: Pacijent je bila devojčica niskog rasta sa normalnom sekrecijom HR. Kod devojčice je, imajući u vidu da je rođena mala za gestaciono doba, zbog niskog rasta započeto sa primenom HR, pre nego što je postavljena dijagnoza sdEDS. Zbog slabog terapijskog odgovora, odnosno spore brzine rasta uz primenu HR, kao i zbog fenotipa, sprovedena su genetska ispitivanja, kojima je postavljena dijagnoza sdEDS usled bialelne mutacije B4GALT gena. Po postavljanju dijagnoze sdEDS, kao i zbog neadekvatnog odgovora na terapiju, terapija HR je prekinuta u uzrastu od 11 godina.
Zaključak: Ovo je prvi prikaz primene terapije HR kod deteta sa sdEDS i normalnom sekrecijom HR, koja ukazuje na veoma ograničen terapijski efekat HR na linearni rast deteta sa sdEDS.

Ključne reči: spondilodisplastični tip Ehlers-Danlosovog sindroma (sdEDS), beta-1,4 galaktoziltransferaza 7 (B4GALT7) , terapija hormonom rasta

Uvod

Ehlers-Danlosov sindrom (engl. *Ehlers-Danlos syndrome - EDS*) predstavlja grupu retkih nasledni poremećaja vezivnog tkiva, koji za posledicu imaju poremećaj sinteze kolagena. Prema međunarodnoj klasifikaciji Ehlers-Danlosovog sindroma, postoji trinaest tipova EDS-a: klasična forma EDS-a, kardio-valvularni, vaskularni, hipermobilni, artrohalazija EDS, dermatosparaksis, kifoskolioza, sindrom krhke rožnjače, spondilodisplastični EDS, mukulokontrakturalni EDS, miopatički EDS, i periodontalni EDS (1).

Spondilodisplastični tip Ehlers-Danlosovog sindroma (sdEDS) može biti uzrokovan mutacijom u B4GALT7 genu (kodira ß1,4-galaktoziltransferazu 7), B3GALT6 (kodira ß1,3-galaktoziltransferazu 6) ili SLC39A13 genu (kodira transmembranski protein transporter cinka). Bialelne varijante u B4GALT7 genu se dovode u vezu sa sdEDS, a do sada su registrovana trideset i tri pacijenta sa značajnom fenotipskom varijabilnošću (2).

B4GALT7 gen se nalazi na hromozomu 5 i kodira ß 1,4-galaktoziltransferazu, koji vezuje glikozaminoglikane za proteoglikane u vezivnim tkivima. Proteoglikani su velika komponenta ekstracelularnog matriksa i važni su za strukturu i funkciju vezivnog tkiva (3,4).

Minimalni klinički kriterijumi koji ukazuju na dijagnozu sdEDS su sledeći: nizak rast i mišićna hipotonija (veliki kriterijumi), u kombinaciji sa barem tri mala kriterijuma i karakterističnim radiografskim abnormalnostima (Tabela 1). Konačna dijagnoza zahteva potvrdu molekularnih genetskih analiza (5).

CASE REPORT

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616-008.9-056.1:615.357
615.357.015.3:577.175.3
DOI: http://doi.org/10.5937/zdravzast50-30794

FIRST REPORT ON GROWTH HORMONE TREATMENT RESPONSE IN A PATIENT WITH SPONDYLODYSPLASTIC TYPE OF EHLERS-DANLOS SYNDROME WITH NORMAL GROWTH HORMONE SECRETION

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SUMMARY

Introduction/Aim: Spondylodysplastic Ehlers-Danlos Syndrome (sdEDS) is a rare genetic disorder of collagen synthesis, caused by a mutation in the B4GALT7, B3GALT6, or SLC39A13 gene. Features of this very rare disorder are short stature, hypotonia, hyperflexible joints, soft, thin, and overly stretchable skin, sparse hair and eyebrows, elderly face, wide forehead and prolonged wound healing. Molecular genetic analysis is needed for definite confirmation of the diagnosis. So far, only three case reports describing growth hormone treatment response in patients with sdEDS have been published. All of these patients had growth hormone (GH) deficiency. We present the first case report regarding growth hormone treatment response in a patient with sdEDS and normal GH secretion (without GH deficiency).
Case report: Patient was a girl with short stature and normal GH secretion. Having in mind that the girl was born small for the gestational age, due to her short stature, she started using HR, before the diagnosis of sdEDS was made. Based on the lack of improvement in growth velocity as well as the girl's phenotype, genetic analyses were performed and the diagnosis of sdEDS due to biallelic mutations of the B4GALT7 gene was established. After the diagnosis of sdEDS was made and due to suboptimal response in growth velocity to the GH treatment, the GH therapy was stopped at the age of 11 years.
Conclusion: This is a first case report regarding GH treatment in a child with sdEDS and normal GH secretion, demonstrating a very limited therapeutic effect of GH on linear growth in the presented patient.

Keywords: spondylodysplastic Ehlers–Danlos Syndrome (sdEDS), beta-1,4-galactosyltransferase 7 (B4GALT7), growth hormone treatment

Introduction

Ehlers-Danlos Syndrome (EDS) represents a group of rare hereditary connective tissue disorders, resulting in a disruption of collagen synthesis. According to the International classification of Ehlers-Danlos Syndrome, there are thirteen types of EDS: Classical EDS, Classical-like EDS, cardiac-valvular, vascular, hypermobile, arthrochalasia EDS, dermatospraxis, kyphoscoliotic, brittle cornea syndrome, spondylodysplastic EDS, musculocontractural EDS, myopathic EDS, periodontal EDS (1).

Spondylodysplastic type of Ehlers-Danlos syndrome (sdEDS) can be caused by mutations in the B4GALT7 (encodes β1,4-galactosyltransferase 7), B3GALT6 (encodes β1,3- galactosyltransferase 6) or SLC39A13 (encodes transmembrane zink like protein 13) genes. Biallelic variants in B4GALT7 have been associated with sdEDS, with thirty-three patients reported to date with significant phenotypic variability (2).

B4GALT7 gene is located on chromosome 5 and it encodes beta-1,4-galactosyltransferase which links glycosaminoglycans to proteoglycans in connective tissues. Proteoglycans are a major component of the extracellular matrix and are important for the structure and function of connective tissue (3,4).

Minimal clinical criteria suggesting the diagnosis of spEDS are: short stature and muscle hypotonia (major criteria), combined with at least three minor criteria and characteristic radiographic ab-

Tabela 1. „Major" i „minor" kriterijumi za dijagnozu spondilodisplastičnog tipa Ehlers-Danlosovog sindroma (1)

„Major" kriterijumi	„Minor" kriterijumi
Nizak rast Mišićna hipotonija Angulacija ekstremiteta	Preterana rastegljivost kože, meka koža poput testa Spušteno stopalo Usporen motorni razvoj Osteopenija Usporen kognitivni razvoj Gen-specifični minorni kriterijumi za B4GALT7 mutaciju: – Radioulnarna sinostoza – Bilateralne kontrakture lakta i ograničena pokretljivost lakta – Generalizovana hipermobilnost zglobova – Simianska linija na dlanu – Karakteristične kraniofacijalne osobine (trouglasto lice, razmaknute oči, proptoza, uska usta, nisko spuštene uši, retka kosa skalpa, abnormalan raspored i broj zuba, ravno lice, široko čelo, plava sklera, i rascep nepca) – Karakteristični radiografski nalazi (uključuju radioulnarnu sinostozu, deformitete metafize, osteopeniju, subluksaciju ili dislokaciju lakta, i kratku ključnu kost sa širokim medijalnim krajevima) – Ozbiljna hipermetropija – Zamagljena rožnjača

Do sada je u medicinskoj literaturi prijavljeno jedanaest pacijenata sa sdEDS i B4GALT7 mutacijom (2,4-7).

Iako je nizak rast prisutan praktično kod svih pacijenata sa sdEDS, ishodi lečenja hormonom rasta su samo sporadično prijavljivani kod ovih pacijenata, a do sada su objavljena samo tri prikaza slučaja pacijenata sa sdEDS koji su primali hormon rasta (GH). Svi ovi pacijenti su imali nedostatak hormona rasta (5,8).

Cilj ovog prikaza slučaja je da prikaže odgovor na terapiju hormonom rasta deteta sa sdEDS i normalnim lučenjem hormona rasta (bez nedostatka ovog hormona).

Prikaz slučaja

Pacijentkinja je devojčica rođena kao drugo dete iz druge, redovno kontrolisane trudnoće. Tokom osmog meseca trudnoće, primećena je intrauterina restrikcija rasta (eng. I*ntrauterine Growth Restriction* - IUGR). Rođena je carskim rezom, u 39. nedelji gestacije, i bila je mala za gestaciono doba: težina na rođenju 2400 grama (< 10-og percentila) i dužina 44 cm (< 10-og percentila), dok je Apgar skor bio 9. Hipotonija je primećena tokom neonatalnog perioda, sa usporenim motornim razvojem tokom perioda odojčeta i ranog detinjstva. Mogla je da sedi bez pomoći sa 12 meseci, dok je samostalno mogla da hoda sa 4 godine. Od perioda odojčeta, išla je na fizikalnu terapiju i konsultacije kod ortopeda zbog usporenog motornog razvoja, luksacije kukova i deformiteta kičme (ozbiljna skolioza: leva torakalna i desna lumbalna skolioza) (Slika 1). Takođe je pratio kardiolog zbog atrijalnog septalnog defekta (ASD). Magnetna rezonanca je urađena sa 12 meseci zbog izbačenog čela i generalizovane hipotonije i pokazala je blagu redukciju bele mase supratentorijalno i ventrikulomegaliju. Takođe, *sella turcica* je opisana kao uvećana sa smanjenim parenhimom hipofize, u skladu sa dijagnozom „sindroma prazne *selle*". Kada je imala 21 mesec, upućena je na konsultacije kod endokrinologa zbog niskog rasta. Devojčicin deda je imao disekciju abdominalne aorte i nije bilo drugih značajnih nalaza u porodičnoj istoriji. Tata je bio visine 192,0 cm, a mama 169,0 cm, tako da je srednja vrednost visine roditelja bila 174,0 cm, sa skorom (z-skor) standardne devijacije (SD) od otprilike +1,5 SD.

Kao što je prikazano na slici 2, u uzrastu od 21 mesec, devojčica je imala ozbiljno nizak rast sa visinom 71,0 cm (z-skor -3,94 SD), telesnom težinom 6.430 g (-4,33 SD) i BMI 12,5 kg/m^2 (-2,67 SD). Bila je u prepubertetskom stadijumu, nije mogla da hoda samostalno. Ostatak fizičkog pregleda nije pokazao značajnije nalaze.

Nivoi kalcijuma, fosfora, alkalne fosfataze, elektrolita, tiroidnih hormona i kortizola, kao i

Table1. Major and minor criteria for diagnosis of spondylodysplastic Ehlers–Danlos Syndrome (1)

Major criteria	Minor criteria
Short stature	Skin hyperextensibility, soft, doughy skin
Muscle hypotonia	Pes planus
Bowing of limbs	Delayed motor development
	Osteopenia
	Delayed cognitive development
	Gene-specific minor criteria for B4GALT7 mutation: – Radioulnar synostosis – Bilateral elbow contractures or limited elbow movement – Generalized joint hypermobility – Single transverse palmar crease – Characteristic craniofacial features (triangular face, wide-spaced eyes, proptosis, narrow mouth, low-set ears, sparse scalp hair, abnormal dentition, flat face, wide forehead, blue sclerae, and cleft palate) – Characteristic radiographic findings (include radioulnar synostosis, metaphyseal flaring, osteopenia, radial head subluxation or dislocation, and short clavicles with broad medial ends) – Severe hypermetropia – Clouded cornea

normalities (Table 1). A final diagnosis requires confirmation by molecular testing (5).

Eleven patients with sdEDS and B4GALT7 mutation have been reported so far in the medical literature (2,4-7).

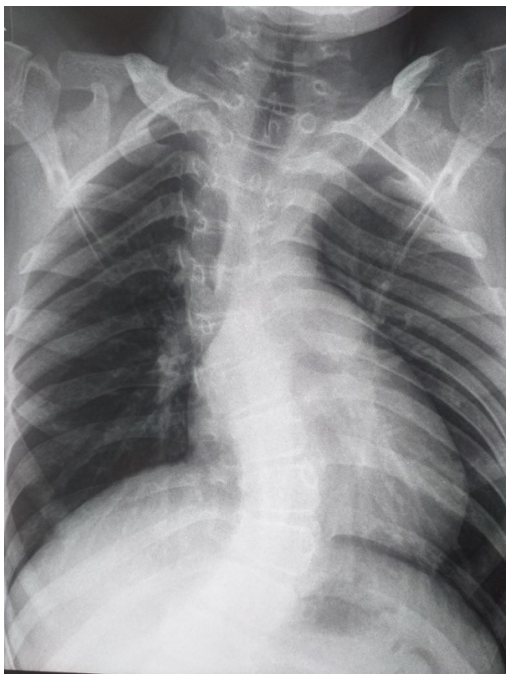
Although short stature, usually severe, is present in virtually all patients with sdEDS, outcomes of growth hormone treatment in these patients has been only sporadically reported, with case reports on only three patients with sdEDS receiving growth hormone (GH) treatment published so far. All of these patients had partial GH deficiency (5,8).

The aim of this case report was to present a response to growth hormone therapy in a child with sdEDS and normal secretion of GH (without GH deficiency).

Case report

The patient was a girl, born as a second child from second, regularly controlled pregnancy. During the eight month of pregnancy, intrauterine growth restriction (IUGR) was observed. She was delivered by caesarean section, at 39 weeks of gestation, small for gestational age (SGA): birth weight was 2400 grams (<10th percentile) and body length 44 cm (<10th percentile), Apgar score was 9. Hypotonia was noted during the neonatal period, with delayed motor development during infancy and early childhood. She was able to sit unassisted at the age of 12 months, walked independently at the age of 4 years. Since infancy, she had physical therapy and orthopedic consults due to slow motor development, hip luxation and spinal deformity (severe scoliosis: thoracic sinistro-convex and lumbar dextro-convex scoliosis) (Figure 1). She was also followed-up by a cardiologist because of an atrial septal defect (ASD). Because of the prominent forehead and generalized hypotonia magnetic resonance imaging (MRI) was performed at the age of 12 months, showing a mild degree of supratentorial white mass reduction and ventriculomegaly. Also, *sella turcic*a was described as enlarged with reduced parenchyma of the pituitary gland, consistent with the diagnosis of the Empty Sella Syndrome. At the age of 21 months, she was referred for an endocrinology consult because of her short stature. Girl's grandfather had an abdominal aortic dissection with no other notable findings in family history. Father's height is 192.0 cm, mother's height 169.0 cm, with girl's mid parental height at 174.0 cm, with standard deviation (SD) score (z-score) of approximately +1.5 SD.

As shown in Figure 2, at the age of 21 months, the girl had a severely short stature with a body height of 71.0 cm (z-score -3.94 SD), bodyweight 6430 g (-4.33 SD) and BMI 12.5 kg/m2 (-2.67). She was in the prepubertal stage of development, she could not walk independently. The rest of her physical exam was unremarkable.



Slika 1. Rendgenski snimak pluća u uzrastu od 10 godina koji pokazuje ozbiljan stepen skolioze

transglutaminska antitela bili su u okviru normalnih vrednosti. Test stimulacije za hormon rasta (glukagon test) pokazao je normalnu sekreciju hormona rasta i kortizola, sa najvećom vrednošću hormona rasta u serumu od 10,0 ng/ml i najvećom vrednošću kortizola od 860 nmol/l. Insulinu sličan faktor rasta 1 (IGF-1) je bio u okviru normalnih vrednosti 53,1 ng/ml (referentne vrednosti 11-206 ng/ml). Starost kostiju je odgovarala uzrastu devojčice. Zaključeno je da je nizak rast posledica intrauterine restrikcije rasta, tako da je savetovano da se dalje prati ubrzani rast pre otpočinjanja lečenja hormonom rasta zbog niskog rasta kod ovog deteta.

Sa tri godine, devojčica je operisana zbog iščašenja levog kuka. Takođe je uvedena kineziterapija i prepisan je ortopedski korset.

Sa 4 godine i 2 meseca, primećeno je da je ubrzani rast izostao i da je njena visina bila i dalje ispod -3 SD (težina 10,2 kg, visina 86,6 cm). Zbog toga je započeto lečenje hormonom rasta, i to u dozi od 0,035 mg/kg/dan (0,24 mg/kg/nedeljno), prema protokolu za lečenje niskog rasta kod dece koja su rođena mala za gestaciono doba (MGD).

Tokom naredne dve godine lečenja hormonom rasta, devojčica je porasla 13,3 cm, sa visinom od -3 SD (99,9 cm). Psihomotorni razvoj je zaostajao za otprilike 18 meseci, uz kašnjenje motorike i govora i sa neurorazvojnim skorom (QR) 50-55.

Sa 10 godina, zbog izostanka adekvatnog odgovora na terapiju hormonom rasta, urađene su dalje analize. Zbog činjenice da je devojčica imala splenomegaliju i leukopeniju, i nekoliko epizoda pneumonije u istoriji bolesti, konsultovan je imunolog i urađene su dodatne analize. Utvrđeno je da je devojčica imala običnu varijabilnu imunodeficijenciju (eng. C*ommon Variable Immunodeficiency* - CVID). Uvedena je terapija imunoglobulina intravenski (IVIG).

Na pregledima koji su usledili utvrđeno je da nije došlo do pogoršanja skolioze, a nisu primećene ni druge komplikacije zbog terapije hormonom rasta. S obzirom da je uvedena terapija IVIG za CVID, devojčica dalje nije imala infekcije. Međutim, nije bilo napredovanja u brzini rasta. Doza hormona rasta je prilagođena na osnovu devojčicine težine, nivoa IGF-1, i u uzrastu od 10 godina dostignuta je maksimalna doza hormona rasta od 0,05 mg/kg/dnevno (0,37 mg/kg/nedeljno). Zbog visoke doze hormona rasta i nivoa IGF-1 koji je bio na donjoj granici referentnog opsega, urađen je test generisanja IGF-1 kojim je dobijeno značajno povećanje nivoa IGF-1 kada je majka ponovo edukovana o pravilnom davanju terapije hormona rasta (od 78,7 do 214 ng/ml). Nakon testa proizvodnje IGF i reedukacije, nivoi IGF-1 su bili u okviru referentnih vrednosti. Međutim, brzina rasta se nije popravila u toku naredne godine (Slika 2). Stoga je, zbog nedostatka efekta terapije, u uzrastu od 11 godina prekinuto lečenje hormonom rasta.

S obzirom da se dijagnoza obične varijabilne imunodeficijencije povezuje sa niskim rastom,

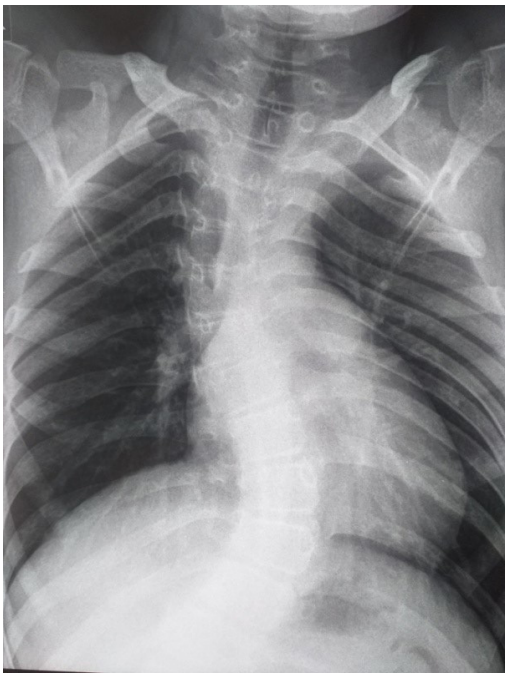


Figure 1. Chest X-ray at the age of ten years, showing the severe degree of scoliosis

Calcium, phosphorus, alkaline phosphatase, electrolytes, thyroid hormones and cortisol levels and tissue transglutaminase antibodies were within normal ranges. Growth hormone provocative testing (glucagon test) demonstrated a normal secretion of GH and cortisol, with a peak serum GH level of 10.0 ng/ml and peak cortisol level of 860 nmol/l. Her insulin-like growth factor 1 (IGF-1) level was normal 53.1 ng/ml (normal range 11-206 ng/ml). The bone age was appropriate for the girl's age. It was concluded that short stature was due to intrauterine growth restriction, so further follow-up for "catch-up" growth was advised before starting the GH treatment for short stature in SGA child.

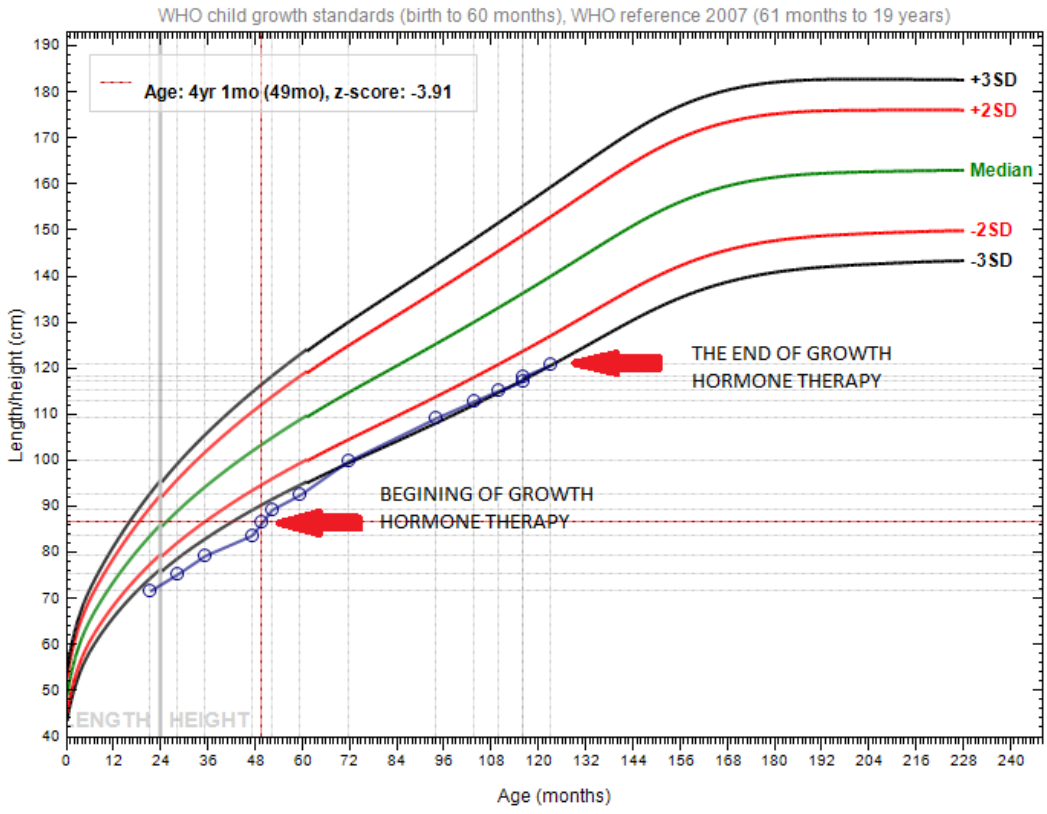
At the age of 3 years, she underwent surgery for left hip dislocation. She was also started on kinesitherapy and an orthopedic corset was prescribed.

At the age of 4 years and 2 months, it was noted that no catch-up growth occurred and her body height was still below -3 SD (BW 10,2kg, BH 86,6cm). Thus, GH treatment was started, in a dose of 0.035 mg/kg/daily (0.24 mg/kg/weekly) as per protocol for the treatment of short stature in SGA child.

During the next two years of GH treatment she grew up 13.3 cm, with body height at -3 SD (99.9 cm). Psychomotor development was lagging by approximately 18 months, with motor and speech delays with neurodevelopmental (QR) score assessed at 50-55.

At the age of 10, because of a lack of proper response to the GH treatment, further analyses were performed. Due to the fact that she had splenomegaly and leukopenia, with a history of several episodes of pneumonia immunologist was consulted and additional tests were performed. It was determined that the girl had common variable immunodeficiency (CVID). Intravenous immunoglobulin (IVIG) therapy was started.

On the follow-up examinations there was no worsening of scoliosis, and no other complications of GH treatment were observed. Since she was started on IVIG treatment for CVID, she had no further infections. However, there was no improvement in the growth velocity. The dose of growth hormone was adjusted according to the girl's weight, and IGF-1 levels, and at the age of 10, the maximum dose of growth hormone of 0.05 mg/kg/day (0.37mg/kg/week) was reached. Because of the high GH dose with IGF-1 levels at the low range, the IGF-1 generation test was performed, showing a significant increase in the level of IGF-1 once the mother was properly re-educated regarding the correct administration of GH (from 78.7 to 214 mg/ml). After the IGF generation test and re-education, IGF-1 levels were kept within reference range. However, growth velocity did not improve during the next year (Figure 2). Therefore, due to the lack of effect of therapy at the age of 11, the GH treatment was stopped.



SD – standardna devijacija

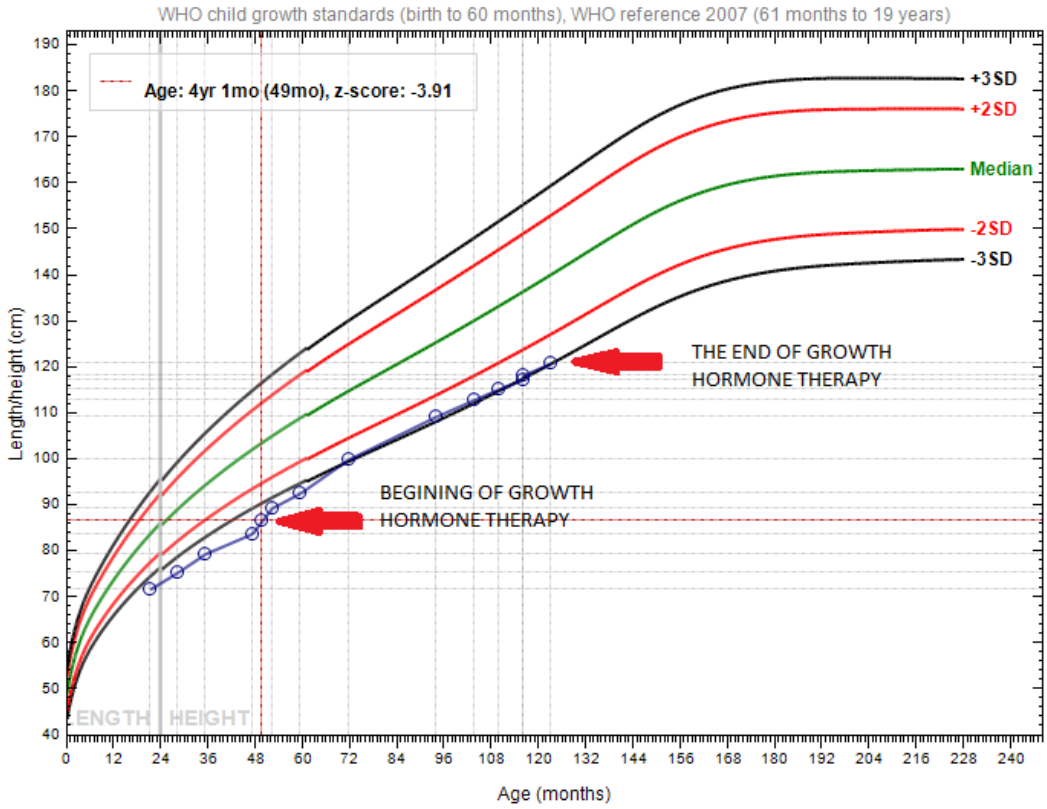
Slika 2. Grafikon rasta koji pokazuje visinu pacijenta pre lečenja hormonom rasta (kreiran uz pomoć *WHO Anthro Plus* softvera)

izraženom torakalnom i lumbalnom skoliozom, dodatnim fenotipskim karakteristikama, koje su postajale izraženije sa godinama (utisak malo starijeg izgleda lica, izbačeno čelo, hipoplastični tragus, tanki i suženi prsti, hiperekstenzija kolena, tanka i retka kosa, elastična i tanka koža), urađeno je sekvenciranje kliničkog egzoma (*QGemonics* laboratorija, Barselona, Španija). Identifikovane su dve „*missense*" varijante (007255:c.573C>A; c.700C>T) u B4GALT7 genu, sa bioinformatičkim sredstvima za predviđanje, koja su ukazala na štetan efekat ovih varijanti na funkciju i strukturu proteina koji gen B4GALT7 kodira. Jedna varijanta je nasleđena od oca, a druga od majke, potvrđujući bialelno nasleđivanje varijanti u B4GALT7 genu, u skladu sa dijagnozom spondilodisplastičnog Ehlers-Danlosovog sindroma tipa 1.

Diskusija

Spondilodisplastični tip Ehlers-Danlosovog sindroma karakterišu nizak rast, mišićna hipotonija, laksitet zglobova i angulacija ekstremiteta, deformiteti skeleta i hiperelastična koža. Do sada je bilo jedanaest pacijenata sa genetički potvrđenom dijagnozom sdEDS sa mutacijom u B4GALT7 genu, a objavljeni su prikazi slučaja u vezi sa primenom terapije hormonom rasta samo za troje od ovih pacijenata (5,8).

Sandler-Wilson i saradnici (8) opisali su slučaj brata i sestre sa radioulnarnom sinostozom, niskim rastom, usporenim motornim i kognitivnim razvojem, osteopenijom, koronarnim rascepom, rascepom nepca i bialelnim patogenetskim varijantama u B4GALT7 genu i kod brata i kod sestre (c.421C>T:P.Arg141Trp; c.808C>T:p.Arg270Cys). Brat i sestra su imali parcijalnu deficijenciju hormona rasta koju je pokazalo provokativno testiranje sa klonidinom i glukagonom (sa najvećom vrednošću serumskog hormona rasta od 6,0 ng/ml). Lečenje hormonom rasta (0,3 mg/kg/nedeljno) tokom tri godine kod brata i sestre je povezivano sa porastom brzine rasta, sa napredovanjem u visini od -4,6 SD u uzrastu od 4 godine do -3,7 SD i -3,5 SD u uzrastu od 5 i 6 godina (8). *Guo* i saradnici (5) su prijavili desetogodišnjeg dečaka sa angulacijom podlaktice, fleksibilnošću zglobova, bilateralnom radioulnarnom sinostozom, mekom, baršunastom, preterano rastegljivom kožom, hipotonijom, smetnjama u učenju, niskim rastom i bialelnim B4GALT7 varijantama (c.122T>C; p.Le-



SD – standard deviation

Figure 2. Growth chart showing the patient's height before and during the treatment with growth hormone (produced using WHO Anthro Plus software)

Because the diagnosis of CVID was associated with short stature, pronounced thoracolumbar scoliosis and additional phenotypic features which were becoming more prominent with advancing age (impression of slightly older facial appearance, prominent forehead, hypoplastic tragus, slender and tapered fingers, hyperextension of knee joints, thin and sparse hair, elastic and thin skin), clinical exome sequencing was performed (QGenomics laboratory, Barcelona, Spain). Two "missense" variants (007255:c.573C>A; c.700C>T) were identified in the B4GALT7 gene, with prediction bioinformatics tools suggesting a deleterious effect of the variants over function or structure of the protein encoded by the B4GALT7 gene. One variant was inherited from the father and one from the mother, confirming the biallelic inheritance of the variants in the B4GALT7 gene, in line with the diagnosis of type 1 spondylodysplastic Ehlers-Danlos Syndrome (EDS).

Discusion

Ehlers-Danlos Syndrome spondylodysplastic type 1 is characterized by short stature, muscle hypotonia, joint laxity and bowing of the limbs, skeletal deformities and skin hyperextensibility. Until now there have been eleven patients with genetically confirmed diagnosis of sdEDS with B4GALT7 mutation and there are case reports published regarding GH treatment for only three of these patients (5,8).

Sandler-Wilson et al. (8) described male and female siblings with radioulnar synostosis, short stature, delayed motor and cognitive development, osteopenia, coronal clefts, cleft palate and biallelic pathogenetic variants in B4GALT7 in both siblings (c.421C>T:P.Arg141Trp; c.808C>T:p.Arg-270Cys). These male and female siblings had partial GH deficiency demonstrated by provocative testing with clonidine and glucagon (with peak serum GH of 6.0 ng/ml). GH treatment (0.3 mg/kg/week) during 3 years in both siblings was associated with an increase in their growth velocity, with height improvement from -4.6 SD at the age of 4 years to -3.7 SD and -3.5 SD at ages 5 and 6 years (8). Guo et al. (5) reported a 10-year-old boy with forearm bowing, joint flexibility, bilateral radioulnar synostoses, soft, velvety, hyperextensible skin, hypotonia, learning disability, short stature and biallelic B4GALT7 variants (c.122T>C; p.Leu41Pro

u41Pro i c.808C>T; p.Arg270Cys). Ovaj pacijent je takođe imao parcijalnu deficijenciju hormona rasta sa najvećom vrednošću hormona rasta od 8,96 ng/ml tokom testa stimulacije hormona rasta. Nakon 4,5 godine lečenja hormonom rasta, nije primećena značajna promena u brzini rasta ove pacijentkinje (5).

Predstavljeni slučaj je prvi prikaz slučaja pacijentkinje sa sdEDS i normalnom sekrecijom hormona rasta, koja je lečena hormonom rasta zbog niskog rasta deteta rođenog malog za gestaciono doba, pre nego što je postavljena dijagnoza sdEDS. Na osnovu izostanka napredovanja u brzini rasta i devojčicinog fenotipa, tražena je genetska analiza i postavljena je dijagnoza sdEDS zbog bialelnih mutacija u B4GALT7 genu. Nakon što je dijagnoza sdEDS postavljena i zbog ograničenog odgovora na terapiju hormonom rasta, terapija hormonom rasta je prekinuta u uzrastu od 11 godina.

Zaključak

Ovo je prvi prikaz slučaja pacijenta sa genetski potvrđenim sdEDS i normalnom sekrecijom HR tokom provokativnog testiranja HR, koji ilustruje veoma ograničen odgovor na terapiju HR kod ovog pacijenta.

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Sukob interesa: Nije prijavljen.
Primljen: 09.02.2021.
Revizija: 25.03.2021.
Prihvaćen: 25.03.2021.

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and c.808C>T; p.Arg270Cys). This patient also had partial GH deficiency, with a peak of GH level of 8.96 ng/ml during GH stimulation test. After 4.5 years of GH treatment, no significant change in the patient's growth velocity was observed (5).

The presented case is the first case report of the patient with sdEDS and normal GH secretion, who received GH treatment due to the lack of "catch-up" growth in a child born SGA, before the diagnosis of sdEDS was clear. Based on the lack of improvement in height velocity as well as the girl's phenotype, genetic analysis was sought and the diagnosis of sdEDS due to biallelic mutations of the B4GALT7 gene was established. After the diagnosis of sdEDS was made and due to limited response to the GH treatment, the GH therapy was stopped at the age of 11 years.

Conclusion

This is the first case report describing a patient with genetically confirmed spondylodysplastic type of EDS and normal secretion of growth hormone during GH provocative testing, illustrating very limited response to growth hormone treatment in this patient.

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Conflict of interest: None declared.
Received: 02/09/2021
Revised: 03/25/2021
Accepted: 03/25/2021

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