Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2018;90:407–413
DOI: 10.1159/000496700

Received: April 9, 2018
Accepted: January 7, 2019
Published online: March 5, 2019

Growth Hormone Improves Short-Term Growth in Patients with Temple Syndrome

Diana S. Brightman[a] Oluwakemi Lokulo-Sodipe[b, c] Beverly A. Searle[d]
Deborah J.G. Mackay[b, c] Justin H. Davies[b, e] I. Karen Temple[b, c] Andrew Dauber[f, g]

[a]Genetic Counseling Program, Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [b]Human Development and Health, Faculty of Medicine, University of Southampton and, Southampton, UK; [c]Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton, UK; [d]Unique – The Rare Chromosome Disorder Support Group, Oxted, UK; [e]Department of Paediatric Endocrinology, University Hospital Southampton NHS Foundation Trust, Southampton, UK; [f]Cincinnati Center for Growth Disorders, Division of Endocrinology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [g]Division of Endocrinology, Children's National Health System, Washington, DC, USA

Keywords
Temple syndrome · Growth · Growth hormone · Imprinting disorder · Maternal uniparental disomy 14

Abstract
Background/Aims: Temple syndrome is an imprinting disorder caused by maternal uniparental disomy of chromosome 14 (mat UPD14), paternal deletion of 14q32 or paternal hypomethylation of the intergenic differentially methylated region (MEG3/DLK1 IG-DMR). Patients with Temple syndrome have pre- and postnatal growth restriction, short stature, hypotonia, small hands and feet and precocious puberty. We sought to determine whether treatment with growth hormone improves growth outcomes in patients with Temple syndrome. ***Methods:*** This was a retrospective observational study reviewing the medical records of 14 patients with Temple syndrome, 7 of whom were treated with growth hormone. ***Results:*** After 1 year of growth hormone treatment, the height standard deviation score (SDS) increased a median of 1.31 SDS with a median increased height velocity of 5.30 cm/year. ***Conclusions:*** These results suggest short-term improvement in height SDS with growth hormone treatment similar to the response in patients treated under the small for gestational age indication. We recommend considering growth hormone therapy in all patients with Temple syndrome who have short stature.

Introduction

Temple syndrome is an imprinting disorder of chromosome 14 that was first described in 1991 [1]. In a comprehensive review of 51 published cases, Ioannides et al. [2] showed that patients with Temple syndrome have reduced pre- and postnatal growth, hypotonia, facial dysmorphia, small feet and hands, and short stature in addition to precocious puberty. Additionally, half of patients with Temple syndrome are obese. Temple syndrome can result from maternal uniparental disomy (UPD) of chromosome 14 (70–80% of cases), paternal deletion of a region including *DLK1* and *GTL2/MEG3* (10% of cases), paternal hypomethylation of the intergenic differentially methylated region (MEG3/DLK1 IG-DMR) (12% of cases) and paternal deletion of the IG-DMR (less than 2% of cases) [2–6]. A smaller paternal deletion in 14q32 only affecting the *DLK1* gene

Andrew Dauber, MD MMSc
Division of Endocrinology, Children's National Health System
111 Michigan Avenue NW
Washington, DC 20010 (USA)
E-Mail adauber@childrensnational.org

causes precocious puberty, one of the features of Temple syndrome [7]. Despite the significant growth attenuation, no Temple syndrome-specific growth curves are available, and little is known about growth response during and after growth hormone treatment in these patients [4].

The incidence of Temple syndrome is unknown, and it is likely underdiagnosed because of variability in the phenotype and overlap of symptoms with other disorders such as Prader-Willi syndrome (PWS) and Silver-Russell syndrome (SRS) [2, 8–10]. The non-specific symptoms of Temple syndrome make clinical diagnosis difficult. A subset of children with Temple syndrome will meet criteria for the clinical diagnosis of SRS [10–13]. Although Temple syndrome and PWS share some clinical features, the tempo of puberty differs between the syndromes. Gonadotropin-dependent precocious puberty is a feature of Temple syndrome whereas premature pubarche and delayed or incomplete puberty is observed in PWS [4].

Precocious puberty, which promotes an early pubertal growth spurt and skeletal maturation, causes bone age acceleration and contributes to short stature in patients with Temple syndrome [4, 14, 15]. As a result, some of these patients are treated with long-acting gonadotropin-releasing hormone (GnRH) analogue to delay puberty [4, 8, 13, 16]. In order to increase stature, growth hormone treatment must occur before puberty triggers bone age acceleration and epiphyseal closure [17].

In clinical practice, some patients with Temple syndrome are treated with growth hormone to increase growth and stature under the currently approved clinical indication of being short secondary to being born small for gestational age. The overlap with SRS is also used as a rationale for growth hormone treatment following the SRS consensus [18]. However, to date, there are only 12 individuals reported in the literature who have been treated with growth hormone [8, 12, 19, 20]. Of these, growth curves were published for 10 individuals, but a quantitative assessment of growth hormone response has not been performed in a cohort of these patients. Therefore, there is inadequate evidence to determine whether or not growth hormone treatment improves height outcomes for patients with Temple syndrome [12, 19, 20]. Here, we report a quantitative review of an additional 6 patients with Temple syndrome who were treated with growth hormone and their outcomes to determine whether growth hormone should be recommended as the standard course of treatment.

Methods

Study Design and Population

This study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center (CCHMC) in Cincinnati, OH, USA. This is a retrospective observational study in which we recruited patients with a molecular diagnosis of Temple syndrome including maternal UPD14 (mat UPD14), paternal deletion of 14q32 and paternal hypomethylation of the MEG3/DLK1 IG-DMR. Recruitment occurred from a number of different sources. First, we recruited a patient with a molecular diagnosis of Temple syndrome from the Genetics and Endocrinology clinics at CCHMC. Other participants were recruited from the Wessex Imprinting Group at the University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK, at which medical and research records for eligible patients were reviewed after patients were contacted for their consent. Some of the cases were also part of the STAARS cohort (the Study of Adults and Adolescents with Russell-Silver syndrome). Additionally, a study announcement was sent to a Temple syndrome parents' support group on Facebook and interested patients were invited to contact the study staff. Similarly, eligible patients from the Unique – Rare Chromosome Disorder Support Group were sent information about the study and invited to contact study staff. To be included, patients or their parent, if under the age of 18, had to be able to participate in a telephone or Skype interview. Participants were excluded if they had other additional genetic diagnoses or a paternal deletion of 14q32 over 5 MB in size because larger deletions could contain other essential genes that alter the phenotype.

Procedures

Informed consent was obtained via telephone or Skype and the patient or their parent (if the patient was under the age of 18) signed a written consent form. Telephone or Skype interviews were performed with the patient's parent to obtain patient demographics, parental heights, pubertal data, height, weight and head circumference at birth, diagnoses of hypotonia, feeding difficulties, history of diabetes and developmental delays as well as history of treatment with growth hormone or medications to delay puberty. Medical records were acquired and growth measurements (height and weight), growth hormone treatment information, timing of puberty and genetic aetiology of Temple syndrome were documented. Standardized case report forms were used for both the interview and data abstraction from the medical record. The most important outcome variable was age-specific height measurements from which height velocity and height standard deviation score (SDS) were calculated using US CDC norms. For patients who received growth hormone, the height velocity (cm/year) for the year prior to growth hormone treatment and the height velocity over the first year of treatment was calculated. For the UK participants, written consent forms were available or completed before the study. Medical records were reviewed for all data collection.

Results

Participant Demographics

We enrolled 14 patients with Temple syndrome (3 male and 11 female) in this study (Table 1). They had a

Table 1. Demographics of 14 participants with Temple syndrome

Participant	Sex	Race	Age, years	Age at diagnosis, years	Aetiology
1	Male	White	4.4	2.0	mat UPD14
2	Female	White	5.2	2.2	mat UPD14
3	Female	White	3.8	0.8	mat UPD14
4	Female	White	4.8	2.0	mat UPD14
5	Female	White	4.8	0.1	mat UPD14
6	Female	White	4.8	0.4	mat UPD14
7	Female	White	2.5	0.1	mat UPD14
8	Male	White	5.1	4.5	mat UPD14
9	Male	White	24.0	19.0	mat UPD14
10	Female	White/Brazilian	1.1	0.8	mat UPD14
11	Female	White	13.3	12.9	mat UPD14
12	Female	White	28.0	13.1	mat UPD14
13	Female	White	1.1	0.3	mat UPD14 10% T14
14	Female	White	21.0	11.0	Epimutation

mat UPD14, maternal uniparental disomy 14; T14, trisomy 14.

median age of 4.8 years (IQR: 3.9–11.2 years). Participants were from the USA, UK, Norway and Australia, all of whom reported Caucasian ancestry with the exception of 1 participant who reported half-Caucasian, half-Brazilian ancestry. Genetic aetiologies include mat UPD14 for 13/14 participants, 1 of whom had additional mosaicism for Trisomy 14, and 1 participant who had an epimutation (paternal hypomethylation of the MEG/DLK1 IG-DMR region). The median age at diagnosis was 2 years (IQR: 0.50–9.4 years).

Clinical Phenotype

All participants (14/14) reported hypotonia and most participants (13/14) were reported to have feeding difficulties in early life. All participants were reported to have at least one developmental delay with 93% reporting motor delay (13/14) and 93% reporting speech delay (13/14). One participant (1/3) had cryptorchidism. Two participants definitely met clinical criteria for SRS, scoring 4 out of 6 on the Netchine-Harbison clinical scoring system (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000496700) [18]. One of these participants previously had negative genetic testing for SRS (for H19 hypomethylation and UPD7). Due to the limitations of a retrospective chart review, we were unable to assess all of the necessary clinical parameters of the Netchine-Harbison scoring system in the majority of subjects, and thus, we cannot provide an accurate estimate of the percentage of patients who met clinical criteria of SRS.

At the time of interview, 5/14 participants (1 male and 4 females) had undergone puberty with the male (participant 8) reporting pubarche between 9 and 10 years of age and the females (participants 4, 11, 12 and 14) reporting thelarche at a median age of 6.8 years (range 4.3–9 years). Two subjects underwent treatment with a GnRH analogue to suppress pubertal development.

Growth

Participants were born at a median of 38 weeks (IQR: 37.0–39.2 weeks) of gestation (Table 2). Three participants were delivered prematurely at 30, 36 and 36.7 weeks, respectively. Participants had a median birth weight of 2,074 g (IQR: 1,984–2,361 g) and a median birth length of 47 cm (IQR: 45.7–48.3 cm), and 86% (12/14) were small for gestational age (birth weight or length below –2 SDS). Of these, 7 were treated with growth hormone. The most recent height SDS or height SDS prior to the start of growth hormone treatment for all participants was a median of –2.60 SDS (IQR: –3.03 to –2.49 SDS).

Participants 1–7 were treated with growth hormone (Table 3). No medical records could be obtained for participant 7. Of the 6 participants for whom we have growth data, the median age at initiation of growth hormone treatment was 3.3 years (range: 2.3–4.1 years) at which the median height SDS was –2.52 SDS (range: –3.32 to –2.28

Table 2. Growth of participants

Participant	Birth weight, g	Birth length, cm	Birth HC, cm	Gestation, weeks	SGA	GH Tx	Age at exam, years	Height SDS
1	2,415	45.7	34	39.7	Yes	Yes	2.3	–2.48
2	2,050	45	n/a	38.7	Yes	Yes	4.1	–2.28
3	2,211	49.5	n/a	37.6	No	Yes	3.0	–2.50
4	2,438	45.7	n/a	40	Yes	Yes	4.8	–2.54
5	1,984	n/a	32.5	38	Yes	Yes	3.9	–2.93
6	895	35	24.5	30	Yes	Yes	3.5	–3.32
7	2,381	47	33	40	Yes	Yes	n/a	n/a
8	2,300	51	n/a	38.5	Yes	No	5.1	–1.12
9	2,025	n/a	31.6	38	Yes	No	24.0	–3.67
10	2,098	47	n/a	37	Yes	No	n/a	n/a
11	2,670	n/a	n/a	39.3	No	No	13.3	–2.54
12	1,870	n/a	n/a	36	Yes	No	28.0	–3.41
13	1,678	n/a	30	36.7	Yes	No	1.1	–2.66
14	1,984	48.3	n/a	37	Yes	No	21.0	–2.73

HC, head circumference; SGA, small for gestation age; GH Tx, growth hormone treatment; height SDS, height standard deviation score; n/a, not available. Age and height SDS are the most recent or height prior to GH start.

SDS). After 1 year of treatment with a median dose of 0.042 mg/kg/day (range: 0.030–0.057 mg/kg/day), the median height SDS had increased to –1.41 SDS (range: –2.16 to –0.66 SDS) with a median change in height SDS of 1.31 SDS (range: 0.58–1.62 SDS). The median height velocity for the year prior to treatment was 7.13 cm/year (range: 6.49–7.67 cm/year) and increased to 11.81 cm/year (range: 9.95–13.20 cm/year) during the first year of treatment.

Discussion

Growth hormone treatment is approved for a variety of indications other than growth hormone deficiency including small for gestational age [21]. As we learn more about the genetic aetiologies of patients who are small for gestational age, patients are being re-characterized by their genetic diagnoses. Many patients with Temple syndrome are also born small for gestational age and some are currently being treated with growth hormone under the small for gestational age indication. Some patients with Temple syndrome also have phenotypic overlap with SRS, another imprinting disorder that includes phenotypes of small for gestational age, postnatal growth failure and feeding difficulties [10–13]. In our study, 2 participants met clinical criteria for SRS using the Netchine-Harbison clinical scoring system with most of the remainder having inadequate data to fully assess. Patients with SRS are treated with growth hormone under the small for gestational age indication, and studies have shown that these patients have increased growth in response to therapy [22]. Whether patients with Temple syndrome, including those who meet clinical criteria for SRS, have improved outcomes with growth hormone treatment has not yet been proven.

In this study we provide a quantitative assessment of response to growth hormone in patients with Temple syndrome. Previously published reports have described treatment of growth hormone in patients with Temple syndrome, but reports have been descriptive and/or included only a small sample size. One previous report described a single patient who was treated with growth hormone and had improvement of height SDS from –2.5 to –1.5 from the age of 6 to 12 years [8]. The report did not include height velocity data or dosage of growth hormone. A second study prospectively followed the response to growth hormone in 2 patients with Temple syndrome in which both patients had increased height SDS over 1 year of treatment (0.9 and 0.8 height SDS) [19]. Another study published growth curves for 8 patients with Temple syndrome who were treated with growth hormone [12]. The authors described accelerated statural growth in 7 of the 8 patients and no response in 1 of the

Table 3. Response to growth hormone treatment

Participant	At GH initiation		1 year post-Tx		GH dose, mg/kg/day	Height velocity, cm/year	
	age, years	height SDS	height SDS	Δ height SDS		pre-Tx	post-Tx
1	2.3	−2.48	−1.89	0.58	0.031	7.19	9.95
2	4.1	−2.28	−0.66	1.62	0.030	7.13	12.96
3	3.0	−2.50	−1.32[a]	1.18	0.033	n/a	11.84
4	2.3	−2.54	−1.05	1.49	0.052	7.67	13.20
5	4.0	−2.93	−1.49	1.44	0.050	6.49	11.79
6	3.5	−3.32	−2.16	1.16	0.057	6.86	10.24

GH, growth hormone; height SDS, height standard deviation score; Tx, treatment; Δ height SDS, increase in height SDS after 1 year of treatment; pre-Tx, height velocity in the year prior to growth hormone treatment; post-Tx, height velocity over the first year of treatment; n/a, not available. [a] Participant 3 only received 9 months of growth hormone treatment.

patients [12]. While this is the largest treated cohort to date, quantitative analysis of the growth response was not included.

Herein, we describe 14 patients with Temple syndrome with a median age of 5 years. Of the patients, 12 were born small for gestational age and 7 were treated with growth hormone. Our study suggests that significant short-term improvement in height SDS occurs when patients with Temple syndrome are treated with growth hormone. In our study, patients who were treated with a median dose of 0.04 mg/kg/day (of growth hormone for 1 year) had a median increased height of 1.31 SDS and increased height velocity of 5.30 cm/year. There are very limited data on long-term response to growth hormone treatment in Temple syndrome. However, these results are similar to the short-term response seen in patients born small for gestational age in which the mean height SDS increased 1.2–2.0 SDS after 3 years of growth hormone treatment at 0.035–0.07 mg/kg/day [23]. Our patients' mean first year height velocity of over 11 cm/year is quite robust. Unfortunately, longitudinal bone age data were not available in our cohort and thus we cannot comment on the effect of growth hormone on predicted adult height.

The patients in our study were quite young and most (9/14) had not yet experienced puberty. Precocious puberty, one of the features of Temple syndrome, can contribute to short stature. It is critical to monitor all of these patients for the development of precocious puberty so that GnRH agonist therapy can be initiated in a timely fashion as early as possible in childhood. Long-term observational studies are required to determine the effects of growth hormone treatment in addition to GnRH agonist treatment on final adult height in the context of precocious puberty in Temple syndrome. In this cohort, all but one patient had Temple syndrome caused by maternal UPD of chromosome 14. We cannot therefore comment on response to growth hormone in Temple syndrome caused by an epimutation or a paternal deletion. Additionally, we were not able to age-match treated with untreated participants due to unavailability of growth data at younger ages for some of the untreated participants. Despite the small number of treated patients in our cohort, the data suggest that patients with Temple syndrome have similar short-term response to growth hormone as patients currently treated under the approved indication of being born small for gestational age. Children with other imprinting disorders (PWS and SRS) are given recombinant growth hormone to optimize body composition and linear growth. It is important to note that all of the patients in our study were diagnosed with hypotonia. It is possible that growth hormone treatment may improve muscle tone in these patients as is seen in PWS, and muscle tone should be monitored for improvement while on treatment. Furthermore, the growth pattern of Temple syndrome mirrors that observed in children born small for gestational age who fail to catch up in growth and that observed in children with SRS. Temple syndrome, another imprinting disorder, has phenotypic features similar to SRS, but effects of growth hormone on body composition or other non-growth-related parameters have not been assessed. Obesity is a particular concern in this patient population and early prevention of obesity is necessary, similar to what has been recom-

mended in SRS [18]. We recommend that growth hormone is considered in all patients with Temple syndrome who have short stature along with careful monitoring of pubertal development and treatment of precocious puberty. These measures may improve growth in patients with Temple syndrome.

Acknowledgements

We would like to thank the patients and their families who participated in this study, without whom this study would not have been possible.

Statement of Ethics

This study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center (CCHMC) in Cincinnati, OH, USA. Informed consent was obtained via telephone or Skype and the patient or their parent (if the patient was under the age of 18) signed a written consent form.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Sources

This paper presents independent research. Oluwakemi Lokulo-Sodipe was funded by the UK National Institute for Health Research (NIHR) – Research for Patient Benefit (RfPB) Programme PB-PG-1111-26003 – VTC. Some of the UK contribution was funded by the NIHR under its RfPB Programme (grant Ref. No. PB-PG-1111-26003) with support from NIHR CRN: Wessex, NIHR Southampton BRC and NIHR Wellcome Trust Southampton Clinical Research Facility. The RfPB grant holders were Prof. Temple, Dr. Davies, Mrs. Child, Prof. Byrne, Dr. Fenwick and Prof. Inskip. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References

1 Temple IK, Cockwell A, Hassold T, Pettay D, Jacobs P. Maternal uniparental disomy for chromosome 14. J Med Genet. 1991 Aug;28(8):511–4.
2 Ioannides Y, Lokulo-Sodipe K, Mackay DJ, Davies JH, Temple IK. Temple syndrome: improving the recognition of an underdiagnosed chromosome 14 imprinting disorder: an analysis of 51 published cases. J Med Genet. 2014 Aug;51(8):495–501.
3 Briggs TA, Lokulo-Sodipe K, Chandler KE, Mackay DJ, Temple IK. Temple syndrome as a result of isolated hypomethylation of the 14q32 imprinted DLK1/MEG3 region. Am J Med Genet A. 2016 Jan;170A(1):170–5.
4 Hoffmann K, Heller R. Uniparental disomies 7 and 14. Best Pract Res Clin Endocrinol Metab. 2011 Feb;25(1):77–100.
5 Kagami M, Sekita Y, Nishimura G, Irie M, Kato F, Okada M, et al. Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes. Nat Genet. 2008 Feb;40(2):237–42.
6 Kagami M, O'Sullivan MJ, Green AJ, Watabe Y, Arisaka O, Masawa N, et al. The IG-DMR and the MEG3-DMR at human chromosome 14q32.2: hierarchical interaction and distinct functional properties as imprinting control centers. PLoS Genet. 2010 Jun;6(6):e1000992.
7 Dauber A, Cunha-Silva M, Macedo DB, Brito VN, Abreu AP, Roberts SA, et al. Paternally Inherited DLK1 Deletion Associated With Familial Central Precocious Puberty. J Clin Endocrinol Metab. 2017 May;102(5):1557–67.
8 Mitter D, Buiting K, von Eggeling F, Kuechler A, Liehr T, Mau-Holzmann UA, et al. Is there a higher incidence of maternal uniparental disomy 14 [upd(14)mat]? Detection of 10 new patients by methylation-specific PCR. Am J Med Genet A. 2006 Oct;140(19):2039–49.
9 Hosoki K, Kagami M, Tanaka T, Kubota M, Kurosawa K, Kato M, Uetake K, Tohyama J, Ogata T, Saitoh S: Maternal uniparental disomy 14 syndrome demonstrates prader-willi syndrome-like phenotype. J Pediatr. 2009 Dec;155(6):900–3.e1. https://doi.org/10.1016/j.jpeds.2009.06.045.
10 Goto M, Kagami M, Nishimura G, Yamagata T. A patient with Temple syndrome satisfying the clinical diagnostic criteria of Silver-Russell syndrome. Am J Med Genet A. 2016 Sep;170(9):2483–5.
11 Kagami M, Mizuno S, Matsubara K, Nakabayashi K, Sano S, Fuke T, et al. Epimutations of the IG-DMR and the MEG3-DMR at the 14q32.2 imprinted region in two patients with Silver-Russell Syndrome-compatible phenotype. Eur J Hum Genet. 2015 Aug;23(8):1062–7.
12 Kagami M, Nagasaki K, Kosaki R, Horikawa R, Naiki Y, Saitoh S, Tajima T, Yorifuji T, Numakura C, Mizuno S, Nakamura A, Matsubara K, Fukami M, Ogata T: Temple syndrome: comprehensive molecular and clinical findings in 32 Japanese patients. Genet Med. 2017 Dec;19(12):1356–66.
13 Geoffron S, Abi Habib W, Chantot-Bastaraud S, Dubern B, Steunou V, Azzi S, et al. Chromosome 14q32.2 Imprinted Region Disruption as an Alternative Molecular Diagnosis of Silver-Russell Syndrome. J Clin Endocrinol Metab. 2018 Jul;103(7):2436–46.
14 Guaraldi F, Beccuti G, Gori D, Ghizzoni L. MANAGEMENT OF ENDOCRINE DISEASE: long-term outcomes of the treatment of central precocious puberty. Eur J Endocrinol. 2016 Mar;174(3):R79–87.
15 Glab E, Wikiera B, Bieniasz J, Barg E: The Influence of GnRH Analog Therapy on Growth in Central Precocious Puberty. Adv Clin Exp Med. 2016 Jan-Feb;25(1):27–32.
16 Takahashi I, Takahashi T, Utsunomiya M, Takada G, Koizumi A. Long-acting gonadotropin-releasing hormone analogue treatment for central precocious puberty in maternal uniparental disomy chromosome 14. Tohoku J Exp Med. 2005 Dec;207(4):333–8.

17 Rekers-Mombarg LT, Kamp GA, Massa GG, Wit JM; Dutch Growth Hormone Working Group. Influence of growth hormone treatment on pubertal timing and pubertal growth in children with idiopathic short stature. J Pediatr Endocrinol Metab. 1999 Sep-Oct;12(5):611–22.
18 Wakeling EL, Brioude F, Lokulo-Sodipe O, O'Connell SM, Salem J, Bliek J, et al. Diagnosis and management of Silver-Russell syndrome: first international consensus statement. Nat Rev Endocrinol. 2017 Feb;13(2):105–24.
19 Stalman SE, Kamp GA, Hendriks YM, Hennekam RC, Rotteveel J. Positive effect of growth hormone treatment in maternal uniparental disomy chromosome 14. Clin Endocrinol (Oxf). 2015 Nov;83(5):671–6.
20 Tohyama J, Yamamoto T, Hosoki K, Nagasaki K, Akasaka N, Ohashi T, et al. West syndrome associated with mosaic duplication of FOXG1 in a patient with maternal uniparental disomy of chromosome 14. Am J Med Genet A. 2011 Oct;155A(10):2584–8.
21 Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J Clin Endocrinol Metab. 2007 Mar;92(3):804–10.
22 Smeets CC, Zandwijken GR, Renes JS, Hokken-Koelega AC. Long-Term Results of GH Treatment in Silver-Russell Syndrome (SRS): Do They Benefit the Same as Non-SRS Short-SGA? J Clin Endocrinol Metab. 2016 May;101(5):2105–12.
23 de Zegher F, Hokken-Koelega A. Growth hormone therapy for children born small for gestational age: height gain is less dose dependent over the long term than over the short term. Pediatrics. 2005 Apr;115(4):e458–62.