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

Diana S. Brightman1, Oluwakemi Lokulo-Sodipe2, Beverly A. Searle3, Deborah JG Mackay2, Justin H. Davies4, I. Karen Temple2 and Andrew Dauber5,6

1. Genetic Counseling Program, Division of Human Genetics, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH 45229
2. Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, and Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton, SO16 6YD UK
3. Unique – The Rare Chromosome Disorder Support Group, The Stables, Station Road West Oxted, RH8 9EE, UK
4. Human Development and Health, Faculty of Medicine, University of Southampton and Department of Paediatric Endocrinology, University Hospital Southampton NHS Foundation Trust, SO16 6YD, UK
5. Cincinnati Center for Growth Disorders, Division of Endocrinology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, 45229
6. Division of Endocrinology, Children’s National Health System, Washington, DC 20010

Corresponding Author:

Andrew Dauber, MD MMSc

Division of Endocrinology, Children’s National Health System

111 Michigan Ave NW

Washington, DC 20010

Phone: 202-476-2121

Email: [adauber@childrensnational.org](mailto:andrew.dauber@cchmc.org)

Dr. Dauber is a member of ESPE and PES.

Running Title: Growth in Temple Syndrome

**Abstract**

Background/Aims: Temple syndrome is an imprinting disorder caused by maternal uniparental disomy of chromosome 14 (mat UPD 14), 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 one 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/yr.

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.

**Key Words**

Temple syndrome, growth, growth hormone, imprinting disorder, maternal uniparental disomy 14

**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. 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 [2]. 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 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 nonspecific symptoms of Temple syndrome make clinical diagnosis difficult. A subset of children with Temple syndrome will meet criteria for the clinical diagnosis of Silver- Russell syndrome [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 Silver Russell syndrome is also used as a rationale for GH treatment following the SRS consensus [20]. However, to date, there are only 12 individuals reported in the literature who have been treated with growth hormone [8, 12, 18, 19]. 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, 18, 19]. 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. This is a retrospective observational study in which we recruited patients with a molecular diagnosis of Temple syndrome including maternal UPD 14, 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 who 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 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 etiology 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 sore (SDS) were calculated using United States 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 have a median age of 4.8 years (IQR: 3.9 to 11.2 years). Participants are from the United States, United Kingdom, Norway and Australia, all of whom reported Caucasian ancestry with the exception of one participant who reported half-Caucasian, half-Brazilian ancestry. Genetic etiologies include maternal UPD 14 for 13/14 participants, one of whom has additional mosaicism for Trisomy 14, and one participant who has an epimutation (paternal hypomethylation of the MEG/DLK1 IG-DMR region). The age at diagnosis was a median age of 2.0 years (IQR: 0.50 to 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 Silver-Russell syndrome, scoring 4 out of 6 on the Netchine–Harbison clinical scoring system (Supplemental Table 1) [20]. One of these participants previously had negative genetic testing for Silver-Russell syndrome (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 Silver-Russell syndrome.

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 old and the females (participants 4, 11, 12 and 14) reporting thelarche at a median age of 6.8 years (range 4.3 to 9 years). Two subjects underwent treatment with a GnRH analogue to suppress pubertal development.

Growth

Participants were born at a median of 38.0 weeks (IQR: 37.0 to 39.2 weeks) gestation (Table 2). Three participants were delivered prematurely at 30 weeks, 36 weeks and 36.7 weeks. Participants had a median birth weight of 2074 g (IQR: 1984 to 2361 g) and a median birth length of 47.0 cm (IQR: 45.7 to 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 is 3.3 years (range: 2.3 to 4.1) at which the median height SDS was -2.52 SDS (range: -3.32 to -2.28 SDS). After 1 year of treatment with a median dose of 0.042 mg/kg/day (range: 0.030 to 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 to 1.62 SDS). The median height velocity for the year prior to treatment was 7.13 cm/yr (range: 6.49 to 7.67 cm/yr) and increased to 11.81 cm/yr (range: 9.95 to 13.20 cm/yr) 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 etiologies 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 Silver-Russell syndrome, another imprinting disorder that includes phenotypes of small for gestational age, postnatal growth failure, and feeding difficulties [10-13]. In our study, two participants met clinical criteria for a Silver-Russell syndrome using the Netchine-Harbinson clinical scoring system with most of the remainder having inadequate data to fully assess. Patients with Silver-Russell syndrome 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 Silver-Russell syndrome, 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 ages of 6 to 12 years old [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 two patients with Temple syndrome in which both patients had increased height SDS over one year of treatment (0.9 and 0.8 height SDS) [18]. 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 one of the 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/yr. There is 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 to 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 was 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 are quite young and most (9/14) have 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 uniparental disomy for 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 in 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 recommended in SRS [20]. 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.

**Disclosure Statement**

The authors have no conflicts of interest to disclose.

**Funding Sources Statement**

This paper presents independent research. Oluwakemi Lokulo-Sodipe was funded by the UK National Institute for Health Research - Research for Patient Benefit programme PB-PG-1111-26003 – VTC. Some of UK contribution was funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number 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 author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

**Statement of Ethics**

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

**References**

1 Temple IK, Cockwell A, Hassold T, Pettay D, Jacobs P: Maternal uniparental disomy for chromosome 14. Journal of medical genetics 1991;28:511-514.

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. Journal of medical genetics 2014;51:495-501.

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. American journal of medical genetics Part A 2016;170a:170-175.

4 Hoffmann K, Heller R: Uniparental disomies 7 and 14. Best practice & research Clinical endocrinology & metabolism 2011;25:77-100.

5 Kagami M, Sekita Y, Nishimura G, Irie M, Kato F, Okada M, Yamamori S, Kishimoto H, Nakayama M, Tanaka Y, Matsuoka K, Takahashi T, Noguchi M, Tanaka Y, Masumoto K, Utsunomiya T, Kouzan H, Komatsu Y, Ohashi H, Kurosawa K, Kosaki K, Ferguson-Smith AC, Ishino F, Ogata T: Deletions and epimutations affecting the human 14q32.2 imprinted region in individuals with paternal and maternal upd(14)-like phenotypes. Nat Genet 2008;40:237-242.

6 Kagami M, O'Sullivan MJ, Green AJ, Watabe Y, Arisaka O, Masawa N, Matsuoka K, Fukami M, Matsubara K, Kato F, Ferguson-Smith AC, Ogata T: The IG-DMR and the MEG3-DMR at human chromosome 14q32.2: hierarchical interaction and distinct functional properties as imprinting control centers. PLoS genetics 2010;6:e1000992.

7 Dauber A, Cunha-Silva M, Macedo DB, Brito VN, Abreu AP, Roberts SA, Montenegro LR, Andrew M, Kirby A, Weirauch MT, Labilloy G, Bessa DS, Carroll RS, Jacobs DC, Chappell PE, Mendonca BB, Haig D, Kaiser UB, Latronico AC: Paternally Inherited DLK1 Deletion Associated With Familial Central Precocious Puberty. The Journal of clinical endocrinology and metabolism 2017;102:1557-1567.

8 Mitter D, Buiting K, von Eggeling F, Kuechler A, Liehr T, Mau-Holzmann UA, Prott EC, Wieczorek D, Gillessen-Kaesbach G: Is there a higher incidence of maternal uniparental disomy 14 [upd(14)mat]? Detection of 10 new patients by methylation-specific PCR. American journal of medical genetics Part A 2006;140:2039-2049.

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. The Journal of pediatrics 2009;155:900-903 e901.

10 Goto M, Kagami M, Nishimura G, Yamagata T: A patient with Temple syndrome satisfying the clinical diagnostic criteria of Silver-Russell syndrome. American journal of medical genetics Part A 2016;170:2483-2485.

11 Kagami M, Mizuno S, Matsubara K, Nakabayashi K, Sano S, Fuke T, Fukami M, Ogata T: Epimutations of the IG-DMR and the MEG3-DMR at the 14q32.2 imprinted region in two patients with Silver-Russell Syndrome-compatible phenotype. European journal of human genetics : EJHG 2015;23:1062-1067.

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. Genetics in medicine : official journal of the American College of Medical Genetics 2017

13 Geoffron S, Abi Habib W, Chantot-Bastaraud S, Dubern B, Steunou V, Azzi S, Afenjar A, Busa T, Pinheiro Canton A, Chalouhi C, Dufourg MN, Esteva B, Fradin M, Genevieve D, Heide S, Isidor B, Linglart A, Morice Picard F, Naud-Saudreau C, Oliver Petit I, Philip N, Pienkowski C, Rio M, Rossignol S, Tauber M, Thevenon J, Vu-Hong TA, Harbison MD, Salem J, Brioude F, Netchine I, Giabicani E: Chromosome 14q32.2 Imprinted Region Disruption as an Alternative Molecular Diagnosis of Silver-Russell Syndrome. The Journal of clinical endocrinology and metabolism 2018;103:2436-2446.

14 Guaraldi F, Beccuti G, Gori D, Ghizzoni L: MANAGEMENT OF ENDOCRINE DISEASE: Long-term outcomes of the treatment of central precocious puberty. European journal of endocrinology 2016;174:R79-87.

15 Glab E, Wikiera B, Bieniasz J, Barg E: The Influence of GnRH Analog Therapy on Growth in Central Precocious Puberty. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 2016;25:27-32.

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. The Tohoku journal of experimental medicine 2005;207:333-338.

17 Rekers-Mombarg LT, Kamp GA, Massa GG, Wit JM: Influence of growth hormone treatment on pubertal timing and pubertal growth in children with idiopathic short stature. Dutch Growth Hormone Working Group. Journal of pediatric endocrinology & metabolism : JPEM 1999;12:611-622.

18 Stalman SE, Kamp GA, Hendriks YM, Hennekam RC, Rotteveel J: Positive effect of growth hormone treatment in maternal uniparental disomy chromosome 14. Clinical endocrinology 2015;83:671-676.

19 Tohyama J, Yamamoto T, Hosoki K, Nagasaki K, Akasaka N, Ohashi T, Kobayashi Y, Saitoh S: West syndrome associated with mosaic duplication of FOXG1 in a patient with maternal uniparental disomy of chromosome 14. American journal of medical genetics Part A 2011;155a:2584-2588.

20 Wakeling EL, Brioude F, Lokulo-Sodipe O, O'Connell SM, Salem J, Bliek J, Canton AP, Chrzanowska KH, Davies JH, Dias RP, Dubern B, Elbracht M, Giabicani E, Grimberg A, Gronskov K, Hokken-Koelega AC, Jorge AA, Kagami M, Linglart A, Maghnie M, Mohnike K, Monk D, Moore GE, Murray PG, Ogata T, Petit IO, Russo S, Said E, Toumba M, Tumer Z, Binder G, Eggermann T, Harbison MD, Temple IK, Mackay DJ, Netchine I: Diagnosis and management of Silver-Russell syndrome: first international consensus statement. Nature reviews Endocrinology 2017;13:105-124.

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. The Journal of clinical endocrinology and metabolism 2007;92:804-810.

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? The Journal of clinical endocrinology and metabolism 2016;101:2105-2112.

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;115:e458-462.