CASE REPORT

DOI: 10.4274/jcrpe.galenos.2022.2022-9-19

J Clin Res Pediatr Endocrinol 2024;16(4):475-480

Long-term Follow-up of a Late Diagnosed Patient with Temple Syndrome

Nikolinka Yordanova[1], Violeta Iotova[1], Deborah J. G. Mackay[2,3], I. Karen Temple[3], Sara Stoyanova[1], Mari Hachmeriyan[4]

[1]Medical University-Varna, Department of Pediatrics, Varna, Bulgaria
[2]Wessex Regional Genetics Laboratory, Salisbury Foundation NHS Trust, Salisbury, United Kingdom
[3]University of Southampton Faculty of Medicine, Department of Medical Genetics, Southampton, United Kingdom
[4]Medical University, Department of Medical Genetics, Varna, Bulgaria

What is already known on this topic?

The presented patient's history and disease course over more than 18 years are consistent with other reported Temple syndrome patients in the literature, regardless of the late diagnosis and childhood follow-up as a suspected other conditions.

What this study adds?

The description of the case shows the significance of multidisciplinary life-long follow-up for the patients with rare endocrine disease. Our patient is the only one genetically confirmed in Bulgaria and the second in the world with signs of clinical and biochemical hyperandrogenism. This is an intriguing finding that deserves future studies. The article is significant because it follows the trend for developing and expansion of the Rare Endocrine Networks all over the world in order to provide specialized multidisciplinary care for the rare patients.

Abstract

Temple syndrome is a rare imprinting disorder, caused by alterations in the critical imprinted region 14q32 of chromosome 14. It is characterized by pre- and postnatal growth retardation, truncal hypotonia and facial dysmorphism in the neonatal period. We report an 18-year-old girl with a late diagnosis of Temple syndrome presenting with all typical signs and symptoms including small for gestational age at birth, feeding difficulties, muscle hypotonia and delayed developmental milestones, central precocious puberty, truncal obesity and reduced growth. The patient is the second reported in the literature with signs of clinical and biochemical hyperandrogenism and the first treated with Dehydrocortisone®, with a good response. The clinical diagnosis of this patient was made after long-term follow up at a single center for rare endocrine diseases, and a molecular genetics diagnosis of complete hypomethylation of 14q32 chromosome imprinting center (DLK/GTL2) was recently established. Growth hormone treatment was not given and although precocious puberty was treated in line with standard protocols, her final height remained below the target range. Increased awareness of Temple syndrome and timely molecular diagnosis enables improvement of clinical care of these patients as well as prevention of inherent metabolic consequences.

Keywords: Temple syndrome, late diagnosis, long-term follow-up

Cite this article as: Yordanova N, Iotova V, Mackay DJG, Temple IK, Stoyanova S, Hachmeriyan M. Long-term Follow-up of a Late Diagnosed Patient with Temple Syndrome. J Clin Res Pediatr Endocrinol. 2024;16(4):475-480

Address for Correspondence: Nikolinka Yordanova MD, Medical University-Varna, Department of Pediatrics, Varna, Bulgaria
E-mail: nikolinka.yordanova@mu-varna.bg; nikolinkayordanova@yahoo.com
ORCID: orcid.org/0000-0003-2806-026X

Conflict of interest: None declared
Received: 14.10.2022
Accepted: 13.12.2022
Epub: 15.12.2022
Publication date: 04.12.2024

Introduction

We present a case report and long-term follow-up of a patient with a late diagnosis of Temple syndrome, to raise awareness among clinicians of the importance of timely diagnosis of this disease. Although some of the patient's conditions arose during her childhood, and she was treated in line with standard protocols, her final outcomes are poorer than she might have achieved if her diagnosis had been established at an earlier age. The report also highlights novel endocrine findings.

Temple syndrome was first described by Temple et al. (1) in 1991, who reported a male, aged 18 years, who inherited a balanced Robertsonian translocation from his mother and as a result had maternal uniparental disomy of chromosome 14 (mUPD14). Gillessen-Kaesbach et al. (2) published eight patients with clinical features of mUPD14 in 2008, expanding the phenotype.

Imprinting defects in Temple syndrome lead to incorrect expression of imprinted genes on chromosome 14q32. Maternally expressed genes in 14q32, *MEG3*, *RTL1as* and *MEG8*, as well as the paternally expressed genes, *DLK1* and *RTL1*, are regulated by two differentially methylated regions (DMR), both methylated on the paternal and unmethylated on the maternal copy (3). Temple et al. (4) reported a patient with aberrant loss of paternal methylation at the 14q32 IG-DMR. A year later, Buiting et al. (5) described three patients with similar genetic characteristics who showed loss of methylation of the paternal copy of the *DLK1-GTL2-DIO3* domain. It is now established that mUPD14, loss of methylation and rare paternal deletions of the locus can cause Temple syndrome (6,7).

Intrauterine growth retardation, low birth weight, early neonatal muscular hypotonia, delayed early motor milestones and feeding problems are the clinical hallmarks of Temple syndrome (ORPHA:254516, OMIM#616222) (1,2). Postnatal clinical course is further characterised by persisting growth retardation, subtle facial dysmorphism (broad forehead and short nose with a wide nasal tip), joint hypermobility, small hands and feet, precocious puberty, truncal obesity and short stature at adulthood (1,8,9,10). Speech delay can be present in infancy to early childhood, but verbal capacity usually normalizes in childhood. Some patients have intellectual delay, and autism has been reported (11,12,13). Patients are prone to late metabolic complications, particularly obesity (8,10).

Informed consent for this publication was obtained from the patient and the family.

Case Report

We report an 18-year-old girl with Temple syndrome. Our patient is the first child of non-consanguineous parents, with a family history of short stature (the paternal grandmother) without other clinical associations.

The singleton pregnancy was uneventful. Delivery was natural at 38th gestational week, with meconium-stained amniotic fluid. Resuscitation was required initially. The girl was small for gestational age (SGA) with a birth weight at the 2nd percentile (2350 g), birth length at the 25th percentile (48 cm) and head circumference at the 10th percentile (34 cm), (https://www.cdc.gov/growthcharts/clinical_charts.htm). Truncal hypotonia, poor growth and lack of weight gain were noticed in the neonatal and early infant period. Nasogastric tube feeding was introduced because of feeding difficulties until three months of age.

At the age of 7 months, Silver-Russell syndrome (SRS) was suspected (Table 1), but genetic testing for maternal UPD 7 and methylation at H19 gave negative results.

The girl demonstrated motor and speech delay. Her first steps were at 18 months and first words at the age of two years, with the help of a speech therapist. At the age of 14 months she had an episode of severe hypoglycaemia with generalized seizure. The inability to endure long periods of fasting remained until pre-school age. The family was educated to recognize, measure and cope with hypoglycaemia at home.

Between birth and six years of age, the patient's height was below the 3rd percentile on the Centers for Disease Control and Prevention appropriate for age and sex growth chart. After four years of age she started to gain weight and moved from the 25th to the 75th weight percentile with no improvement in linear growth (Figure 1). At the age of 6 years and 10 months, because of a further decrease of growth velocity, recombinant human growth hormone (rhGH) treatment was prescribed under the approved indication of being born SGA without postnatal catch-up. During the process of supplying the family with rhGH, the patient presented with signs of precocious puberty. Over three months, at the age of 7 years 2 months, she developed thelarche, pubic hair, and increased growth velocity. Her bone age accelerated to 9.5 years by the Greulich and Pyle method. Due to the rapidity of pubertal progression luteinizing hormone releasing hormone (LHRH) agonist treatment (triptorelin 3.75 mg i.m. every 28 days) was started at the age of 7 years 5 months, with good compliance. Of note, rhGH was never used.

The girl was treated until 11 years of age without further pubertal progression and with decreased growth velocity,

but with continuing rapid weight gain. The discrepancy between her short stature and progressive truncal obesity increased with time (Figure 1). Prader-Willi syndrome (PWS) was suspected at 10 years of age because of the clinical overlap in the neonatal period, some of the dysmorphic features and most of all, the uncontrollable weight gain (Figure 2). However, the methylation test gave a negative result for PWS. Facial acne appeared for the first time at the age of nine years.

After LHRH agonist therapy was withdrawn, rapid pubertal progression followed, with menarche at 12 years 4 months. Elevated 17-hydroxyprogesterone (17-OHP), testosterone, and androstendione were detected at the age of 16 years 10 months in parallel with worsening of acne, complaints of oily hair and mild hirsutism (Ferriman-Gallwey score of 13 out of 36 points). Prednisone was started at a daily dose of 5 mg prior to night sleep for six months. An attempt was made to reduce prednisone to 2.5 mg/d thereafter but because of a worsening of hyperandrogenism the dose was again increased to 5.0 mg/d (Table 2).

The accumulating features and events during the whole 18-year patient follow-up led to a clinical diagnosis of Temple syndrome, which was molecularly confirmed at the Wessex Regional Genetic Laboratory, United Kingdom, after written informed consent from the patient and the family. The patient's DNA showed complete hypomethylation of the *DLK1/GLT2* imprinting centre on chromosome 14q32, consistent with the diagnosis of Temple syndrome.

After diet and physical activity counseling throughout childhood and adolescence, the patient lost weight and is now controlling her weight successfully. Her adult height is 141 cm [-4.76 standard deviation score (SDS)], 5 cm below the lower limit of the target range, with current BMI of 23.6 kg/m^2 (0.48 SDS) (Figure 1). The patient's metabolic markers (blood glucose level, insulin level, homeostasis model assessment-estimated-insulin resistance, lipids) are all within reference range. Facial acne improved with time and treatment. Clinical and biochemical hyperandrogenism abated and gradual improvement in menstrual regularity followed. She is seen every six months because of the increased risk of metabolic complications. Transition to adult endocrinologists at the same rare endocrine diseases expert center is ongoing.

Discussion

The presented girl is the first described and confirmed Bulgarian patient with Temple syndrome. Her history demonstrates the natural history of this condition after

Table 1. Differential diagnosis - clinical overlap with Silver-Russell and Prader-Willi syndrome, based on Ioannides et al. (8), Kagami et al. (10), Wakeling et al. (23), Goldstone et al. (24)

Clinical feature	Our patient	Silver-Russell syndrome (24)	Prader-Willi syndrome (23)	Features of Temple syndrome, Kagami et al. (10) (n = 32)	Features of Temple syndrome, Ioannides et al. (8) (n = 51)
Intrauterine growth retardation	+	+	Mild	84 %	75 %
Postnatal growth retardation	+	+	+	94 %	79 %
Delayed early motor milestones	+	+	+	*	83 %
Feeding problems	+	+	+	63 %	*
Early neonatal hypotonia	+	-	+	68 %	93 %
Broad forehead	+	+	-	63 %	*
Small feet	+	-	+	91 %	96 %
Obesity	+	+	+	11 %	49 %
Precocious puberty	+	+	Rarely	76 %	86 %
Short stature at adulthood	+	+	+	*	*
Diabetes mellitus	-	+	+	11 %	*

*: no data

Table 2. Androgen levels and treatment doses of prednisone during follow-up

	16 y 10 mo	17 y 1 mo	17 y 7 mo
17-hydroxyprogesterone, ng/mL	**9.78** (0.2-1.3)	1.2 (1-4.5)	**1.59** (0.2-1.3)
Androstendione, nmol/L (1-11.5)	**13.4**	6.3	11.5
Testosterone, nmol/L (0-1.38)	**2.13**	-	-
Prednisone	**5 mg**	**2.5 mg**	**5 mg**

y: year, mo: month

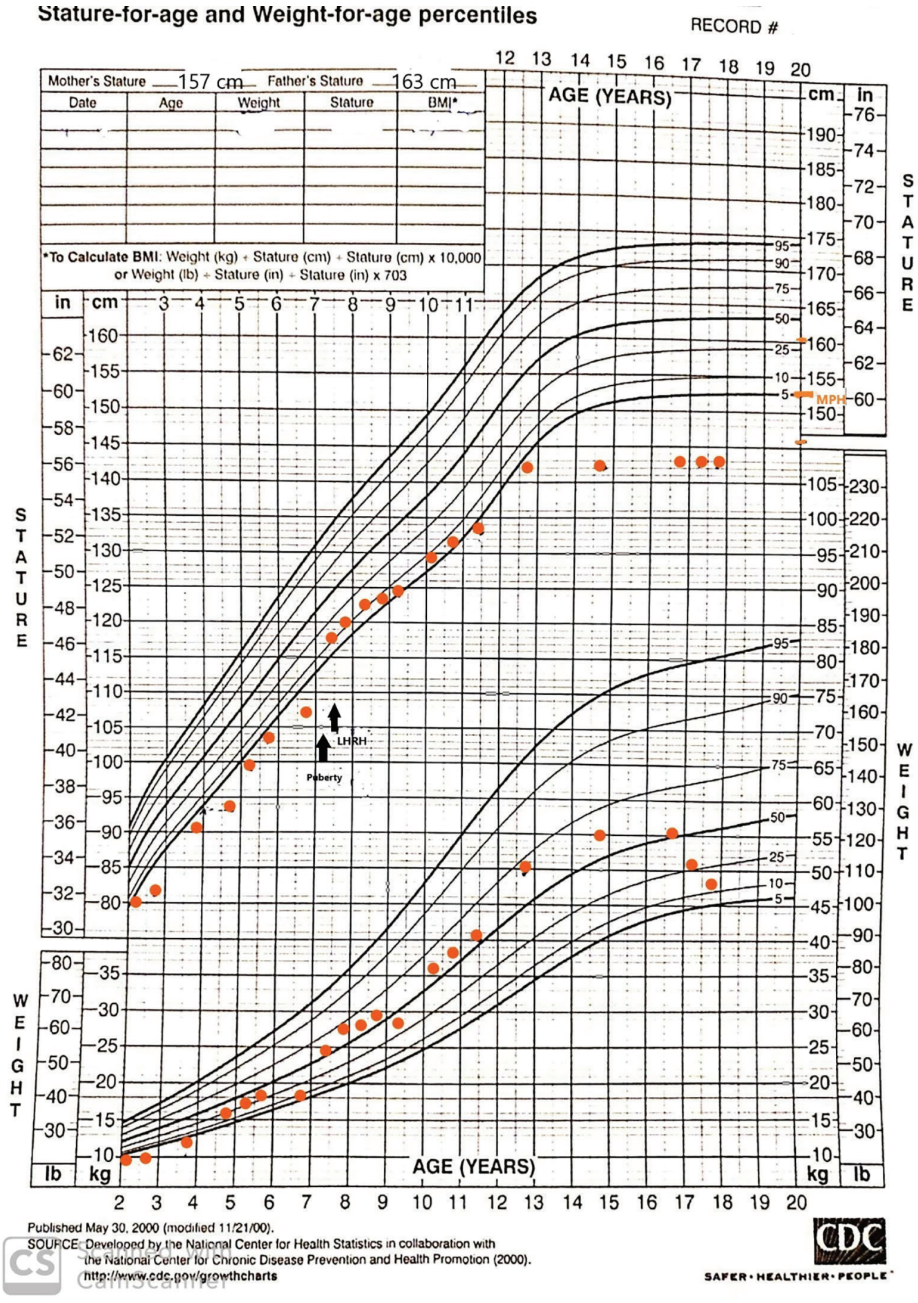

Figure 1. Growth chart (https://www.cdc.gov/growthcharts/clinical_charts.htm)

careful follow-up over 18 years in a single center, and provides insights into the complex growth pattern that is observed in the absence of rhGH treatment. To our knowledge, there are only two other reports of patients with late diagnosis of Temple syndrome, detailing long term follow up of 13 years and at 33 years (6,13). Previous testing for two imprinting conditions (SRS and PWS) adds to the literature showing the clinical similarity between these conditions and patients with Temple syndrome, and showing that multi-locus imprinting investigation is warranted if an imprinting disorder is suspected (14).

Clinical features of Temple syndrome are heterogeneous and age dependent (15,16). Patients often present with some of the features of SRS (17). Kagami et al. (10) showed that SRS-like phenotype was present in 20% of patients with Temple syndrome, differential diagnosis being particularly difficult in infancy (11,18). Genetic confirmation of Temple syndrome has been reported among patients previously tested for PWS (15,19).

Evidence clearly indicates that Temple syndrome is more prevalent than previously recognized (8,10,16). When

Figure 2. The patient self-taken photograph at 10 years of age

clinical findings for SRS and PWS are observed and there is no genetic confirmation, Temple syndrome should be the next suspected condition.

The final diagnosis, established at the age of 18 years in the presented patient, is an important achievement for her. Although there is currently no causal treatment for Temple syndrome, concomitant features and especially metabolic complications can be prevented or treated (13). A failure of early diagnosis prevented the patient from accessing rhGH treatment under the SGA indication for children without postnatal catch-up. However, not all patients with Temple syndrome are eligible for rhGH under this indication, because their early growth parameters may fall within low normal ranges (20). Children who were treated with a median rhGH dose of 0.040 mg/kg/day, had a median 1.31 SDS increase in height for the first year and increased height velocity of 5.30 cm/year. They had similar short-term response to rhGH as other treated SGA patients (21). An established diagnosis of Temple syndrome could facilitate the treatment process, and would have led to rhGH treatment of the current patient regardless of the difficulties in the supplies at that time. The missed opportunity for therapy with rhGH is one of the shortcomings in the patient's management.

As mentioned above, at the age of 16 years the patient presented with signs of hyperandrogenism. To the best of our knowledge, there is only one published report of a patient with Temple syndrome with isolated hypomethylation of the 14q32 imprinted *DLK1/MEG3* region who had clinical signs of hyperandrogenism (6). Our patient's results indicated markedly elevated basal 17-OHP. Although ACTH stimulation test was not done, the findings were consistent with non-classical congenital adrenal hyperplasia (NCAH). According to Nördenstrom and Falhammar, basal 17-OHP of above 15 nmol/L (4.7 ng/mL) and/or ACTH-stimulated 17-OHP of more than 30 nmol/L (9.43 ng/mL), in females during the follicular phase of the menstrual cycle, is considered to be diagnostic for NCAH (22). For that reason, the clinical diagnosis of NCAH was established in our patient and therapy with prednisone was prescribed, with good response nine months after the start of treatment (Table 2). Further genetic testing may be warranted to exclude NCAH. Hyperandrogenism may also be a metabolic consequence of Temple syndrome that is not yet investigated in patients of the appropriate age.

Patients with Temple syndrome may develop obesity, type 2 diabetes mellitus, hypercholesterolemia/hyperlipidemia, and obstructive sleep apnea (12,13). To date, the patient has not shown any of these features, most likely because of her current successful weight control.

Conclusion

The clinical history of this patient over more than 18 years of follow up is consistent with other reports of patients with Temple syndrome who received late diagnosis after earlier clinical investigation for SRS and PWS. The observation of adrenal hyperandrogenism is an intriguing finding that deserves future study and further investigation. Outcomes in Temple syndrome may be improved by aggregation of knowledge, development of targeted, multidisciplinary, life-long care, and education of health professionals to enable patients with Temple syndrome to access earlier diagnosis and therefore better clinical management.

Ethics

Informed Consent: Informed consent for this publication was obtained from the patient and the family.

Acknowledgement

We owe a debt of gratitude to the patient, her family and all the clinicians, who took part in the long term care of the girl. We also thank Dr. Justin Davies for critical reading of the manuscript and important suggestions.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Sara Stoyanova, Mari Hachmeriyan, Concept: Violeta Iotova, Design: Violeta Iotova, Data Collection or Processing: Violeta Iotova, Sara Stoyanova, Analysis or Interpretation: Nikolinka Yordanova, Literature Search: Nikolinka Yordanova, Violeta Iotova, Writing: Nikolinka Yordanova, Violeta Iotova, Deborah J. G. Mackay, I. Karen Temple.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Temple IK, Cockwell A, Hassold T, Pettay D, Jacobs P. Maternal uniparental disomy for chromosome 14. J Med Genet. 1991;28:511-514.
2. Gillessen-Kaesbach G, Albrecht B, Eggermann T, Elbracht M, Mitter D, Morlot S, van Ravenswaaij-Arts CMA, Schulz S, Strobl-Wildemann G, Buiting K, Beygo J. Molecular and clinical studies in 8 patients with Temple syndrome. Clin Genet. 2018;93:1179-1188. Epub 2018 Mar 25
3. Beygo J, Mertel C, Kaya S, Gillessen-Kaesbach G, Eggermann T, Horsthemke B, Buiting K. The origin of imprinting defects in Temple syndrome and comparison with other imprinting disorders. Epigenetics. 2018;13:822-828.
4. Temple IK, Shrubb V, Lever M, Bullman H, Mackay DJ. Isolated imprinting mutation of the DLK1/GTL2 locus associated with a clinical presentation of maternal uniparental disomy of chromosome 14. J Med Genet. 2007;44:637-640. Epub 2007 Jun 29
5. Buiting K, Kanber D, Martín-Subero JI, Lieb W, Terhal P, Albrecht B, Purmann S, Gross S, Lich C, Siebert R, Horsthemke B, Gillessen-Kaesbach G. Clinical features of maternal uniparental disomy 14 in patients with an epimutation and a deletion of the imprinted DLK1/GTL2 gene cluster. Hum Mutat. 2008;29:1141-1146.
6. 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;170:70-175. Epub 2015 Sep 23
7. Kagami M, Yanagisawa A, Ota M, Matsuoka K, Nakamura A, Matsubara K, Nakabayashi K, Takada S, Fukami M, Ogata T. Temple syndrome in a patient with variably methylated CpGs at the primary MEG3/DLK1:IG-DMR and severely hypomethylated CpGs at the secondary MEG3:TSS-DMR. Clin Epigenetics. 2019;11:42.
8. 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;51:495-501. Epub 2014 Jun 2
9. 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;83:671-676. Epub 2015 Jul 28
10. 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;19:1356-1366. Epub 2017 May 31
11. Luk HM. Temple syndrome misdiagnosed as Silver-Russell syndrome. Clin Dysmorphol. 201;25:82-83.
12. Hoffmann K, Heller R. Uniparental disomies 7 and 14. Best Pract Res Clin Endocrinol Metab. 2011;25:77-100.
13. Kimura T, Kagami M, Matsubara K, Yatsuga S, Mukasa R, Yatsuga C, Matsumoto T, Koga Y. Temple syndrome diagnosed in an adult patient with clinical autism spectrum disorder. Clin Case Rep. 2018;7:15-18.
14. Mackay D, Bliek J, Kagami M, Tenorio-Castano J, Pereda A, Brioude F, Netchine I, Papingi D, de Franco E, Lever M, Sillibourne J, Lombardi P, Gaston V, Tauber M, Diene G, Bieth E, Fernandez L, Nevado J, Tümer Z, Riccio A, Maher ER, Beygo J, Tannorella P, Russo S, de Nanclares GP, Temple IK, Ogata T, Lapunzina P, Eggermann T. First step towards a consensus strategy for multi-locus diagnostic testing of imprinting disorders. Clin Epigenetics. 2022;14:143.
15. 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. Am J Med Genet A. 2006;140:2039-2049.
16. Lande A, Kroken M, Rabben K, Retterstøl L. Temple syndrome as a differential diagnosis to Prader-Willi syndrome: Identifying three new patients. Am J Med Genet A. 2018;176:175-180. Epub 2017 Nov 21
17. Azzi S, Salem J, Thibaud N, Chantot-Bastaraud S, Lieber E, Netchine I, Harbison MD. A prospective study validating a clinical scoring system and demonstrating phenotypical-genotypical correlations in Silver-Russell syndrome. J Med Genet. 2015;52:446-453. Epub 2015 May 7
18. 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;170:2483-2485. Epub 2016 Jun 30
19. 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;155:900-903. Epub 2009 Oct 1
20. 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;92:804-810. Epub 2007 Jan 2
21. Brightman DS, Lokulo-Sodipe O, Searle BA, Mackay DJG, Davies JH, Temple IK, Dauber A. Growth Hormone Improves Short-Term Growth in Patients with Temple Syndrome. Horm Res Paediatr. 2018;90:407-413. Epub 2019 Mar 5
22. Nordenström A, Falhammar H. MANAGEMENT OF ENDOCRINE DISEASE: Diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency. Eur J Endocrinol. 2019;180:127-145.
23. 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, Grønskov 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, Tümer Z, Binder G, Eggermann T, Harbison MD, Temple IK, Mackay DJ, Netchine I. Diagnosis and management of Silver-Russell syndrome: first international consensus statement. Nat Rev Endocrinol. 2017;13:105-124. Epub 2016 Sep 2
24. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M; speakers contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab. 2008;93:4183-4197. Epub 2008 Aug 12 Erratum in: J Clin Endocrinol Metab. 2010;95:5465.