

Case report

A Long-term Follow-up of a Late Diagnosed Patient with Temple Syndrome – a Case Report

Yordanova et al. The First Bulgarian Patient with Temple Syndrome

N. Yordanova¹, V. Iotova¹, D. J. G. Mackay^{2,3}, I. K. Temple³, S. Stoyanova¹, M. Hachmeriyan⁴

¹Dept. of Pediatrics, Medical University – Varna, Bulgaria

²Wessex Regional Genetics Laboratory, Salisbury Foundation NHS Trust, Salisbury, UK

³Faculty of Medicine, University of Southampton, Southampton, UK

⁴Dept. of Medical Genetics, Medical University – Varna, Bulgaria

what is already known about 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 to the literature

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 (TS) 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 a 18-year-old girl with a late diagnosis presenting all typical signs and symptoms of Temple syndrome - 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 achieved after a long-term follow up at a single center of rare endocrine diseases, and a molecular genetics diagnosis of complete hypomethylation of 14q32 chromosome imprinting center (DLK/GTL2) was recently established. Growth hormone (GH) treatment was not given and although precocious puberty was treated in line with standard protocols, patient's 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 (TS), late diagnosis, long-term follow-up.

Nikolinka Yordanova, Pediatrics, Medical university "Prof. Dr. Paraskev Stoyanov", Varna, Bulgaria
+ 00359888890340

nikolinka.yordanova@mu-varna.bg; nikolinkayordanova@yahoo.com

<https://orcid.org/0000-0003-2806-026X>

14.10.2022

13.12.2022

Published: 02.02.2023

Background

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 less good than she might have achieved if her diagnosis had been established at an earlier stage. The report also highlights novel endocrine findings.

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

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. reported a patient with aberrant loss of paternal methylation at the 14q32 IG-DMR. [4] A year later, Buiting et al. described three patients with similar genetic characteristics who showed loss of methylation of the paternal copy of the *DLK1-GTL2-DIO3* domain [5]. It is now established that maternal UPD 14, loss of methylation and rare paternal deletions of the locus can cause TS. [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.

Case presentation

We report a 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 3 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 2 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 CDC 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. At the age of 6 years and 10 months, because of 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 according to the Greulich&Pyle atlas. Because of the rapidity of pubertal progression 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; 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 (shown in Additional file 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 (shown in Additional file 2). Methylation test gave negative result for PWS. Facial acne appeared for the first time at the age of 9 years.

After LHRH agonist therapy was withdrawn, rapid pubertal progression followed, with menarche at 12 years 4 months. Elevated 17-hydroxyprogesterone, 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 6 months. An attempt was made to reduce Prednisone to 2.5 mg/d thereafter but because of 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 UK, 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 SDS), 5 cm below the lower limit of the target range, with current BMI of 23.6 kg/m² (0.48 SDS). (Additional file 1) The patient's metabolic markers (BGL, insulin level, HOMA-1R, 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 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 TS patients with late diagnosis, 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 TS patients, and showing that multi-locus imprinting investigation is warranted if an imprinting disorder is suspected. [14]

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

Evidence clearly indicates that TS is more prevalent than previously recognized. [8, 10, 16] When clinical findings for SRS and PWS are observed and there is no genetic confirmation, TS should be the next suspected condition.

The proper diagnosis, established at the age of 18 in the presented patient, is an important achievement for her. Although there is currently no causal treatment of TS, 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 TS patients 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 lead to rhGH treatment of the current patient regardless of the difficulties in the supplies at that time. The missed opportunity of rhGH treatment is one of the shortcomings in the patient's management.

As mentioned above, at the age of 16 the patient presented with signs of hyperandrogenism. To our knowledge there is only one published report of a TS patient 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-hydroxyprogesterone (17OHP). Although ACTH stimulation test was not done, the findings were consistent with non-classical congenital adrenal hyperplasia (NCAH). According to Nördenstrom and Falhammar, basal 17OHP of above 15 nmol/L (4.7 ng/ml) and/or ACTH-stimulated 17OHP 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 9 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 TS that is not yet investigated in patients of the appropriate age.

Patients with TS 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.

Conclusions

In conclusion, the clinical history of this patient over more than 18 years is consistent with other reports of TS patients who received late diagnosis after earlier clinical investigation of SRS and PWS. The observation of adrenal hyperandrogenism is an intriguing finding that deserves future studies. Outcomes in Temple Syndrome can be improved by aggregation of knowledge, development of targeted, multidisciplinary life-long care, and education of health professionals to enable patients to access early diagnosis and management.

List of abbreviations

- TS - Temple syndrome

- mUPD – maternal uniparental disomy
- DMR - differentially methylated regions
- SGA - small for gestational age
- SRS - Silver-Russell syndrome
- rhGH – recombinant human growth hormone
- PWS – Prader-Willi syndrome
- BGL - blood glucose level
- NCAH - non-classical congenital adrenal hyperplasia

Declarations

Authors' contributions:

VI and NY followed the patient. VI, NY and SS drafted the manuscript. DJGM, KT and MH participated in the analysis and the interpretation of the data. DJGM, KT and VI critically revised the manuscript. All the authors read and approved the final manuscript.

Acknowledgment:

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.

References

1. Temple K, Cockwell A, Hassild T, Pettay D, Jacobs P, Maternal uniparental disomy for chromosome 14, *J Med Genet* 1991; 28:511-14, doi: 10.1136/jmg.28.8.511
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 Jun;93(6):1179-1188. doi: 10.1111/cge.13244
3. Beygo J, Mertela 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, DOI:10.1080/15592294.2018.1514233
4. Temple K, Shrub V, Lever M, Bullman H, Mackay DJG, 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 published 2007, doi: 10.1136/jmg.2007.050807
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 Sep;29(9):1141-6. doi: 10.1002/humu.20771
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 Part A* 170A:170–175, DOI 10.1002/ajmg.a.37400
7. Kagami M, Yanagisawa A, Ota M, Matsuoka K, Nakamura A, Matsubara K, Nakabayashi K, Takada Sh, 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 <https://doi.org/10.1186/s13148-019-0640-2>
8. Ioannides Y, Lokulo-Sodipe K, Mackay DJ, Davies JH, Temple KI, Temple syndrome: improving the recognition of an underdiagnosed chromosome 14 imprinting disorder: an analysis of 51 published cases *J Med Genet*, doi:10.1136/jmedgenet-2014-102396
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 Nov;83(5): 671–6, doi: 10.1111/cen.12841
10. Kagami M, Nagasaki K, Kosaki R, Horikawa R, Maiki 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):1356-1366. doi: 10.1038/gim.2017.53
11. Ho-Ming Luk, Temple syndrome misdiagnosed as Silver–Russell syndrome, *Clinical Dysmorphology* 2016, 25:82–83, DOI: 10.1097/MCD.0000000000000114
12. Hoffmann K, Heller R, Uniparental disomies 7 and 14, *Best Practice & Research Clinical Endocrinology & Metabolism* 25 (2011) 77–100, doi: 10.1016/j.beem.2010.09.004
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 Nov 8;7(1):15-18. doi: 10.1002/ccr3.1895.
14. Mackay D, Bliet 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 Nov 7;14(1):143. doi: 10.1186/s13148-022-01358-9. PMID: 36345041; PMCID: PMC9641836.
15. Mitter D, Buiting K, von Eggeling F, Kuechler A, Liehr T, Mau-Holzmann UA, Prott EC, Wiczorek 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 Oct 1;140(19):2039-49. doi: 10.1002/ajmg.a.31414.
16. Lande A, Kroken M, Rabben K, Retterstol L, Temple syndrome as a differential diagnosis to Prader–Willi syndrome: Identifying three new patients, *Am J Med Genet A*, 2017, DOI: 10.1002/ajmg.a.38533
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 Jul;52(7):446-53. doi: 10.1136/jmedgenet-2014-102979.
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 Part A* 170A:2483–2485, doi: 10.1002/ajmg.a.37827
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 Dec;155(6):900-903.e1. doi: 10.1016/j.jpeds.2009.06.045
20. Clayton P, 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, *JCEM*, 92(3):804–810, 2007, doi: 10.1210/jc.2006-2017
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(6):407-413. doi: 10.1159/000496700.
22. Nordenstrom 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*. 2018; EJE-18-0712.R2. doi:10.1530/EJE-18-0712

23. Wakeling EL, Brioude F, Lokulo-Sodipe O, O'Connell SM, Salem J, Blik 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 Feb;13(2):105-124. doi: 10.1038/nrendo.2016.138.

24. Goldstone, A. P., Holland, A. J., Hauffa, B. P., Hokken-Koelega, A. C., Tauber, M. (2008). Recommendations for the Diagnosis and Management of Prader-Willi Syndrome. *JCEM*, 93(11), 4183–4197. doi:10.1210/jc.2008-0649

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

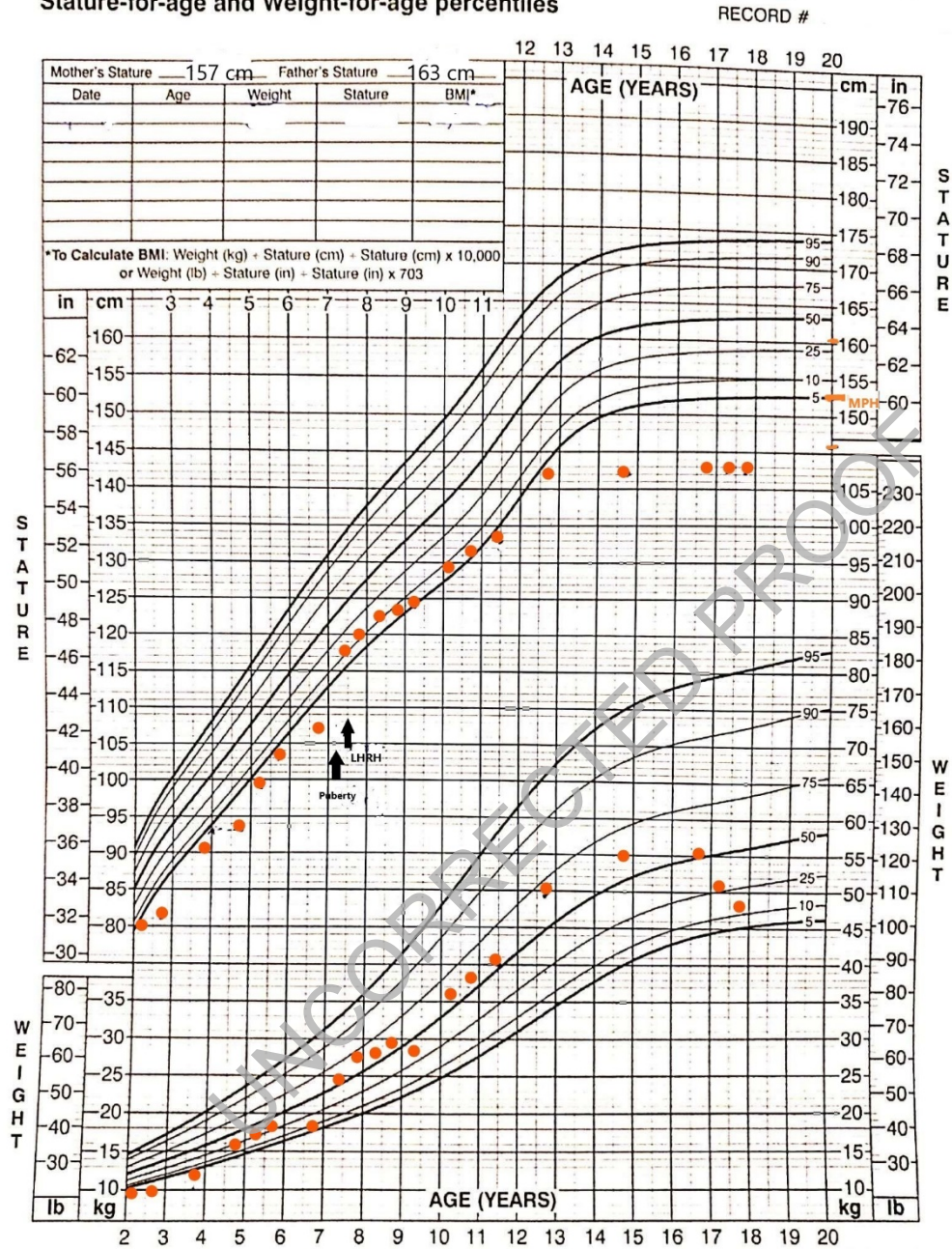
Clinical feature	Our patient	Silver-Russell syndrome	Prader-Willi syndrome	Features of TS, Kagami et al (n=32)	Features of TS, Ioannides et al. (n=51)
intrauterine growth retardation	+	+	Mild	84%	75%
postnatal growth retardation	+	+	+	94%	79%
delayed early motor milestones	+	+	+	*	83%
feeding problems	+	+	+	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

Figure 1
Stature-for-age and Weight-for-age percentiles



Published May 30, 2000 (modified 11/21/00).
 SOURCE: Developed by the National Center for Health Statistics in collaboration with
 the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>

CDC
 SAFER • HEALTHIER • PEOPLE

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

