**Temple syndrome – improving the recognition of an under-diagnosed chromosome 14 imprinting disorder: an analysis of 51 published cases**

Yiannis Ioannides(1), Kemi Lokulo-Sodipe(1,2), Deborah JG Mackay(1,3), Justin H Davies(4), I Karen Temple(1,2)\*

1. Academic Unit of Human Development and Health, Genetics and Genomics Medicine group, Faculty of Medicine, University of Southampton, Southampton, UK
2. Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Princess Anne Hospital, Southampton, SO16 5YA. UK
3. Wessex Regional Genetics Laboratory, Salisbury NHS Foundation Trust, Salisbury, UK
4. Department of Paediatric Endocrinology, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO16 6YD. UK

\*corresponding author

Academic Unit of Human Development and Health, Princess Anne Hospital, Coxford Road, Southampton, Hampshire. SO16 5YA. United Kingdom

Tel: 023 8120 6170

Fax: 023 8120 4346

E-mail: ikt@soton.ac.uk

Keywords: Imprinting, Temple syndrome, UPD14mat, chromosome 14q32

Word count: 2801

**Introduction**

Temple syndrome (TS) is an imprinting disorder that was first described by Temple et al in 1991 in a report of a male aged 18 years with maternal uniparental disomy of chromosome 14.[1]

There is one known imprinted locus on human chromosome 14, at 14q32. Genomic imprinting is an epigenetic marking mechanism that regulates gene expression dependent on parent of origin. The chromosome 14 imprinted locus (Figure 1) has a cluster of reciprocally imprinted genes; the protein coding genes *DLK1, RTL1,* and *DIO3* are expressed from the paternal allele, while the imprinted genes expressed from the maternal allele are all non-coding RNAs (*GTL2/MEG3, MEG8, RTL1as,* multiple additionalmiRNAs and snoRNAs). Imprinted expression is controlled by a primary imprinting control region (intergenic differentially methylated region or IG-DMR) located between *DLK1* and *GTL2/MEG3*, which is normally methylated only on the paternal allele. The imprint on the IG-DMR is acquired in the male germ line, and subsequently directs acquisition of methylation on the paternal allele of a somatic DMR within the *GTL2/MEG3*. The unmethylated IG-DMR on the maternal allele is associated with expression of *GTL2/MEG3* and *RTL1as*, one of whose functions is to repress expression of *DLK1* and *RTL1* in cis.

TS is associated with dysregulation of expression of genes at this imprinted locus. This, in principle can arise from four molecular causes: (i) chromosomal error (ie. uniparental disomy), (ii) copy number change (eg. deletions and duplications), (iii) mutation of expressed coding genes and (iv) epigenetic error (either secondary to a genetic mutation altering gene regulation, or primary, ie. without apparent genetic cause). Maternal uniparental disomy of chromosome 14 (UPD14mat) is the most widely-recognised cause of TS; it results in loss of expression of all paternally expressed genes and overexpression of maternally expressed genes within this domain. However, the study of rare TS patients with copy number changes enabled Kagami et al.[2] to confine the region of interest to a 108KB paternal deletion involving *DLK1* and *GTL2/MEG3*. The two patients with this deletion had many features of TS, but stature was more severely affected in a third reported case with a larger deletion (411 KB) which included *RTL1* (but not *DIO3*). To our knowledge silencing mutations in these genes have not been reported in humans but in the mouse null mutations of *DLK1* and *RTL1* inherited from the male have TS features.[3,4]

There are not enough data as yet to draw out key medical differences between cases with a primary epigenetic aberration confined to the 14q32 IG-DMR (see Figure 1) and patients with other causes of TS. In a murine model, hypomethylation of the IG-DMR resulted in reduced expression of *DLK1*.[5] Therefore all mechanisms are predicted to result in reduced expression of protein-coding imprinted genes from the paternal allele.

The lack of specific congenital malformations or widely used screening methods means that the disorder is likely underdiagnosed in clinical practice and there have been no studies to determine its prevalence. Cases have been coincindentally identified from cohorts of patients who test negative for Prader-Willi (4/33)[6] and Russell-Silver syndromes (1/127)[7] and these are now considered in the differential diagnosis of TS.[6]

The use of the name Temple syndrome is not universal as yet but Buiting et al. suggested this after the first author of the first paper, rather than the somewhat cumbersome use of ‘maternal uniparental disomy of chromosome 14 related conditions’.[8] We have evaluated 51 patient reports from the literature since the first report in 1991, until 2013. By bringing together this body of information, it is hoped that this paper will enhance the recognition of this under-diagnosed condition.

**Methods**

A PubMed search identified 38 articles with 52 cases from 11 countries.[1,2,6,8-42] We excluded one case of a patient with a large deletion of 6.55 MB as this involved several genes and presented with a complex phenotype.[38]

All publications with UPD14mat/epimutations and paternal deletions at 14q32 were reviewed. Of the cases included, 43 full descriptions were available and 8 cases were described in abstracts. 40 cases were maternal UPD 14, 6 showed loss of methylation at the IG-DMR, and 5 demonstrated a paternal deletion confined to the imprinted region.

We included all growth measurements from the reports against age. To adjust for the influence of age and gender on height and weight, standard deviation scores (SDS) were used. In many papers height and weight SDS were already reported but where only centiles were recorded these were converted to SDS values. If multiple growth measurements for an individual were available, these were converted to SDS and the mean value over 12 months of growth was used.

**Clinical Description**

For each clinical feature in the text, prevalence is stated as both a percentage and the number of cases where that feature is present, compared with the total number of cases where that feature is considered (see Table 1).

**Growth**

Poor growth in utero (intrauterine growth retardation) was documented in 75% of cases during pregnancy. The incidence of prematurity (born <37 weeks gestation) was high at 30% (12/40) and greater than that expected in the UK (6.2% quoted by the UK Office of National Statstics)[43] or globally (9.6% estimated by the World Health Organisation).[44]

The median birth weight standard deviation score (SDS) was –1.88 (preterm and term), and none had a birthweight SDS >0. The median birth length SDS was ‑1.64 (total cohort). The median birth weight and length of preterm babies with TS was similar to those born at term (Figure 2). During childhood (below 16 years) the majority of children had a height SDS <-1.0 (Figure 3). The median final height SDS was -2.04.

Figure 3 shows weight, height and head circumference SDS from childhood to adulthood. The median final height SDS was ‑2.04 and the median adult weight SDS was -1.07 demonstrating a relatively greater weight for height in TS adults. The term ‘obesity’ was recorded in 49% of cases. However, the median BMI for patients >16 years of age was 26.6 kg/m2. BMI is shown for the whole cohort in Figure 5.

**Puberty**

It is possible that the improved height SDS (Figure 3) in mid-childhood is related to early puberty with an accompanying pubertal growth spurt. However, the increase in weight SDS at 7-16 years was more marked than the increase in height SDS over the same time period. Early puberty is reported in 86%. There was no clear agreement among authors as to the way that puberty timing was assessed although some include Tanner stages. In eight females the age of menarche was recorded and occurred at a mean age of 10 years 2 months with a range of 8 to 11 years. There are insufficient data to make conclusions with regard to whether premature puberty is linked to adrenarche or gonadotrophin-dependent puberty. Likewise, bone age is reported as delayed in younger ages and advanced in older children.

**Head size**

The median occipto-frontal circumference (OFC) SDS at birth was -0.8 (n=25) with an interquartile range from -1.28-0. The most severe case of microcephaly was that of Tohyama et al (-3.9 SDS)[42] but the child was genetically atypical in that there was an additional marker chromosome and UPD14mat. Subsequently, head circumference was reported in 34 cases and the median head size SDS was below average except during late childhood. Hydrocephalus developing in the first few months of life was reported in 4 cases, which resolved spontaneously.[1,10,11,29]

Of note, relative macrocephaly (TS mean birth OFC SDS -0.8 with mean length SDS ‑1.68) is present in TS but is not as striking as seen in some other imprinting disorders, such as Russell-Silver syndrome (RSS). 55.9% demonstrate a difference in height SDS and OFC SDS of ≥1.0 (data not shown but taken from 68 patient measurements where both OFC and height or length were taken at the same time) compared to 70‑90% in RSS.[45] Furthermore, in RSS, patients frequently have a greater degree of relative macrocephaly and the definition used by Netchine et al.[46] was a difference in OFC SDS and birth weight or height SDS >1.5. In that study 96% of patients with RSS caused by hypomethylation at the imprinting control region (ICR) 1, and 64.3% of patients with RSS and a normal ICR1, met this criterion. This review has found that in TS 39.7% of cases had relative macrocephaly with an SDS difference >1.5.

**Neurological and developmental characteristics**

The most consistent neurological finding in early childhood was truncal hypotonia which was reported in the majority of patients (93%, 38/41). Motor delay was also recorded in 83% of patients (34/41) and scoliosis in 23% (7/30).

Developmental concerns were not limited to the motor systems however, and 63% were recorded to have had speech delay and 39% had some degree of ‘mental retardation’. IQ has been recorded in 6 reports and ranges in all but one from 75-95.[9,10,23,25,26,42] Only one case is reported with severe global developmental delay and that case is atypical in that the female patient developed West syndrome and had a mosaic supernumerary marker chromosome including the gene, *FOXG1* in addition to maternal UPD 14.[42] It is important to note, however, that 20/33 patients were reported as having no intellectual problems and indeed the first patient reported was applying to further education courses at the age of 18 years.[1] The oldest patient reported was 62 years of age and had a child and grandchildren.[2]

**Feeding difficulties**

22 patients were reported with feeding difficulties/weak suck, although this feature was not mentioned in early reports of older patients. Of the 22 cases 10 required tube feeding at least in the neonatal period.[6,21-23,28,39,42] This aspect may have been underestimated in early reports. In some cases it was noted that there was an appetite improvement after 4 years.[6,39] One patient was reported to have ‘an insatiable appetite’ by 6 years and 9 months of age.[39]

In comparison, in Prader-Willi syndrome feeding problems in infancy are present in 78% [47] (compared to 43% of the overall TS cases) and described as ‘almost always present’ before the development of hyperphagia between the ages of 1 and 4 years.[48] The poor feeding results from poor sucking, hypotonia as well as early fatigue and requirement for assisted feeding is nearly universal during the first four to six months of life.[49]

**Dysmorphic features**

Although there was no consistent description in terms of ‘descriptors’ used by researchers in articles, there are facial similarities to many of the patients. Most notably patients have a broad, tall forehead. The nose is often short with a wide, fleshy nasal tip and a relatively short philtrum. Two cases report almond-shaped eyes and several report posteriorly rotated ears. Clinodactyly of the fifth finger is present in at least eight cases. Small hands and feet are recorded in 87% and 96% of cases respectively and is a useful indicator (see Figure 4).

In contrast to Prader-Willi syndrome, cryptorchidism was reported in only three males.[1,12,23] Female genital anomalies were not reported.

**Metabolic**

Of 15 patients over the age of 11 years, three developed diabetes mellitus; at the ages of 12 years,[6] 19 years[25] and 20 years.[31] All three patients were described as having features of type 2 diabetes and one case was confirmed as negative for anti-pancreatic antibodies. Where treatment was described, oral hypoglycaemics were effective.[31] BMI was significantly raised in two of the three patients (BMI 40.8[6] and 30.8[25]) however the third had a normal BMI of 24.1.[31]

In contrast, two patients in the cohort were reported to have recurrent hypoglycaemia in early childhood (3-5 years).[6,23] One of these patients subsequently was shown to be growth hormone deficient and was started on treatment.[6] In the other patient, it was associated with a rapid gain in weight and ketosis.[23]

Five patients were reported with evidence of hyperlipidaemia: hypertriglyceridaemia in one[6] and hypercholesterolaemia in the others.[10,11,18,25] although in one case there was a strong family history.[10] One patient with hyperlipidaemia[6] and one with hypercholesterolaemia[25] were also diagnosed with diabetes (see above).

**Associated features**

There were relatively few congenital anomalies recognised at birth. Early reports of TS highlighted scoliosis and hydrocephalus, however in this review these features were found in only 20% (6/30) and 11% (4/35) respectively.

Only two patients are reported with cleft palate/bifid uvula[1,13] although several were reported to have high palates. Recurrent otitis media has previously been reported in TS. In this review ear infections were commonly reported (9 patients).

**Prognosis**

Among the cohort we have evidence of two patients who died in the first year of life; one with renal failure[29] and the other from an incarcerated inguinal hernia.[27] One patient developed a renal cell carcinoma and adenocarcinoma of the stomach by the age of 44 years.[8]

**Treatment**

The treatment described in four cases was as follows: two patients were given growth hormone[6,42] but in only one of these cases was the child shown to be growth hormone deficient.[6] Lutenising hormone releasing hormone (LHRH) agonist was given to one patient[6] and Leuprolide, a long acting gonadotropin releasing hormone (GnRH) analogue was given to one patient to delay puberty.[35] One patient required oral diabetes treatment to control hyperglycaemia[31] and one patient required adrenocorticotrophic hormone (ACTH) and clobazam to treat epilepsy.[42] Of the remaining cases, no other treatment was reported.

**Surveillance**

No optimal surveillance program has been established in this condition. However from the data it is clear that patients should be monitored life-long for height, weight and cardiovascular risk factors until the natural history is clearly delineated. Control trials are required to determine whether growth hormone and/or delaying puberty has an impact on final height.

**Genotype-phenotype differences**

See Table 1. There is limited information to be gained from such a review, as the numbers of patients with epigenetic aberrations and paternal deletions are low. However, of interest, premature delivery was seen only in maternal UPD 14 cases. Speech delay was reported in 100% of cases with an epigenetic or paternal deletion compared to 45% in cases with maternal UPD 14. Note that patients with normal intellect are reported in all three subgroups.

**Differential diagnosis**

There is clinical overlap between TS and other imprinting disorders. Many papers have reported similarities to Prader-Willi syndrome.[6,32] More recently overlap with RSS is discussed.[7] A table comparing features of TS and RSS (see Table 2) shows that relative asymmetry is a useful discriminator and more common in RSS. The facial appearance of patients with TS differs from that of RSS, particularly with regard to the shape of the nose and the lack of triangular facies. Also, relative macrocephaly is seen more commonly and to a greater degree in RSS, but is also a feature in some patients with TS. However of note, final height in TS is also significantly reduced, similar to that seen in RSS. Poole and Azzi have shown that in a proportion of cases of RSS there is also loss of methylation at the TS locus[7,50] and yet this has not been assessed in the majority of older reports of RSS.

**Clinical testing**

It can be difficult at presentation to distinguish TS from other causes of neonatal hypotonia and failure to thrive. Genetic testing based on ratiometric measurement of methylated and unmethylated DNA within the DMR can be used as a screening test. 14q32 testing should be included in the first line testing for children presenting with IUGR, hypotonia and poor feeding. In view of the overlap with Prader-Willi syndrome, TS testing should be performed in all cases of neonatal hypotonia. TS should also be considered as a cause of early puberty and unexplained proportional short stature.

**Conclusion**

Temple syndrome is a short stature disorder of imprinting. The cardinal features are low birth weight, hypotonia and motor delay, feeding problems in early life, early puberty and significantly reduced final height. Facial features include a broad forehead and short nose with a wide nasal tip and the majority of people have small hands and feet. However many of the clinical features are non-specific and diagnosis can be difficult in early childhood or adulthood. It is important to note that isodisomy may reveal recessive disorders and this may influence the phenotype in UPD14mat cases.

The long term outcome is still not fully known although over half are reported with truncal obesity and with three reports of patients with early onset type 2 diabetes there may well be an increased risk of the metabolic syndrome as with other imprinting disorders.

While developmental outcome is of huge importance, only modest conclusions can be drawn from these retrospective data. Some patients are reported as having normal intellectual development but given that measured IQs are within the low normal range, it is possible that this condition skews intellectual attainment downwards.

Although the condition can be stratified by (epi)genotype, there are not enough cases to make key observations. This may be possible in the future if an easy screening test for this condition is used more extensively.

**Acknowledgements**

KLS is supported by a NIHR Research for Patient Benefit grant. KLS, DJGM and IKT are members of the COST Action BM1208.

**Competing interests**

There are no competing interests.

 **Table 1.** Clinical features frequently reported in 51 cases of Temple syndrome, subdivided by (epi)genotype. Terms are used as documented in the texts of reports. IUGR=intrauterine growth retardation. Not all of the clinical features were reported in all cases and therefore the percentages documented in this paper are based on cases where the feature could be definitely assessed as either being present or absent.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All cases** | **UPD14mat** | **Epimutation** | **Paternal deletion** |
| Number (n) | 51 | 40 | 6 | 5 |
| References (multiple patients in some reports) | [1, 2, 6, 8-37, 39-41] | [1, 6, 9-35, 40] | [6, 8, 36, 37, 39] | [2, 6, 41] |
|  |  |  |  |  |
| Male, female (n) | 23,28 | 18,22 | 4,2 | 1,4 |
| **Growth**  | %  | n | %  | n | % | n | %  | n |
| IUGR  | 75 | 27/36 | 80 | 23/29 | 50 | 2/4 | 67 | 2/3 |
| Premature birth  | 30 | 12/40 | 47 | 14/30 | 0 | 0/6 | 0 | 0/4 |
| Birth weight < 5th percentile | 87 | 33/38 | 86 | 24/28 | 83.3 | 5/6 | 100 | 4/4 |
| Birth length < 5th percentile | 56 | 17/30 | 55 | 12/22 | 40 | 2/5 | 100 | 3/3 |
| Birth head circumference < 5th percentile | 27 | 7/26 | 28 | 5/18 | 0 | 0/5 | 67 | 2/3 |
| Postnatal short stature (<5th percentile)  | 81 | 38/47  | 81 | 30/37  | 50 | 3/6  | 100 | 5/5 |
| Small hands | 87 | 34/39 | 83 | 25/30 | 100 | 6/6 | 100 | 3/3 |
| Small feet | 96 | 26/27 | 95 | 19/20 | 100 | 6/6 | 100 | 1/1 |
| Obesity | 49 | 20/41 | 50 | 15/30 | 67 | 4/6 | 20 | 1/5 |
| Early onset puberty | 86 | 19/22 | 87 | 13/15 | 100 | 4/4 | 67 | 2/3 |
| **Neurological & musculoskeletal** |  |  |  |  |  |  |  |  |
| Hypotonia | 93 | 38/41 | 91 | 29/32 | 100 | 6/6 | 100 | 3/3 |
| Feeding problems |  | 22 |  | 16 |  | 5 |  | 1 |
| Hyperextensible joints | 63 | 12/19 | 60 | 9/15 | 100 | 3/3 | 0 | 0/1 |
| Scoliosis  | 23 | 7/30 | 26 | 6/23 | 33 | 1/3 | 0 | 0/4 |
| Motor developmental delay | 83 | 34/41 | 81 | 26/32 | 83.3 | 5/6 | 100 | 3/3 |
| Speech delay | 63 | 17/27 | 45 | 9/20 | 100 | 5/5 | 100 | 2/2 |
| Mental retardation | 39 | 13/33 | 42 | 11/26 | 33 | 1/3 | 25 | 1/4 |
| Fine motor/coordination problems  |  | 6 |  | 3 |  | 2 |  | 1 |
| **Facial & other abnormalities** |  |  |  |  |  |  |  |  |
| Frontal bossing or prominent forehead |  | 17 |  | 11 |  | 2 |  | 4 |
| Micrognathia  |  | 12 |  | 7 |  | 3 |  | 2 |
| High palate |  | 13 |  | 11 |  | 2 |  |  |
| Short philtrum |  | 9 |  | 7 |  | 2 |  |  |
| Almond shaped eyes |  | 2 |  | 2 |  | 0 |  | 0 |
| Broad nose |  | 6 |  | 5 |  | 1 |  |  |
| Depressed nasal bridge |  | 4 |  | 4 |  |  |  |  |
| Anteverted nares |  | 4 |  | 4 |  |  |  |  |
| Clinodactyly  |  | 8 |  | 6 |  | 2 |  |  |
| **Miscellaneous**  |  |  |  |  |  |  |  |  |
| Recurrent otitis media  |  | 9 |  | 8 |  | 1 |  |  |
| Hypercholesterolemia |  | 5 |  | 4 |  | 1 |  |  |
| Maturity onset diabetes of the young/early onset diabetes |  | 3 |  | 2 |  | 1 |  |  |
| Cryptoorchidism |  | 3 |  | 3 |  |  |  |  |
| Cleft palate/bifid uvula |  | 2 |  | 2 |  |  |  |  |

**Table 2.** Clinical features of Temple syndrome obtained from literature review, expressed as percentages, (bold denotes result where positive and negative findings available, otherwise percentages calculated from positive results compared to whole cohort). Clinical features of Russell-Silver syndrome as reported by Wakeling et al.[45].

 \*<5th percentile in Temple syndrome; ≤-2 SDS in Russell-Silver syndrome

\*\*included reports of 1 bifid uvula, 1 cleft palate, 1 anteriorly placed anus, 1 ventriculo-septal defect, 1 absent sphenoid bone, 1 case of cutis aplasia, 1 patient with neck webbing and 1 case of hypoplastic nails.

|  |  |  |
| --- | --- | --- |
|  | **Temple syndrome** | **Russell-Silver syndrome** |
|  | **(%, n)** | **ICR1 hypomethylation (%)** | **UPD7mat (%)** |
|  |  |  |  |
| **Growth** |
| Low birth weight\*  |  **35** (14/40) | 82 | 70 |
| Short stature\*  |  **81** (38/47)  | 57 | 65 |
| Relative macrocephaly |  **56** (38/68)  | 70 | 90 |
| Assymetry |  4 (2/51)  | 68 | 30 |
| **Development** |
| Mental retardation | **39** (13/33)  | 20 | 65 |
| Motor delay | **83** (34/41)  | 26 | 7 |
| Speech delay or speech therapy  | **63** (17/27)  | 32 | 67 |
| **Other problems** |
| Feeding difficulties | 43 (22/51)  | 84 | 90 |
| Hypoglycaemia | 4 (2/51)  | 24 | 29 |
| Excessive sweating |  | 64 | 75 |
| Congenital abnormalities\*\* | 16 (8/51)  | 36 | 10 |
| Early onset puberty | **86** (19/22)  |  |  |
| **Craniofacial features** |
| Frontal bossing or prominent forehead | 33 (17/51)  | 60 | 60 |
| Micro/retrognathia | 24 (12/51)  | 64 | 35 |
| Ear abnormalities | 20 (10/51)  | 36 | 75 |
| **Other clinical signs** |
| 5th finger clinodactyly | 16 (8/51)  | 75 | 45 |
| Joint contractures | 8 (4/51)  | 11 | 0 |

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**Figure Legends**

**Figure 1.**

This figure shows the imprinted region on chromosome 14q32 and demonstrates expression of imprinted genes on the maternal allele (upper) and paternal allele (lower) for 6 genes. Note that *DLK,*  *RTL1* and *DIO3* are expressed from the paternal allele and non-coding RNAs, *GTL2/MEG3*, *MEG8* and *RTLas* are expressed from the maternal allele. Two differentially methylated regions(DMR) are shown with methylation on the paternal allele, IG-DMR, the germ line DMR and MEG3-DMR.

**Figure 2.**

Birth growth data: length (red) birth weight (green) and head circumference (blue) for preterm and term babies with Temple syndrome.

**Figure 3.**

Height (red), weight (green) and head circumference (blue) from early childhood to adulthood in children with Temple syndrome.

**Figure 4.**

Photographs to show a patient with Temple syndrome due to maternal UPD 14 as a teenager and as an adult. Note the small hands with clinodactyly. This patient has been reported in more detail by Cox et al[32] but these photos are in later life. The characteristic facial features include a broad, tall forehead, short nose with fleshy nasal tip and a relatively short philtrum. Almond-shaped eyes are frequently present.

**Figure 5.**

Changes in BMI (kg/m2) in children with Temple syndrome throughout childhood.