CLINICAL QUIZ (p232) ANSWER

What is the diagnosis?

The clinical features of this child (facial dysmorphism, developmental delay and supravalvular aortic stenosis) were compatible with Williams syndrome (WS, also known as Williams-Beuren syndrome). Genetic investigation by using Multiplex ligation-dependent probe amplication (MLPA) showed he had heterozygous deletion of *ELN* gene in the chromosome 7q11.23 region. Therefore the clinical and molecular diagnoses of WS in this child were substantiated.

Williams syndrome is a multisystem disorder characterised by cardiovascular disease (elastin arteriopathy, supravalvular aortic stenosis, peripheral pulmonary stenosis, hypertension etc.), distinctive facial features, connective tissue abnormalities, intellectual disability, outgoing personality characteristics, growth abnormalities and/or endocrine problems (hypercalcaemia, hypercalciuria, hypothyroidism and early puberty etc.). The prevalence of WS is approximately 1 in 7500 live births.[1]

When to consider WS as one of the differential diagnosis clinically?

WS should be considered clinically with distinctive clinical features. Scoring system was developed for clinical diagnosis (Table 1).[2]

Children with WS usually have characteristic facial profile include periorbital fullness, short nose and full nasal tip, malar hypoplasia, long philtrum, wide mouth, full lips, dental malocclusion and mild micrognathia. These tend to become more distinctive with advancing age.[4] Mild prenatal growth deficiency and postnatal growth problem are also consistently observed.[5] As children with WS are generally smaller than the children of their age, specific growth charts for WS would be used during clinical evaluation.[6]

What are the major complications associated with WS?

The majority of children with WS have cardiovascular anomalies. The most common cardiovascular defect is supravalvular aortic stenosis.[7] It is usually progressive and requires surgical repair. For peripheral pulmonary artery stenosis, it is often present in infancy and tends to improve with time. Mitral valve prolapse and aortic insufficiency have been reported in adults.[8] Other vascular problems, e.g. coarctation of aorta, renal artery stenosis and systemic hypertension may worsen over time if presented.

Idiopathic infantile hypercalcaemia is another special feature of WS that can lead to extreme irritability, vomiting, constipation and muscle cramping.[9] Symptomatic hypercalcaemia usually resolves when children grow older, however, lifelong abnormalities of calcium and vitamin D metabolism may persist. Hypercalciuria will predispose to nephrocalcinosis. The aetiologies of hypercalciuria and hypercalcaemia in WS are still unknown.

Most children with WS have some degree of intellectual disability which can range from severe to mild. WS children also have special cognitive profile. WS children had strength in verbal short-term memory and language but extreme weakness in visuo-spatial construction. The characteristic personality profile of WS includes social disinhibition, excessive empathy, overfriendliness and attention problem.[10]

Other medical problems, e.g. gastrointestinal reflux, colic, Chiari I malformation, strabismus, chronic otitis media, hypodontia, malocclusion, bowel or bladder diverticula, hernias, joint laxity, spinal problems, urinary tract malformations, hydronephrosis,[11] hypothyroidism and rectal prolapse have also be reported in WS children.

Table 1 Scoring system for Williams syndrome (WS)

Growth (Past or Present Evidence of)

If 3 of 5 items are checked, score 1 point

1. Post-term birth >41 wk gestation
2. Failure to thrive / height and weight <5th percentile
3. Vomiting or gastroesophageal reflux
4. Prolonged colic >4 m irritability
5. Chronic constipation

Behaviour and Development

If 3 or 6 items are checked, score 1 point

1. Overly friendly personality
2. Hypersensitivity to sound
3. Anxiety
4. Developmental delay or mental retardation
5. Visuospatial problems
6. Delayed speech acquisition, followed by excessive talking

Facial Features

If 8 of 17 items are checked, score 3 points

1. Bitemporal narrowing
2. Epicanthic folds or flat nasal bridge
3. Strabismus
4. Short nose or anteversion of nares
5. Full cheeks
6. Long philtrum
7. Small, widely spaced teeth
8. Wide mouth
9. Prominent ear lobes
10. Broad brow
11. Periorbital fullness
12. Stellate lacy iris pattern
13. Bulbous or full nasal tip
14. Malar hypoplasia (flat cheek bones)
15. Full prominent lips
16. Malocclusion
17. Small jaw

Cardiovascular Problems (by Echocardiography) (a)

If 1 of 2 items are checked, score 5 points

1. SVAS*
2. Peripheral pulmonary artery stenosis

Cardiovascular Problems (b)

If 1 of 3 items are checked, score 1 point

1. Other congenital heart disease
2. Cardiac murmur
3. Hypertension

Connective Tissue Abnormality

If 2 of 6 items are checked, score 2 points

1. Hoarse voice
2. Inguinal hernia
3. Bowel or bladder diverticula
4. Long neck or sloped shoulders
5. Joint limitation or laxity
6. Rectal prolapse

Calcium Studies

If 1 of 2 items are checked, score 2 points

1. Hypercalcaemia
2. Hypercalciuria

If the score is <3, a diagnosis of Williams syndrome is unlikely. If the score is >=3, genetic studies should be considered. (Mean score for Williams syndrome was 9 [standard deviation=2.86].[3]

*If supravalvular aortic stenosis (SVAS) is present, referral to geneticist and genetic studies are recommended.

How is the diagnosis established in WS?

The diagnosis of WS is confirmed by demonstrating heterozygous deletion of the William-Beuren syndrome critical region (WBSCR) that encompasses the elastin gene (*ELN*) in the proband. WBSCR is located at long arm 11.23 region of chromosome 7 (7q11.23). More than 99% of individuals with the clinical diagnosis of WS have this gene deletion which can be detected using fluorescent in situ hybridization (FISH) and/or dosage testing like multiplex ligation-dependent probe amplification (MLPA) or chromosomal microarray (CMA).[12]

WS is an autosomal dominant condition with penetrance of almost 100%. However, the phenotypic features are highly variable. The WBSCR deletion comprises 1.55 megabases (Mb) in 95% of individuals with WS and 1.84 Mb in 5% of WS.[13] A more severe phenotype with lower cognitive ability is found in patients with very large deletion (e.g. >2Mb) that include the WBSCR than in individuals with typical WBSCR deletion.

What are the recommendations for management and surveillance for WS?

Concerning the management of WS, some baseline and regular surveillance are recommended (Table 2). Clinical guideline for the management of WS in different age groups is also available.[6,14,15]

Table 2 Recommended investigations in WS

- Complete physical and neurological examination
- Ophthalmology assessment and baseline audiologic evaluation
- Developmental assessment
- Genetic evaluation / consultation, e.g. phenotype review, and recurrence risk counselling

Clinical features of WS	*Baseline investigations*
Congenital heart defects	• Full cardiac assessment by cardiologist including blood pressure (4 limbs), echocardiogram, ECG
Failure to thrive / feeding problem / reduced growth velocity	• Plotting of growth parameters on WS specific growth charts[5] at regular intervals • Routine paediatric investigations for FTT and reduced growth velocity
Calcium metabolism problems	• Serum concentration of calcium or ionised calcium • Calcium / creatinine ratio on spot urine sample[15]
Thyroid function abnormalities	• Measure TSH level • If elevated, consider thyroid scan and refer to endocrinologists.
Urinary tract abnormalities	• Renal ultrasound annually. If nephrocalcinosis is present, refer to nephrologist for 6 monthly screening. • Serum concentration of BUN and creatinine • Urinalysis
Behavioural problems	• Look out for attention deficit and anxiety in patients

There are special considerations for the children diagnosed with WS. Multivitamin preparations should be avoided due to potential deleterious effects of vitamin D. Diligent use of sunscreen to minimise autologous production of vitamin D is recommended. There is general management guideline for hypercalcaemia in WS patients.[15] Periodic cardiovascular assessment including hypertension evaluation should be performed despite baseline examination with normal findings.

For our patient, his cardiac problem was continued to follow up by cardiologist. His growth, calcium and thyroid condition would be regularly monitored in Paediatrics clinic.

Acknowledgement

We would like to thank the patient and the family for their contribution.

References

1. Strømme P, Bjørnstad PG, Ramstad KJ. Prevalence estimation of Williams syndrome. J Child Neurol 2002:17;269-71.
2. Committee on Genetics. American Academy of Pediatrics: Health care supervision for children with Williams syndrome. Pediatrics 2001; 107;1192-204.
3. Colleen A. Morris, MD; Frank Greenbery, MD; Paige Kaplan, MD; Martin Levinson, MD; and Barbara Pober, MD; with data analysis by Carolyn B. Mervis, PhD and Byron F. Robinson, MA; presented at the 1994 Williams Syndrome Association Convention; July 31, 1994; San Diego, CA.
4. Jones KL, Smith DW. The Williams elfin facies syndrome: A new perspective. J Pediatr 1975;86:718-23.
5. Wu YQ, Sutton VR, Nickerson E, et al. Delineation of the common critical region in Williams syndrome and clinical correlation of growth, heart defects, ethnicity, and parental origin. Am J Med Genet 1998;78:82-9.
6. The Williams Syndrome Association, PO Box 297, Clawson, MI 48017; telephone: 248/541-3630; https://williams-syndrome.org/growth-charts/growth-charts.
7. Lopez-Rangel E, Maurice M, McGillivray B, Friedman JM. Williams syndrome in adults. Am J Med Genet 1992;44:720-9.
8. Collins RT 2nd, Kaplain P, Somes GW, Rome JJ. Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. Am J Cardiol 2010;105:874-8.
9. Marin ND, Snodgrass GJ, Cohen RD. Idiopathic infantile hypercalcemia: a continuing enigma. Arch Dis Child 1984;59:605-13.
10. Morris CA. The behavioral phenotype of Williams syndrome: A recognizable pattern of neurodevelopment. Am J Med Genet 2012;50: 340-6.
11. Pankau R, Partsch CJ, Winter M, Gosch A, Wessel A. Incidence and spectrum of renal abnormalities in Williams-Beuren syndrome. Am J Med Genet 1996;63:301-4.
12. GeneReviews [internet]: Williams Syndrome by Colleen A Morris, MD, FACMG. https://www.ncbi.nlm.nih.gov/books/NBK1249/ (assessed on 20/10/2016)
13. Bayés M, Magano LF, Rivera N, Flores R, Pérez Jurado LA. Mutational mechanisms of Williams-Beuren syndrome deletions. Am J Hum Genet 2003;73:131-51.
14. https://www.orpha.net/data/patho/Pro/en/WilliamsGuidelines_2010.pdf.
15. Sargent JD, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. J Pediatr 1993;123: 393-7.