DOI: 10.7860/JCDR/2026/77916.22696

Case Report

Paediatrics Section

Diagnostic Challenge and Management Dilemma of William Syndrome: A Case Report

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ABSTRACT

Facial dysmorphism can be a manifestation of different congenital syndromes. However, diagnosing them remains a challenge. William syndrome is a relatively rare genetic multi-system disorder occurring due to a microdeletion on the chromosomal locus 7q11.23. Herein, a case of a 13-year-old child is being reported, who presented with complaints of delayed attainment of developmental milestones, syndromic facies, intellectual delay, poor scholastic performance and unclear speech. Fluorescent In-Situ Hybridisation (FISH) confirmed the diagnosis. Treatment was started with a multidisciplinary approach, including behavioural counselling, genetic counselling, occupational therapy and treating the electrolyte disturbances. After detailed counselling and discussion with the parents as well as the child, the child is doing fine and improving in various domains of life. The quality of life of the child seems to be improving. Uniquely, this child had persistent learning difficulties with an IQ score of 73.8, mild corpus callosum stenosis on Magnetic Resonance Imaging (MRI), and a rare finding of transient asymptomatic hypercalcaemia (14.3 mg/dL) in adolescence, which is most reported in infancy. The child had no cardiovascular involvement, such as supravalvular aortic stenosis, which is typically seen in 70-80% of cases. This case underscores the expanding neurodevelopmental and biochemical phenotype of Williams syndrome. Recent studies also stress the role of early neuropsychological assessments, ongoing cardiac surveillance and individualised learning strategies for long-term outcomes.

Keywords: Cognitive delay, Elfin facies, Multidisciplinary treatment, Supravalvular aortic stenosis

CASE REPORT

A 13-year-old girl came to the paediatric Outpatient Department (OPD) with complaints of delayed attainment of developmental milestones, abnormal facies, a history of recurrent cold and cough and gaining weight at a slower rate as compared to her siblings since 3 months of age. The patient had trouble speaking and understanding things. She was studying in the first standard and had poor scholastic performance with unclear speech, according to attendants. There were two reasons for that, the child was intellectually delayed and her father had a transferrable job for which she was not sent to school very early.

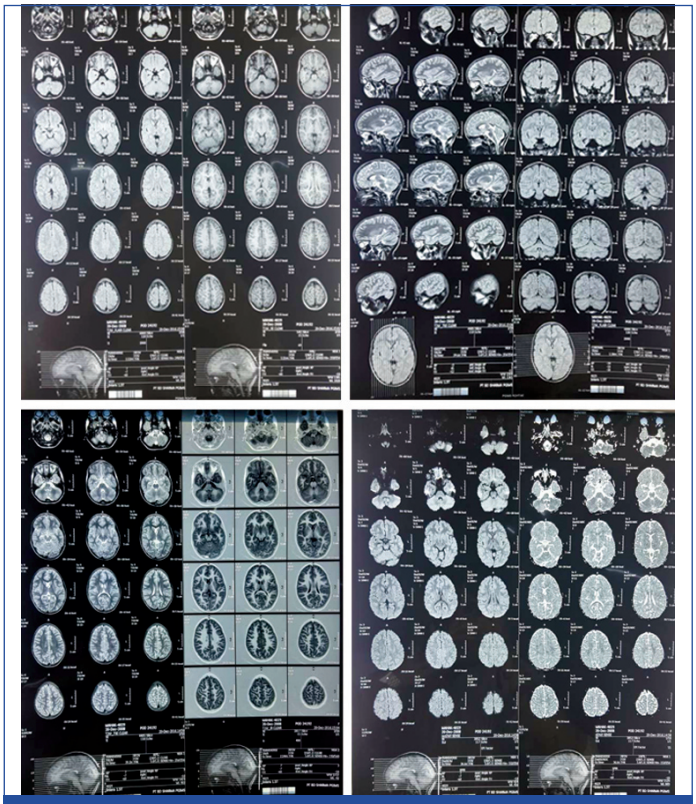
She attained neck holding at 8 months, sitting at 1 year, and standing at 2.5 years. The child started walking and speaking at the age of 3 years. There was no history of any drug intake in the antenatal period by the mother, and no history of any radiation exposure or fever with rash during the period. There was no history of any delayed cry at birth, no history of neonatal jaundice or any admissions to hospital prior to this, and no history of any abnormal body movements. There was no history of any cyanosis, feeding diaphoresis, suck rest suck cycle in the neonatal period or infancy. There was no history of palpitations, excessive sweating or difficulty breathing. There was no history of similar complaints in the family.

On examination, a broad forehead, epicanthal folds, prominent eyeballs, broad tip of nose, large ears, small chin, long fingers, and hyperextensibility of joints were present [Table/Fig-1]. There was pallor and grade 2 clubbing of the fingers. Her vitals were: Pulse rate- 102 bpm, respiratory rate- 24/min and blood pressure was 108/70 mmHg. Laboratory investigations revealed low haemoglobin (10.8 gm/dL) and hypercalcaemia (14.3 mg/dL). Other laboratory parameters were within normal limits [Table/Fig-2]. Central Nervous System (CNS) examination was abnormal in terms of higher mental functions, with a relatively short attention span, frequent distractibility, preserved verbal memory, poor visual-spatial memory and a delayed language development. The MRI brain revealed mild stenosis of the corpus callosum in the body [Table/Fig-3]. The child exhibited a highly sociable personality, with overfriendliness and a strong inclination to interact even with strangers. According to the mother, the child had difficulty sequencing tasks and maintaining goal-directed behaviour. She had poor scholastic performance, particularly in mathematics and non-verbal tasks. Tone was normal and power was 5/5 in all four limbs. The rest of the systemic examination was normal.

[Table/Fig-1]: Depicts the atypical facies of the child; i.e. broad forehead, epicentral folds, prominent eyeballs, broad nasal tip, large ears and small chin.

Investigation	Values	Normal range
Hb (gm/dL)	10.8	12-15
WBC (/mm3)	6500	4000-11000
Neutrophils	45%	40-70% of total WBCs
Lymphocyte	44%	20-40% of total WBCs
Platelet count (lakh/mm3)	3	1.5-4.5
Urea/Creatinine (mg/dL)	22/0.6	15-40; 0.5-1
Serum calcium level (mg/dL)	14.3	8.5-10.5
SGOT/SGPT (U/L)	45/54	<50
Total /Direct bilirubin (mg/dL)	1.2/0.4	0.3-1.3
Serum alkaline phosphatase (IU/L)	239	130-560
Serum phosphorus (mg/dL)	4.9	3.5-5.5
Na/K (mEq/L)	136/4.7	135-145; 3.5-5.0
T4/TSH	6 mcg/dL 2.4 µIU/mL	5-12 mcg/dL; 0.5-5.0 µIU/mL
IQ testing	Borderline intellectual delay (IQ-73.8)	Average IQ: 90-109
Echocardiography	No evidence of supravalvular aortic stenosis, trivial mitral regurgitation seen (could be normal).	Normal echo
MRI brain	Mild stenosis of the corpus callosum (in body).	Abnormal finding
FISH	Deletion of Williams Syndrome (7q11.2 locus). Deletion confirmed in all three germ line cells i.e. ectoderm, mesoderm, and endoderm. Deletion also confirmed by QF-PCR with D7S613 primer.	Abnormal finding

[Table/Fig-2]: Haematological and clinical findings of the patient.
Hb: Haemoglobin, WBC: White blood cell, SGOT: Serum glutamate oxaloacetate transaminase, SGPT: Serum glutamate pyruvate transaminase, TSH: Thyroid stimulating hormone



[Table/Fig-3]: MRI image of the patient.

The patient's Intelligence Quotient (IQ) was recorded as borderline according to Malin's Intelligence Scale for Indian Children (MISIC); i.e. 73.8 [1]. The child had aggressive behaviour as per the attendants and thereby, noticed on some visits.

On the basis of the presenting features, William syndrome was the most probable diagnosis; yet Sotos syndrome, Noonan syndrome were also kept as differentials. The final diagnosis was confirmed using the FISH technique, which revealed deletion of the WS locus i.e. 7q11.2 locus [Table/Fig-4]. The management was planned to deal with abnormal behaviour patterns, over-friendliness and aggression in an efficient way by providing behavioural therapy. Occupational therapy was also advised. One reading of asymptomatic hypercalcaemia (14.3) along with Electrocardiogram (ECG) changes was recorded in one of the visits for which the child was admitted, and calcium levels were corrected by giving intravenous fluids. In the rest, all the follow-up visits were done biweekly; calcium came out to be normal and therefore, no intervention was needed afterwards. The patient was kept on a low calcium and low vitamin D-containing diet afterwards. The child was discharged in a haemodynamically stable condition. Parents were told about the danger signs related to hypercalcaemia, cardiovascular defects and the signs and symptoms related to hypertension, which can develop in the later stages of life. Regular follow-ups were also advised so that any abnormal findings can be ruled out and the improvement could be tracked accordingly.

Referal Diagnosis: **William Syndrome**

FISH Probe Clone Details: **RP5-1127A24 (7q11.2 locus)**

Interphase FISH

Total Nuclei Counted	One Signal	Two Signals	Three Signals	Four Signals	Remarks
500	480	20	--	--	Deletion

Metaphase FISH

Total Metap. Counted	One Signal	Two Signals	Three Signals	Four Signals	Remarks
05	05	--	--	--	Deletion

Interpretation: **Deletion of William Syndrome (7q11.2 locus). Deletion confirmed in all three germ line cells i.e. ectoderm, mesoderm, endoderm. Deletion also confirmed by QF-PCR with D7S613 primer.**

Parental FISH: **Not Required**

[Table/Fig-4]: FISH report of the patient.

DISCUSSION

Williams's syndrome (OMIM 194050) is attributed to a hemizygous microdeletion on chromosome 7. Its prevalence is seen to be 1:7500 individuals [2]. The genetic basis of Williams syndrome is linked to deletion of an elastin allele (ELN) chromosome 7q caused by <2 Mbp (millionbase pair) microdeletion on chromosome 7q11.23 [3].

The characteristic features include involvement of the cardiovascular system due to elastin arteriopathy leading to narrowing of medium and large-sized arteries, ultimately causing hypertension in some cases, though in later childhood, atypical facies and a distinct personality, mild to moderate intellectual delay, endocrine and connective tissue growth-related defects. There has been evidence of a noticeable personality profile, including short attention span, anxiety issues, non-social phobias, over-friendliness and/or distractibility [4]. There have been reports of epilepsy in cases of typical deletions [5]. However, the extent and exact involvement of organs vary from patient to patient. In some atypical mutations, hypercalcaemia (serum calcium >12.0 mg/dL) can also be seen [6]. There can be prolonged colic in infants having difficulty feeding because of oral motor delays and they may have difficulty gaining weight [7].

The diagnosis might be confused with a few other disorders that seem to have a similar pattern of organ involvement, like foetal alcohol syndrome, Rasopathies, and FG syndrome. The testing approaches include FISH, polymorphic microsatellite markers, Multiplex Ligation-Dependent Amplification (MLPA) and Chromosome Microarray Analysis (CMA) [8].

In the index case, there were facial dysmorphisms, personality abnormalities, aggressive behaviour, hypercalcaemia and borderline IQ. Paediatric cardiologist's opinion was taken and there was only MVP and trivial MR; the rest findings were normal on echocardiography. MRI Brain was suggestive of mild thinning of the corpus callosum. For final diagnosis, FISH was done and was suggestive of deletion of the Williams syndrome (7q11.2 locus). The deletion was confirmed in all three germ lines i.e. ectoderm, mesoderm, and endoderm. The deletion was also confirmed by QF-PCR with D7S613 primer.

For the management part, there can be a variety of approaches that may target the gene/gene products, thereby aiming to treat the signs and symptoms. However, there is a challenge in the management due to the different phenotypes of Williams syndrome that exist and therefore, different gene/gene products and/or functional pathways need to be targeted [9]. The array of problems emerging in Williams syndrome, i.e. intellectual disability, medical problems, behavioural, psychological and adaptive impairments, may lead to considerable limitations in Quality of Life (QOL).

Hypercalcaemia, although usually presenting in infancy, has also been reported in adolescents and even adults with Williams syndrome. In one report, a 13-year-old with asymptomatic hypercalcaemia was evaluated as a part of a routine investigation [10]. Another study described two infants with symptomatic hypercalcaemia and nephrocalcinosis successfully managed with intravenous fluids and a low-calcium diet [11]. Pamidronate has been used in selected severe cases with renal impairment [12]. Interestingly, a case of a middle-aged woman diagnosed in adulthood after recurrent hypercalcaemia episodes highlights the need for awareness in older age groups [13].

In the index case, the child psychologist's opinion was taken. Behavioural therapy and occupational therapy were advised. Regular follow-up visits to rule out hypertension were advised, as there are reports of the development of hypertension in later childhood in some microdeletions of Williams syndrome. Danger signs were explained to the parents related to abnormal behavioural patterns, hypercalcaemia, hypertension and cardiovascular defects.

CONCLUSION

Williams syndrome is a rare multisystem genetic disorder that may present with diverse clinical features, including distinctive facies, cardiovascular anomalies, neurodevelopmental delay, and metabolic abnormalities such as hypercalcaemia. A high index of suspicion is essential for early diagnosis, especially in children presenting with behavioural abnormalities, intellectual disability, and suggestive dysmorphism. Timely genetic testing and a multidisciplinary approach involving cardiology, endocrinology, psychology, and rehabilitation services are crucial for optimal management and long-term quality of life. Regular follow-up is essential to monitor evolving complications like hypertension and behavioural issues.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 13, 2025
- Manual Googling: Nov 03, 2025
- iThenticate Software: Nov 05, 2025 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jan 07, 2025**
Date of Peer Review: **Feb 24, 2025**
Date of Acceptance: **Nov 07, 2025**
Date of Publishing: **Apr 01, 2026**