Williams syndrome (WS), also known as Williams-Beuren syndrome, or elfin-facies syndrome was described by Dr. J. C. P. Williams and Dr. A. J. Beuren. This multisystem, congenital and panethnic disorder is characterized by a number of developmental and physical abnormalities. Williams syndrome is estimated to effect between 1:10,000 and 1:50,000 individuals, but the incidence may be even higher because of underdiagnosis. The disorder was known in the past as idiopathic hypercalcemia—supravalvular aortic stenosis syndrome in spite of the fact that both features are frequently absent. It has been suggested that the syndrome may represent a spectrum that overlaps with hypercalcemia with or without mental retardation and supravalvular aortic stenosis with or without mental retardation. Infants in the first year of life manifest a broad range of problems, including failure to thrive (81%), feeding difficulties (71%), and vomiting (40%). Some of these symptoms are expressions of idiopathic infantile hypercalcemia (IIH). To date, all the severe cases are apparently sporadic but in some instances patients had relatives with supravalvular aortic stenosis.

DIAGNOSIS

Diagnosis is usually made during mid-childhood when the characteristic facial features, cognitive profile, and cardiac findings become more apparent. The diagnosis of WS is seldom considered in infants and young children because they lack the cardinal WS findings of supravalvular aortic stenosis (SVAS) and/or hypercalcemia. These children are usually diagnosed later when developmental delay and/or growth retardation appear. One of the first indications that a neonate may have WS is “prolonged gestation,” classically more than 42 weeks, with birth weight and length in the 5th-50th percentile. Other manifestations are feeding difficulties, profuse vomiting, and failure to thrive. Owing to variability in the clinical findings, diagnosis is usually confirmed by chromosomal fluorescent in-situ hybridization analysis, detecting submicroscopic deletions of 7q11.23, or by polymerase chain reaction. Prenatal diagnosis of the deletion is available for families at risk, using chorionic villous sampling or amniocentesis. There is no screening test for the general population.

ETIOLOGY

WS is thought to be caused by a microdeletion of approximately 1.6 megabase pairs from the long arm of chromosome 7 at 7q11.23. The disorder has no sex, race, or ethnic predilection. Most cases result from
a spontaneous new deletion, but few have arisen through parent-to-child transmission. Because an autosomal dominant inheritance pattern has been established, affected individuals have a 50% chance of transmitting the disorder to their offspring. For healthy parents who have a child with WS, the recurrence risk is usually low, but somatic cell mosaicism remains a theoretical possibility.

Ewart et al revealed that the submicroscopic deletion includes the elastin (ELN) gene. Absence or abnormality of ELN typically leads to SVAS and possibly other connective tissue features such as hernias, lax joints, deep voice, and soft skin.

Table I describes the main characteristics and features of patients with Williams syndrome.

### Table I. Description of the main characteristics and features of patients with Williams syndrome

<table>
<thead>
<tr>
<th>Main characteristics</th>
<th>Features</th>
<th>Description</th>
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<tr>
<td>Physical</td>
<td>Facial features (striking during childhood, giving appearance of looking older)</td>
<td>Curly hair, prematurely gray. Broad forehead, depressed nasal bridge, flattened midface, prominent ears, broad nasal tip, anteverted nostrils, long philtrum, broad flattened upper lip, wide intercommisural distance, thick lips, wide smile, open mouth. Full and drooping cheeks, small chin. Occasionally facial asymmetry.</td>
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<tr>
<td>Body features</td>
<td>Short stature, sloping shoulders, relatively shorter limbs, cervical kyphosis, and radioulnar synostosis. Prominent muscle mass. Soft skin, deep and husky voice. Approximately half have inguinal and umbilical hernias.</td>
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<tr>
<td>Growth and development</td>
<td>Short stature (50%) leading diagnostic criteria. Small Head circumference. Feeding problems, vomiting and failure to thrive common during the first year of life. Puberty onset usually early. Bone age delayed during childhood. Premature and abbreviated pubertal growth spurt. Joint laxity common during early infancy. By childhood and adolescence joint contractures may develop (incidence is 50%). Lipid storage in muscles may be seen, extra sacral creases, hyperplastic nails, and fifth finger clinodactyly.</td>
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<td>Neurological Function</td>
<td>Infants tend to be hypotonic with joint laxity and hypereflexia. Occasional infantile spasms and hyperreflexia. Mental deficiency (75%-95%) with IQ 41-80, mild neurological dysfunction (50%), atypical personality (65%). Intelligence correlates to severity of condition. Language performance below normal. Ability to tell time relatively poor. Impairment of perceptual-motor integration, including auditory and other modalities. Muscle hypotonia prevents reaching motor milestone. Hyperacusis (over sensitivity to sounds) in 74%-95%. Brain volume reduced.</td>
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<tr>
<td>Behavior</td>
<td>In childhood, most appear happy and friendly but have difficulties in concentrating. Delayed cognitive development (95%), poor coordination, and awkward gait in early childhood. Social isolation, distractibility, inflexibility, and ritualism may be described as autistic features. In older children overfriendliness and uncontrollable loquacity. Hyperactivity observed in 63%-87%. Children are 4 times more likely to have attention deficit and hyperactivity disorder, approximately 80% of patients exhibited generalized anxiety disorder.</td>
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<tr>
<td>Cardiovascular</td>
<td>More than one congenital heart defects (53%-80%), most frequently supravalvular aortic stenosis and peripheral pulmonic stenosis. Most great vessel constricted before 5 years.</td>
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<tr>
<td>Renal &amp; hypertension</td>
<td>Renal aplasia, renal hypoplasia, kidney duplication, horseshoe kidney, renal dystopia, renal cysts, and bladder diverticula (most common defect). Children showing all signs (type I) appear to have very high frequency of anomalies of the urinary tract. Nephrocalcinosis with impaired renal function and elevated blood urea nitrogen and creatinine levels. 60% have hypertension.</td>
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<tr>
<td>Eyes and ears</td>
<td>Visuospatial contraction in 95%. Impaired ability to recognize faces. Ocular findings: medial eyebrow flaring, shallow palpebral fissures, hypotelorism, epicantal folds, periorbital fullness, and strabismus. Over 60% of the patients have blue or hazel eyes with a satellite or lacy iris pattern.</td>
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OROPHARYNGEAL AND DENTAL FINDINGS

Facial dysmorphology is considered to be a diagnostic feature in patients with WS. The dysmorphology is composed of soft tissue and skeletal components.
According to Mass and Belostoky, 4 skeletal features contribute to the facial appearance of children with WS: 1) a short anterior cranial base; 2) the steep angle of the mandibular plane; 3) an unusual proportion of upper-to-lower anterior facial height and posterior-to-anterior facial height, despite normal facial height; and 4) a deficient chin, although the mandible could not be classified as retrognathic. Patients demonstrated a higher than normal prevalence of Class II and III occlusions, open and deep bites, and anterior cross-bites. Others describe mild micrognathia, widened mandibular angle, osteosclerotic changes in the lamina dura (particularly in the premolar-molar region), and a small chin. Folding and thickening of the buccal mucous membranes, and prominent accessory labial frenula are observed. Hypoplasia of teeth, including bud-shaped maxillary primary second molars and mandibular permanent first molars, have been reported. Abnormal tooth morphology was noted in 12.5% of the primary dentitions and in 40.7% of the permanent dentitions. With the exception of the primary mandibular central incisors in males, all mesiodistal incisor crown dimensions were significantly smaller when compared with norms. Findings also included microdontia (95%), small roots, malocclusion (85%), delayed mineralization, and absence of some teeth, as well as invagination of the incisors. Tongue thrusting was present in 67.7%, while more than 50% of the patients had excessive interdental spacing.

No single dental finding was pathognomonic of WS; however, 2 constellations of findings, each occurring in approximately a third of the sample, were observed: 1) microdontia, anterior cross-bite, tongue thrusting, and excessive interdental spacing, and 2) microdontia, deep or open bite, and excessive interdental spacing. The thyroid cartilage becomes more prominent with age.

LABORATORY FINDINGS

Usually an elevation of the calcium level is not found in the serum of these children, although there seems to be some relation to the calcium metabolism. Hypercalcemia is a feature in some instances, and it usually disappears during the second year of life. A disorder of vitamin D has been repeatedly implicated, although abnormalities of vitamin D metabolism may be secondary. It is generally agreed that the response of serum calcium to a calcium-loading test is abnormal. Renal calculi are also known to occur.

The intention of this paper is to describe 3 children with Williams syndrome who underwent dental treatment in the Department of Pediatric Dentistry at the Hebrew University—Hadassah School of Dental Medicine in Jerusalem. These children represent the variety of signs and symptoms found in the WS.

CASE 1

A 14-year-old boy, diagnosed as suffering from WS, was brought to the pediatric dental clinic for a routine check-up.

Medical history

The boy was born to healthy parents. He had hypocalcemia of the newborn, bilateral inguinal hernias, ventricular septal defect, cardiac murmurs, congenital aortic stenosis, and mild mental retardation. He was first diagnosed with WS a few weeks after birth. One month after birth, the bilateral inguinal hernia was corrected. At the age of 4 years SVAS was diagnosed through catheterization, and an open-heart aortic valvuloplasty with pericardial patch augmentation was performed.

Dental history

The boy first visited our pediatric dental clinic when he was 10 years old for a routine check-up. Treatment was performed under sedation using 9 mg diazepam and 50% N2O/O2 sedation and included fissure sealants and calculus removal. One hour prior to the treatment the patient received 3 g amoxicillin as prophylaxis for subacute bacterial endocarditis (SBE) followed by 1.5 g amoxicillin 6 hours after the procedure. One year later, dental examination revealed no caries. The first maxillary primary molars were extracted due to overretention, and calculus was removed under the same regimen used previously. At the age of 12, stainless steel crowns were performed on the permanent second molars. The patient was sedated with 5 mg midazolam PO and 50% N2O/O2 and was given the same regimen of prophylactic antibiotics for SBE.

At the age of 13.5 years, the child was uncooperative and showed poor oral hygiene and carious second permanent molars. All third permanent molars were missing as well as the maxillary and mandibular right second premolars.

Dental treatment

Owing to lack of cooperation and the amount of dental treatment required it was decided to carry out the dental treatment under general anesthesia. Medical approval for the procedure was obtained. The planned treatment included amalgam and composite restorations, stainless steel crowns, extractions, scaling, and fluoride application.

Immediately after the induction, the blood pressure rose to values of 220/120 mm/Hg. Signs of desaturations (SpO2% = 90) and lung grunts were observed. Because there was no improvement when halothane was replaced with enflurane the treatment was stopped. The patient had an elevated blood pressure, reaching levels that
could not be measured because of pulmonary edema; however, kidney, urinary tract, and cardiac function tests were normal. The patient was urgently taken to the pediatric intensive care unit under an adrenalin drip. Electrocardiogram (ECG) established a decrease in the left heart functions with septal hypokinesis. The patient was then diagnosed as suffering from a left heart edema and pulmonary edema. A few hours later the condition stabilized, and the patient remained in hospital for a few days for observation. Dental treatment was completed a year later under general anesthesia (with 5 mg midazolam as premedication prior to induction in order to control the induction) and was uneventful.

Fig 1. A child, 10 years old, demonstrates the appearance of Williams syndrome. He has a flattened midface, broad forehead, depressed nasal bridge, broad nasal tip, a broad flattened upper lip, long philtrum, thick lips, wide smile, an open mouth, full and loose cheeks, prominent ears, and a small chin.

Four years later, when he was 19 years old, the patient needed an extraction of another permanent second molar. Treatment was performed under IV sedation using propofol, and 50% N₂O/O₂. Prior to the procedure, chest x-ray and ECG were preformed in addition to the regular examinations. No complications were reported during the treatment.

CASE 2 (Fig 1)
A 4-year-old boy first visited the pediatric dental clinic for a check-up. Examination revealed the absence of the primary lower lateral incisors. Oral hygiene was poor and the patient had a few initial carious lesions. Owing to lack of cooperation, he was referred to treatment under hydroxyzine 3.7 mg/kg and 50% N₂O/O₂ sedation. The parents did not return him for treatment until 2 years later when the patient was 6 years old.

Medical history
The boy was born to healthy parents. At the age of 1 month he was hospitalized owing to feeding difficulties, and was identified as suffering from innocent cardiac murmur, ventricular septal defect (VSD), and mild mental retardation. The VSD closed spontaneously by the age of 6 years; however, a very mild supra-aortic narrowing that did not require prophylactic antibiotics for SBE was noted. In addition, the child had reduced muscle tonus.

Dental treatment
When he was 7 years old, dental treatment was performed using 6 mg diazepam and 50% N₂O/O₂ sedation and included composite-resin and amalgam restorations, stainless steel crowns, fissure sealants, and extractions.

Three years later, when the patient was 10 years old, oral and dental examination revealed an open bite, increased overjet with posterior cross-bite and a tongue-to-lower lip oral seal (Figs 2 and 3). New cavities were noted. Treatment was conducted again under 9 mg diazepam and 50% N₂O/O₂ sedation and included preventive resin restorations and fissure sealants.

CASE 3 (Fig 4)
A 14-year-old girl presented to the pediatric dental clinic for dental examination.

Medical history
WS, congenital heart defect—mitral valve prolapse with regurgitation—and mild mental retardation were diagnosed before the patient was 2 years old.

Dental history
When she was 6 years old, the girl was diagnosed for rampant caries. Due to total lack of cooperation, extraction of posterior teeth had been performed under general anesthesia.
Present dental treatment
The patient received 2 g prophylactic antibiotics for SBE 1 hour prior to treatment. Treatments were done under 5 mg diazepam and 50% N₂O/O₂ sedation. Composite restorations, stainless steel crowns, and extraction of anterior primary teeth were carried out. After completion of dental treatment, the patient visited our clinic on a regular basis every 6 months for 2 years until she was 8 years old. Cleaning of the teeth and fluoride application were performed at every visit, along with oral hygiene instructions.

The patient returned to our clinic when she was 12 years old owing to nonspecific pain in her teeth. Her oral hygiene was extremely poor. She had Angle Class II malocclusion with an open bite and posterior cross-bite. Extensive carious lesions were noted in the permanent dentition. The maxillary central incisors appeared hypoplastic (Fig 5). Orthodontic evaluation suggested possible correction of the open bite and reduction of the Class II malocclusion by simple orthodontic means. The first stage was to extract some of the primary molars to facilitate the eruption of the premolars. Owing to the extensive treatment needs and the patient’s minimal cooperation, it was suggested to perform the treatment under general anesthesia. The treatment rendered under general anesthesia was complicated by his medically compromised condition: Elevated blood pressure (220/120 mm/Hg), signs of desaturation (SpO₂ = 90), and lung grunts were observed. Treatment was ceased and the child was urgently transferred to the intensive care unit.

Cardiovascular and renal impairments tend to progress with age. Therefore, prior to any dental treatment, the severity of the disease should be assessed. Myocardial infarction or cardiac arrest has been reported after catheterization (under general anesthesia) in infancy. Furthermore, the major cause of morbidity and early (sudden) death in children with WS is narrowing of arteries due to stenosis, hypoplasia, or coarctation.

The chain of events in case 1 may have been as follows: the elevated aortic blood pressure resulted in pulmonary edema, which in turn caused desaturation and a life-threatening condition. Interestingly, the second general anesthesia session 1 year later, in which PO premedication was administered prior to the intubation, was uneventful.

In the second case, a younger child was treated. Here, even though lack of cooperation was one of the characteristics of the child’s behavior, we were able to...
perform the dental treatment with oral and inhaled sedation. The child’s physician approved the sedation regimen as the child had a very mild supra-aortic narrowing that was functionally not significant, and did not require any prophylactic antibiotics for SBE. Congenital heart defects usually appear in 53%-80% of the affected patients.12 This phenomenon requires both reduction of anxiety (usually evoked by dental treatment) and administration of prophylactic antibiotics for SBE. In younger children, when bearing in mind the tendency to anorexia and vomiting, early dental evaluation and parental counseling are important. Preventive dental regimens and dietary counseling must be individually designed and implemented.18,24

The third case adds another aspect to the restorative dental treatment in patients with WS, that of improving esthetics and the quality of life. In this case, extraction of primary molars to facilitate the eruption of the premolars as a first step to further improving esthetics was performed. There is no doubt that orthodontic treatment requires full cooperation from the parents.

In children with WS, orthodontic evaluation is generally recommended as soon as the patient’s behavior allows treatment.10 Simple intervention, as presented in the case, may minimize or even prevent the development of malocclusions. Mucogingival problems caused by anterior cross-bite and pseudo Class III malocclusions should also be treated in primary and mixed dentition.10

The dental treatment plan for patients with WS should take into consideration the apprehension and hyperactive behavior of these children and adolescents. Seventy-five percent to 95% of children with WS have mild to moderate mental retardation, and approximately 80% of patients exhibit generalized anxiety disorder and are more likely to have attention deficit and hyperactivity disorder.5 The majority (74%-95%) of children with WS are sensitive to sounds.25,26 As demonstrated in the cases presented, treatment at a younger age using oral and inhaled sedation can help to reduce anxiety and uncooperative behavior, and help the patient to cope with dental treatments. This is applicable when a small amount of dental treatment is needed.

As in the cases presented, in older children who are uncooperative and need extensive dental treatment, treatment under general anesthesia seems more appropriate. Consultation with a pediatrician prior to treatment is particularly important when general anesthesia is considered, because there is a danger of an elevation in blood pressure. Elevated blood pressure, which can induce pulmonary edema, is a life-threatening situation, as demonstrated in the first case. There is a perception that general anesthesia carries a greater risk in this group of patients than in the healthy population.23,27,29 General anesthesia can be safely administered to WS patients if complications regarding cardiovascular and renal
impairments are considered. Renal impairment may lead to decreased drug metabolism, thus the dosage of drugs given prior to the treatment or during general anesthesia should be adjusted.\textsuperscript{30,31} According to Butler et al, potential complications in sedation and anesthesia may include difficult intubation and hypotonia, which may lead to masster spasms, scoliosis, renal and bladder defects, pectus, and hypercalcemia.\textsuperscript{32} These authors recommended warming the anesthetic agents prior to surgery and avoiding halothane with suxamethonium, always looking for possible upper airway obstruction, monitoring cardiac and renal function, and checking the electrolytes.\textsuperscript{32}

The literature is inconsistent in regard to the caries rate in children with WS. Boraz\textsuperscript{24} and Oncag et al\textsuperscript{18} found that more than half of the patients (59.1\%) with WS were both caries free and restoration free, whereas only 13.6\% presented with clinically active caries. This finding is in contrast with other studies which reported high caries rates.\textsuperscript{18,24} According to Kaplan et al, caries rate is not more frequent in individuals with WS than in the normal population.\textsuperscript{4} Cohen relates the etiology of high caries rate and anomalies to delayed mineralization, which is related to type III of WS.\textsuperscript{33} In the cases presented, the children had caries in their primary and permanent dentitions. Obviously, this condition tends to deteriorate with age rather than improve. The children also presented anomalies such as missing teeth and malocclusion that required orthodontic consultations and sometimes even direct intervention on the part of the dentist. No differences in caries rate relative to the general population were recorded in the presented cases.

A delay in diagnosing WS can influence morbidity and prognosis. Given optimal medical, educational, and community support, the quality of life of affected individuals can be improved.\textsuperscript{13,14} An early multidisciplinary intervention program should be instituted as soon as the diagnosis has been made. Ongoing assessment and periodic review at appropriate ages must be carried out. At each period, evaluation comprises a growth and developmental estimation using WS growth charts, cardiac evaluation, feeding habits, and laboratory examinations.\textsuperscript{5} Because facial and dental anomalies are common to children with WS, the dentist may contribute to the successful management of these patients. Child dental care, nutrition counseling, and dental restorative treatments are important for maximizing the quality of life of patients with WS.\textsuperscript{31}

CONCLUSION

Treating a patient with WS should take into account the apprehension and hyperactive behavior of those children and adolescents. Oral and inhaled sedation can help to reduce anxiety and uncooperative behavior in the younger age group and to cope with the dental situation when minimal dental treatment is required. Treatment under general anesthesia seems more appropriate for older children and adolescents, with an increase in the needed dental procedures and a decrease in cooperation. Special attention should be given to evaluating patients prior to treatment under general anesthesia, especially because aortic stenosis tends to intensify with age. The latter, with the progressive renal impairment, can escalate blood pressure elevation.

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REFERENCES

22. Bockoven JR, Kaplan P, Namey T, Gleason M. Williams syndrome: the first decade is crucial for cardiovascular monitoring. 7th International Professional Conference on Williams Syndrome, 996

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