Health Care Supervision for Children With Williams Syndrome

ABSTRACT. This set of guidelines is designed to assist the pediatrician to care for children with Williams syndrome diagnosed by clinical features and with regional chromosomal microdeletion confirmed by fluorescence in situ hybridization.

ABBREVIATIONS. WS, Williams syndrome; FISH, fluorescence in situ hybridization.

INTRODUCTION

Williams syndrome (WS, also Williams-Beuren syndrome), now recognized to be caused by a microdeletion of chromosome 7, is a multisystem disorder first identified as a distinct clinical entity in 1961. It is present at birth and affects boys and girls equally. As routine genetic amniocentesis does not typically detect chromosome microdeletions, children with WS usually come to the attention of pediatricians during infancy or childhood. Initially thought to be a rare genetic disorder, increased awareness of the clinical features and establishment of a reliable diagnostic test have revealed WS to be one of the more commonly recognized genetic disorders in childhood. Williams syndrome is characterized by dysmorphic facies (100%), cardiovascular disease (most commonly supravalvar aortic stenosis [80%]), mental retardation (75%), a characteristic cognitive profile (90%), and idiopathic hypercalcemia (15%) (Table 1).

The diagnosis historically has been made on the basis of clinical criteria (Fig 1), but recently it has been shown that 99% of patients with WS have a hemizygous submicroscopic deletion of 7q11.23 (Table 1). The deleted portion of the chromosome includes the ELN gene that codes for the structural protein elastin, an important component of the elastic fibers found in the connective tissue of many organs. The elastin deletion explains some of the characteristics of WS, such as some of the facial features, hoarse voice, bladder and bowel diverticula, cardiovascular disease, and orthopedic problems. The pathogenesis of other characteristics, such as hypercalcemia, mental retardation, and unique personality traits, remains unexplained. One possibility is that the loss of 1 or more genes contiguous to the ELN gene contributes to the phenotype.

The pediatrician can use knowledge of the clinical manifestations (Table 1) and natural history of WS to anticipate medical problems and to educate the family. Most children with WS are described as having similar facial features. Although these features are often subtle, they tend to become more distinctive with advancing age. Facial features often include periorbital fullness, short nose with bulbous nasal tip, long philtrum, wide mouth, full lips, and mild micrognathia. Infants have full cheeks and a flat facial profile, whereas older children and adults often have a long narrow face and a long neck.

Blue- and green-eyed children with WS have a prominent “starburst” pattern to their irides (stellate iris). Mild prenatal growth deficiency and a postnatal growth rate about 75% of normal are consistently observed features of the condition.

The majority of children with WS have cardiovascular anomalies. The most common cardiovascular defect is supravalvar aortic stenosis, an often progressive condition that may require surgical repair. Peripheral pulmonary artery stenosis is often present in infancy and usually improves over time. Coarctation of the aorta, renal artery stenosis, and systemic hypertension are complications that when present may worsen over time. Because the elastin protein is an important component of elastic fibers in the arterial wall, any artery may become narrowed.

Idiopathic infantile hypercalcemia is an intriguing feature of WS that can contribute to the presence of extreme irritability, vomiting, constipation, and muscle cramps associated with this condition. Symptomatic hypercalcemia usually resolves during childhood, but lifelong abnormalities of calcium and vitamin D metabolism may persist. Hypercalciuria is common and predisposes to nephrocalcinosis. The cause of the abnormality in calcium metabolism is unknown.

An infant with WS often has difficulty feeding and may be brought for medical care because of gastroesophageal reflux, colic, or failure to thrive. Other medical problems include Chiari I malformation, strabismus, hypothalamic obesity, chronic otitis media, hypertonia, malocclusion, bowel or bladder diverticula, hernias, joint laxity, joint contractures, kyphosis, lordosis, renal or urinary tract malformations, hypothyroidism, and rectal prolapse.

Children with WS have a unique cognitive and

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.
Cognitive, motor, and language delay are universal, and in 75% of the children, mental retardation is ultimately diagnosed. Older children demonstrate a relative strength in language and auditory memory, with a significant weakness in visuospatial cognition. Behavioral problems may include hypersensitivity to sound, sleep problems, attention-deficit/hyperactivity disorder, and anxiety. Overfriendliness and an empathetic nature are commonly observed.
The medical care of children with WS requires an understanding of the natural history of the disorder, awareness of potential clinical complications, and ongoing assessment and periodic review at appropriate ages (Fig 2). Because the clinical manifestations during the neonatal period are variable, the diagnosis may not be suspected during early infancy. Accordingly, this statement includes a series of evaluations that should be considered at the time the diagnosis is suspected clinically; the diagnosis

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**Growth (Past or Present Evidence of)**

<table>
<thead>
<tr>
<th>Scored Points*</th>
<th>If 3 of 5 items are checked, score 1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Post-term birth &gt; 41 wk gestation</td>
<td>[ ] Prolonged colic &gt; 4 m irritability</td>
</tr>
<tr>
<td>[ ] Failure to thrive/height and weight &lt; 5th percentile</td>
<td>[ ] Chronic constipation</td>
</tr>
<tr>
<td>[ ] Vomiting or gastrolesophageal reflux</td>
<td></td>
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</tbody>
</table>

**Behavior and Development**

<table>
<thead>
<tr>
<th>If 3 of 6 items are checked, score 1 point</th>
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</thead>
<tbody>
<tr>
<td>[ ] Overly friendly personality</td>
</tr>
<tr>
<td>[ ] Hypersensitivity to sound</td>
</tr>
<tr>
<td>[ ] Anxiety</td>
</tr>
<tr>
<td>[ ] Developmental delay or mental retardation</td>
</tr>
</tbody>
</table>

**Facial Features**

<table>
<thead>
<tr>
<th>If 8 of 17 items are checked, score 3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Bitemporal narrowing</td>
</tr>
<tr>
<td>[ ] Epicanthal folds or flat nasal bridge</td>
</tr>
<tr>
<td>[ ] Strabismus (present or past)</td>
</tr>
<tr>
<td>[ ] Short nose or anteversion of nares</td>
</tr>
<tr>
<td>[ ] Full cheeks</td>
</tr>
<tr>
<td>[ ] Long philtrum</td>
</tr>
<tr>
<td>[ ] Small, widely spaced teeth</td>
</tr>
<tr>
<td>[ ] Wide mouth</td>
</tr>
</tbody>
</table>

**Cardiovascular Problems (by Echocardiography) (a)**

<table>
<thead>
<tr>
<th>If 1 of 2 items are checked, score 5 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] SVAS†</td>
</tr>
</tbody>
</table>

**Cardiovascular Problems (b)**

<table>
<thead>
<tr>
<th>If 1 of 3 items are checked, score 1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Other congenital heart disease</td>
</tr>
<tr>
<td>[ ] Cardiac murmur</td>
</tr>
</tbody>
</table>

**Connective Tissue Abnormality**

<table>
<thead>
<tr>
<th>If 2 of 6 items are checked, score 2 points</th>
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<tbody>
<tr>
<td>[ ] Hoarse voice</td>
</tr>
<tr>
<td>[ ] Inguinal hernia</td>
</tr>
<tr>
<td>[ ] Bowel or bladder diverticula</td>
</tr>
</tbody>
</table>

**Calcium Studies**

<table>
<thead>
<tr>
<th>If 1 of 2 items are checked, score 2 points</th>
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</thead>
<tbody>
<tr>
<td>[ ] Hypercalcemia</td>
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</tbody>
</table>

**Total Points:**

* If the score is < 3, a diagnosis of Williams syndrome is unlikely. If the score is ≥ 3, FISH studies should be considered. (Mean score for Williams syndrome was 9 [standard deviation = 2.86]. The scoring system is based on a study of 107 persons with Williams syndrome [confirmed by FISH] evaluated by Colleen A. Morris, MD; Frank Greenberg, 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.)

† If supravalvar aortic stenosis (SVAS) is present, referral to a geneticist and FISH studies are recommended.

Fig 1. Williams syndrome diagnostic scoring table: clinical diagnosis.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Infant (NB - 1 Year)</th>
<th>Early Childhood (1-5 Years)</th>
<th>Late Childhood</th>
<th>Adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype/FISH Review*</td>
<td>•</td>
<td>*</td>
<td></td>
<td></td>
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<tr>
<td>Phenotype Review*</td>
<td>•</td>
<td>*</td>
<td></td>
<td></td>
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<tr>
<td>Recurrence Risks</td>
<td>*</td>
<td>*</td>
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<td></td>
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</tbody>
</table>

**Anticipatory Guidance**

<table>
<thead>
<tr>
<th>Early Intervention</th>
<th>Family Support</th>
<th>Support Groups*</th>
<th>Long-term Planning</th>
<th>Sexuality</th>
<th>Therapy (pt, ot, speech)</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
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</tbody>
</table>

**Medical Evaluation**

<table>
<thead>
<tr>
<th>Growth feeding</th>
<th>Thyroid Screening</th>
<th>Hearing Screening</th>
<th>Vision Screening</th>
<th>2-Arm Blood Pressure</th>
<th>Cardiology Evaluation*</th>
<th>UA/BUN/Cr*</th>
<th>Urine Ca/Cr*</th>
<th>Serum Calcium*</th>
<th>Renal Ultrasoundography*</th>
<th>Musculoskeletal Eval</th>
<th>Pneumorax</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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</table>

**Psychosocial**

<table>
<thead>
<tr>
<th>Development</th>
<th>School Performance</th>
<th>Socialization</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

\*Assure compliance with the AAP \*Recommendations for Preventive Pediatric Health Care
\*Or at time of diagnosis
\*Discuss referral to specialist
\*As needed
\**Referral

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**Fig 2. Health supervision for children with Williams syndrome**. 
HEALTH CARE SUPERVISION FOR CHILDREN WITH WILLIAMS SYNDROME

5. Establish a medical home with clear emphasis on management of the child as a partner in the ongoing management and care of the child.

4. Baseline cardiology evaluation by a cardiologist with pediatric expertise and experience.

3. Annual cardiology evaluation from 1 to 5 years (Fig 3A–F)

2. Developmental evaluation and growth evaluation using WS growth charts (Fig 3A–F)

1. Annual health maintenance examinations and baseline evaluation (including careful auscultation of chest and abdomen for murmurs or bruits)

SPECIAL CONSIDERATIONS FOR THE CHILD DIAGNOSED WITH WS

1. Do not give multivitamin preparations to children with WS because of the potential deleterious effects of vitamin D. Recommend diligent use of sunscreen to minimize autologous production of vitamin D.

2. Perform periodic cardiovascular evaluations, even after a baseline examination with normal findings.

3. Baseline cardiology evaluation should be performed by a cardiologist with pediatric expertise and experience.

4. Screen for the development of hypertension periodically according to guidelines of the American Academy of Pediatrics.

5. Establish a medical home with clear emphasis on continuity of care and the role of the family members as partners in the ongoing management and care of the child.

HEALTH SUPERVISION FROM BIRTH TO 1 YEAR (INFANCY)

Examination

1. Review and note clinical features and confirm diagnosis with FISH analysis

2. Routine health maintenance examinations and baseline evaluation

3. Growth and developmental evaluations using WS growth charts (Fig 3A–F)

4. Baseline cardiology evaluation by a cardiologist with pediatric expertise and experience

5. Review feeding issues (reflux, refusal, disordered suck or swallow, vomiting or symptoms of colic).

6. Consider pediatric ophthalmologic evaluation for strabismus, amblyopia, and refractive errors

7. Check for inguinal hernia

8. Objective hearing assessment at 6 to 12 months (recurrent otitis media is common)

9. Blood pressure measurement (both arms) annually and careful evaluation of femoral pulses

10. Early recognition and management of constipation

11. Pediatric anesthesia consultation for any child requiring surgery (several reports of unexpected deaths have been associated with the administration of anesthesia)22

Laboratory

1. Williams Syndrome Chromosomal Region FISH to confirm clinical diagnosis

2. Serum creatinine level

3. Urinalysis

4. Calcium levels
   a. Serum*
   b. Spot urine test to determine calcium-creatinine ratio†

5. Thyroid screen for newborns (according to state mandate)

6. Baseline ultrasonographic examination of the bladder and kidneys

Anticipatory Guidance

1. Individual support for the family (by family, friends, clergy), support groups, or both (see list)

2. Review increased risk for otitis media

3. Feeding (difficulty in transition to textured foods)

4. Do not prescribe multivitamin preparations containing vitamin D

5. Refer to early childhood intervention program

HEALTH SUPERVISION FROM 1 TO 5 YEARS (EARLY CHILDHOOD)

Examination

1. Annual health maintenance examinations and baseline evaluation (including careful auscultation of chest and abdomen for murmurs or bruits)

2. Developmental evaluation and growth evaluation using WS growth charts (Fig 3A–F)

3. Annual cardiology evaluation from 1 to 5 years

4. Feeding issues: watch for rectal prolapse and avoid constipation with stool softeners if necessary

5. Annual hearing and vision screening; objective audiologic evaluation and an ophthalmologic evaluation before age 3 years

6. Orthopedic issues: musculoskeletal and neurologic assessments to evaluate joints, muscle tone, spasticity, and hyperactive reflexes17

*If hypercalcemia is found, dietary calcium restriction should be implemented and diet should be monitored in conjunction with a pediatric dietitian/nutritionist. Referral to a pediatric renal specialist should be considered.

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Downloaded from http://pediatrics.aappublications.org/ by guest on October 22, 2017
7. Pediatric anesthesia consultation for any child requiring surgery (several reports of unexpected deaths have been associated with the administration of anesthesia)22
8. Annual blood pressure measurement (both arms) and careful examination of femoral pulses
9. Multidisciplinary developmental assessment and treatment in early intervention programs (0–3 years) or school based programs (3 years and older)1,5,19

10. Dental referral

**Laboratory**
1. Yearly urinalysis
2. Annual total calcium measurement if the level was elevated at baseline or as needed if the child becomes symptomatic; if level was normal, measure every 2 to 3 years
3. Urinary calcium-creatinine ratio every 2 years
4. Thyroid function test every 4 years

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**Fig 3A. Williams syndrome—stature, females.**

5. Serum creatinine level every 4 years

Anticipatory Guidance
1. Individual support for the family (by family, friends, clergy), support groups, or both
2. Review increased risk for otitis media
3. Ongoing feeding and dietary assessments
4. Therapy as needed (physical, speech and language, and occupational, including sensory integration)
5. Review constipation as a possible problem
6. Children with unexplained fever should be evaluated for urinary tract infection
7. Discuss developmental status, early intervention programs, and preschool programs
HEALTH SUPERVISION FROM 5 YEARS TO 12 YEARS (LATE CHILDHOOD)

Examination
1. Annual health maintenance examinations and baseline evaluation
2. Developmental evaluation and growth evaluation using WS growth charts (Fig 3A–F)
3. Annual blood pressure measurements (both arms) and careful evaluation of femoral pulses
4. Cardiology evaluation as indicated by previous clinical findings. If results of previous evaluations are negative, repeated cardiology evaluation (for arterial stenoses, hypertension) should be performed at puberty
5. Ophthalmologic evaluation for strabismus and hyperopia
6. Orthopedic problems (eg, joint limitation, kyphosis, lordosis, scoliosis, and spasticity)
7. Hearing and vision screening annually
8. Pediatric anesthesia consultation for any child requiring surgery (several reports of unexpected deaths have been associated with the administration of anesthesia22)
9. School readiness and placement and Individual Educational Plan at 5 years
10. Developmental and psychoeducational assessment; formal evaluation for attention-deficit hyperactivity disorder, anxiety, or both and discussion of treatment options23

**Laboratory**
1. Yearly urinalysis
2. Thyroid function tests every 4 years
3. Annual total calcium level if baseline result was elevated or child becomes symptomatic; otherwise measure level every 4 years
4. Urinary calcium-creatinine ratio every 2 years
5. Serum creatinine level every 2 to 4 years

**Anticipatory Guidance**
1. School readiness and placement

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![Figure 3D. Williams syndrome—weight, males.](image-url)
2. Therapy as needed (physical, speech and language, and occupational, including sensory integration)
3. Long-term vocational planning
4. Discuss sexuality and adolescence; puberty is often early in WS, but true precocious puberty is rare
5. Discuss diet and exercise as obesity may become apparent in late childhood

6. Discuss treatment options for anxiety (counseling, relaxation techniques, and medications)
7. Estate planning for parents of a child with special needs

**HEALTH SUPERVISION FROM 13 YEARS TO 18 YEARS (ADOLESCENCE)**

Progressive medical problems including hypertension, progressive joint limitations, recurrent urinary
tract infections, and gastrointestinal problems are common beginning in this age group and continuing throughout adult life.

Examination
1. Annual health maintenance examinations and baseline evaluation; blood pressure measurement (both arms)
2. Developmental evaluation and growth evaluation using WS growth charts (Fig 3A–F)
3. Cardiology evaluation if indicated by previous clinical findings
4. Pediatric anesthesia consultation for any child requiring surgery (several reports of unexpected deaths have been associated with the administration of anesthesia22)
5. Consider ophthalmologic evaluation for hyperopia
6. Orthopedic problems (eg, joint limitation, kyphosis, lordosis, scoliosis, and spasticity)

Fig 3F. Williams syndrome—head circumference, males.

7. Hearing and vision screening annually
8. Developmental and psychoeducational assessment; school placement and resource enhancement; vocational training; social skills training for peer interaction
9. Gastrointestinal issues: consider diverticulitis and diverticulosis, cholelithiasis, and chronic constipation in adolescents with abdominal pain
10. Screen for generalized anxiety disorder

Laboratory
1. Yearly urinalysis
2. Thyroid function test every 4 years
3. Total calcium level only if adolescent becomes symptomatic, otherwise, every 4 years
4. Urinary calcium-creatinine ratio every 2 years
5. Bladder and renal ultrasonography at puberty and every 5 years thereafter
6. Serum creatinine level every 2 to 4 years

Anticipatory Guidance
1. School placement
2. Therapy as needed (physical, occupational, speech, and language)
3. Discuss diagnosis with the adolescent; support groups for the adolescent (see American Academy of Pediatrics statement on "Transition of Care Provided for Adolescents With Special Needs")
4. Discuss sexuality and reproductive issues
5. Encourage career counseling
6. Foster independence
7. Assist in transition to adult care (especially for cardiology care). Many pediatricians feel comfortable continuing to provide primary care well into young adulthood
8. Encourage daily exercise to include range of motion
9. Encourage prompt medical attention for urinary tract or gastrointestinal symptoms
10. Mental health issues

<table>
<thead>
<tr>
<th>Age</th>
<th>Calcium-Creatinine Ratio (mg/mg ratio) (95th Percentile for Age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 mo</td>
<td>0.86</td>
</tr>
<tr>
<td>7–18 mo</td>
<td>0.6</td>
</tr>
<tr>
<td>19 mo–6 y</td>
<td>0.42</td>
</tr>
<tr>
<td>Adults</td>
<td>0.22</td>
</tr>
</tbody>
</table>

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American College of Obstetricians and Gynecologists
James W. Hanson, MD
American College of Medical Genetics
Cynthia A. Moore, MD, PhD
Centers for Disease Control and Prevention
Michele Lloyd-Puryear, MD, PhD
Health Resources and Services Administration

REFERENCES


**RESOURCES FOR PARENTS**

March of Dimes, 1275 Mamaroneck Ave, White Plains, NY 10605; Telephone: 914/428-7100; [http://www.modimes.org](http://www.modimes.org)

The Williams Syndrome Association, PO Box 297, Clawson, MI 48017; Telephone: 248/541-3630; [http://www.williams-syndrome.org](http://www.williams-syndrome.org)

Williams Syndrome Foundation, University of California, Irvine, CA 92679; Telephone: 949/824-7259; [http://www.wsf.org](http://www.wsf.org)
Health Care Supervision for Children With Williams Syndrome
Committee on Genetics
Pediatrics 2001;107;1192

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BIBLIOGRAPHY

General Review

Audiologic Evaluation

Otorrhea

Indications for Tympanostomy Tube Removal

Sequelea of Tympanostomy Tube Extrusion/Removal

ERRATUM

Several errors occurred in a figure in the policy statement “Health Care Supervision for Children With Williams Syndrome,” which appeared in the May 2001 issue of Pediatrics (2001;107:1192–1204). In Fig 2, first column, the 11th row heading under Medical Evaluation should read “Musculoskeletal Eval,” and the 12th row heading should read “Pneumovax.” In the footnotes, the explanation with the double dagger should read “If hypercalciumia is found, 2 repeated urine studies of the calcium-creatinine ratio (morning and afternoon) should be performed. If the level is still elevated, repeat measurement of the serum calcium level and perform renal ultrasonography for nephrocalcinosis. Assess dietary calcium intake.” The explanation for the abbreviation O should read “Objective . . .”
Health Care Supervision for Children With Williams Syndrome

Committee on Genetics

*Pediatrics* 2001;107;1192

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An erratum has been published regarding this article. Please see the attached page for:

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