Williams Syndrome: A Multidisciplinary Approach to Care

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Williams syndrome (WS) is a highly distinct genetic syndrome with a unique constellation of medical and developmental problems and an associated characteristic personality profile. It is a disorder that should be well-known to most pediatricians, in generalities if not in specifics. Although the management of certain problems may be best provided by a single specialist, other common challenges are best approached through a multidisciplinary lens for both diagnostic evaluation and treatment. The etiology of these latter problems can be viewed on a continuum; at one end are symptoms manifesting in one system caused by pathology in another (e.g., abdominal pain caused by anxiety), while at the other end are symptoms whose causes are truly multifactorial (e.g., abdominal pain due to celiac disease which is also exacerbated by anxiety).

**WILLIAMS SYNDROME**

In 1961, Dr. JCP Williams described four unrelated individuals who had supravalvular aortic stenosis, mental “deficiency,” and a facial resemblance to each other (see Figure 1, page 457).¹ A year later, a pediatric cardiologist, Dr. Alois Beuren, reported four additional patients with similar findings.² This disorder has subsequently borne their name, and is designated either as Williams syndrome (WS) or Williams-Beuren syndrome (WBS).

Today, we know WS is a relatively rare genetic syndrome, estimated to affect around 1 in 10,000 persons. Research into etiology demonstrated that individuals with WS carry a ~1.5 million base (Mb) pair deletion of DNA on one of their copies of chromosome 7.³ This segment contains more than two dozen contiguous genes, including the gene elastin (ELN). Deletion of ELN leads to many of the classic cardiovascular abnormalities of WS. Although larger and smaller deletions have been reported, almost all individuals with WS have what is called a “common deletion” resulting in loss of 26 or 28 genes (see Figure 2, page 458).⁴ The areas flanking the WS deletion consist of highly repetitive sequences of DNA; misalignment between these repetitive sequences during meiosis is the mechanism that most often causes the deletion. WS is not caused by parental behavior or exposures.
Because the WS deletion cannot be seen on a routine chromosome analysis it is referred to as a microdeletion. For this reason, testing for the presence or absence of the elastin gene by fluorescent in situ hybridization (FISH) is required to confirm the diagnosis (see Figure 2b, page 458). A newer methodology, known either as chromosomal microarray analysis (CMA) or comparative genomic hybridization (CGH), has become clinically available and is now increasingly used to establish the diagnosis of WS (Figure 2c, see page 458). CMA can detect small deletions or duplications anywhere in the genome, and offers specific particular advantages over FISH testing for elastin. One, the diagnosis of WS need not be considered in advance of testing, and two, the approximate size of the deletion and the number of deleted genes is provided.

A MULTI-SYSTEM DISORDER

Although the initially noted features were restricted to a few organ systems, WS is now recognized as a multi-system disorder with the potential to involve any organ as well as multiple developmental systems including the cognitive, social and emotional. The commonly involved systems are described in what follows.

When to Consider WS

Features suggestive of WS are variable and can differ by age. During infancy or young childhood, cardiovascular disease of the “typical” supravalvular aortic stenosis (SVAS) or supravalvular pulmonary stenosis variety, or endocrine abnormalities such as hypercalcemia, generally raise suspicion of the diagnosis. More frequently, however, it is a combination of relatively non-specific but common problems in infants and young children such as impaired growth, hypotonia and joint laxity, prolonged “colic” associated with multiple formula changes, small primary teeth, frequent ear infections, esotropia, inguinal hernia, and developmental delay that should prompt the pediatrician to consider WS. In older children, the diagnosis of WS should be considered when cognitive challenges, short attention span and impulsivity (usually labeled as attention deficit hyperactivity disorder or ADHD), and a generally friendly (or over-friendly) personality, are present in combination with worry or even frank anxiety about stimuli such as fireworks, thunderstorms, escalators or “shots.”

Auditory/ENT findings

Ear infections are common and insertion of myringotomy tubes can be required. Monitoring for hearing loss (either conductive caused by otitis media or middle ear fluid, or sensorineural with unknown causes) is important.7
Figure 2. Depiction of the WS critical region and methods of diagnosis. Ideogram of chromosome 7 with an enlargement of the WS critical region (WSCR) (depicted in A, each rectangle represents a gene). The diagnosis of WS is most commonly confirmed by one of two methods. Fluorescent in situ hybridization or FISH (depicted in B) only detects the presence or absence of the elastin genes on chromosome 7. Chromosomal microarray analysis or CMA is increasingly used and can identify small deletions or duplications in the entire WSCR (depicted in C). Drawings are not to scale.

Heightened sensitivity to sudden loud noises, also called hyperacusis, is almost universal by school age.\(^9\)

### Cardiovascular Findings
Approximately 50% to 75% of patients with WS have clinically demonstrable cardiovascular disease.\(^9,10\) The most common lesions are vascular stenoses of any medium or large sized artery, caused by overgrowth of the vessel media and narrowing of the lumen. The single most common location for stenosis is above the aortic valve, so-called SVAS. Stenoses of the pulmonary arteries are common and stenoses at other sites have been reported but their true frequency is currently unknown. The natural history of these stenoses is variable; some patients never develop clinically significant narrowing, although others require surgery in infancy for relief of severe obstruction. The highest risk period for progression of SVAS is infancy and early childhood. Close and ongoing monitoring by a cardiologist is required, and the specific timetable is dictated by the patient’s age and severity of findings. The lifelong risk of developing hypertension is \(~50\%\). However, hypertension can have its onset in childhood, so “desensitization” to blood pressure determinations should begin in the pediatrician’s office. Surgically correctable vascular causes of hypertension, such as renal artery stenosis, are infrequently found but should be considered especially when hypertension is new in onset or severe. An extremely rare complication of vascular disease in WS is stroke.

### Dental Findings
Dental eruption is usually within normal limits, but primary teeth are small and sometimes abnormally shaped.\(^11\) An increased frequency of absent teeth as well as occlusal abnormalities are reported. Similar changes are present in the secondary dentition so that many adolescents undergo orthodontic correction. Excess dental caries is not a feature of WS per se and suggests a secondary cause such as reflux or “bottle teeth.” Formal dental care should begin at the routine age though due to heightened oral sensitivity a process of desensitization is often needed. Poor visuospatial skills necessitate continuous parental involvement in dental care at home.

### Endocrine Findings
The WS endocrine abnormality most commonly written about is hypercalcemia. Perhaps somewhat surprisingly, it is the least often documented of the endocrine pathologies, occurring in only around 15% of individuals.\(^3\) Hypercalcemia may be detected more frequently than hypercalcemia. Although calcium problems most commonly manifest during infancy and young childhood, they can occur in older individuals as well. Shorter term treatment options include hydration and furosemide while longer term treatment options consist of dietary calcium restriction and administration of a bisphosphonate.\(^12\) The etiology of hypercalcemia remains unknown. Congenital hypothyroidism, requiring thyroid hormone supplementation, is uncommon though reported. Subclinical (or compensated) hypothyroidism, consisting of an elevated thyroid stimulating hormone level in the setting of a normal thyroxine (T4) level, is more commonly detected.\(^13\) The decision to treat with thyroid hormone supplementation requires input from a pediatric endocrinologist. Early puberty for both males and females with WS is well documented. Treatment options include the administration of Lupron to delay puberty, but extensive communication among the family, pediatric endocrinologist, and pediatrician is necessary as circumstances are unique for each patient. Finally, a high prevalence of diabetes mellitus and impaired glucose tolerance (IGT, a pre-diabetic state) is found in adolescents and adults with WS compared with their peers in the general population.\(^14\) The pediatrician has a key role in providing anticipatory guidance to emphasize physical activity and healthy food choices, in an attempt to minimize the long-term risk of developing diabetes.

### Genitourinary Findings
Problems include structural abnormalities of the kidneys (horseshoe kidney or ectopic kidney) in \(~15\%) of patients with WS;\(^15\) bladder diverticuli (though their exact prevalence and age of onset is un-
known); delayed bladder training (particularly with acquisition of nighttime training for some boys); and urinary frequency (which is extremely common). The cause or causes of this are not understood but contributing factors appear to include anxiety, abnormal detrusor muscle contractions, and bladder diverticuli.16

Musculoskeletal Findings

Low muscle tone in association with joint laxity is an almost universal finding in infants and young children with WS. Over time, joint contractures can develop, particularly in the lower extremities, leading to diminished heel cord range of motion.17 Long-term physical therapy and stretching improves joint motion, but for some, especially those with persistent toe walking, surgery may still be required. Lordosis is extremely common in WS, whereas scoliosis is far less common but can become severe enough to require surgical correction.

Gastrointestinal Findings

Causes of several typical gastrointestinal (GI) problems are elaborated in what follows, along with a discussion of Figure 3. Most of the conditions noted can adversely affect weight gain. However, two-thirds of adults become overweight or obese, making proper anticipatory guidance important. Although this proportion is similar to that of the general population, the accumulation of fat in adults with WS is in a distinct pear-shaped distribution and potentially can exacerbate other problems such as hypertension and diabetes.

Neurological Findings

Hypotonia is extremely prevalent in children with WS and generally improves over time. Most patients have a non-focal though abnormal neurological examination, one in which symmetric hyper-reflexia and even several beats of clonus are commonly observed.18 Although MRI scans of the brain are usually normal, type I Chiari malformation, in which the cerebellar tonsils extend into the foramen magnum, has been reported.19

Developmental Findings

A specific developmental profile is observed in most individuals with WS. Cognition ranges from an average full-scale IQ with learning disabilities to mild-moderate mental retardation with a unique pattern of strengths and weaknesses.20 Individuals with WS typically have strengths in language domains and challenges in visual-spatial domains, often rendering full-scale IQ scores invalid. Specific personality traits including a strong social orientation with social disinhibition, emotional lability, hyperacusis, musicality, anxiety, and phobias (often sound related and almost never social phobias) are frequently seen. Despite a strong social orientation, difficulties with higher level social interaction almost always co-exist.21 Fears of sound and tactile issues are very common (eg, alarms, balloons, blenders, haircuts) as are Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) mental health diagnoses of ADHD and anxiety. Anxiety becomes more prevalent during childhood, occurring in up to 50% of adolescents with WS.22

A MULTIDISCIPLINARY APPROACH

Children with WS may have difficulties in many areas of health and daily functioning potentially requiring the input of several specialists. Although we recommend a multidisciplinary model, this need not take place within a single clinic housing specialists across disciplines. Such clinics make multidisciplinary care much easier for families and pediatricians, however, in the current healthcare funding climate, there are very few such clinics. Those that exist may not have the capacity to provide ongoing treatment or multidisciplinary evaluation of complex problems on short notice. The multidisciplinary approach we describe here requires a specific model for thinking about complex problems, stressing knowledge of these problems and re-
ferrals to other specialists, but it does not require a single multidisciplinary clinic.

Two complex problems that commonly occur in children with WS, GI issues and behavioral issues, are further discussed below to illustrate problems that are best evaluated and treated within a multidisciplinary model.

**GI/Feeding/Weight Issues**

For individuals with WS, gastrointestinal, feeding, and weight problems are numerous, complex, and potentially interrelated. As depicted in Figure 3 (see page 459), there are many potential etiologies rather than an obligatory single causative factor. Because medical causes of GI and feeding problems are relatively common, they must be considered, addressed, and “ruled out” before deciding that nonmedical factors, such as behavioral and mental health causes, are operational.

The pediatrician should be the initial care provider to assess the child with GI issues and to begin the process of determining whether the problem is “unifactorial” (eg, failure to gain weight solely because of inadequate caloric intake caused by dysregulated sucking and swallowing), or whether it is multifactorial (eg, caused by gastroesophageal reflux [GER] in conjunction with food aversion that has developed because of the pain of reflux). The pediatrician initiates additional studies and referral to specialists as needed. The data from all observations (which consist of, but are not limited to, progress of the child in response to treatment, results of laboratory investigations, and differential diagnoses) must be interpreted and synthesized by the pediatrician in light of cumulative experience and specific knowledge of causes of GI disorders in WS (as depicted in Figure 3, see page 459). In infants and young children, problems of oral and upper GI function are the most common causes of failure to gain weight, feeding difficulties, and/or abdominal pain. Colic is common in WS and can last up to 8 to 12 months. Even once colic has resolved, advancing the diet to include baby foods and table foods is complicated by textured food intolerance. A specific etiology for these problems is rarely elucidated, but after a process of elimination it is often considered developmental/neurological in origin. Motility of the GI tract seems disordered in that GER and constipation are extremely common, sometimes requiring consultation, management support, or even medication advice from a gastroenterologist. Further, the pediatrician must maintain a high index of suspicion of underlying pathology, especially of GER, given the cognitive limitations and high pain tolerance reported by some. Non-GI or systemic problems need to be considered as well, such as hypercalcemia or exceptionally rare cases of vascular insufficiency of the GI tract. Proper evaluation and treatment of these causes can require specialist input as well. Among young children, learned patterns of avoidant behavior (such as gagging at the sight of food, originally stemming from the textured food intolerance described above) are a reflection of the anxiety that is common in WS. If sufficiently severe, amelioration of this problem can be especially challenging, benefiting from a multi-modal approach which includes feeding therapy, behavior modification often involving playful desensitization activities, and possibly even anxiolytic medication. Many of the same problems can produce abdominal pain or weight loss in older children and adults with WS. However, it is also important to add diverticular disease to the differential diagnosis since symptomatic diverticulitis has been detected in teenagers with WS. Presumably elastin deficiency in the bowel wall in combination with chronic constipation predisposes to diverticulosis and diverticulitis.

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**Figure 4. Depiction of causes of problems in peer relationships in individuals with WS. The three smallest boxes indicate different systems of functioning that can interfere with successful peer relationships, while the larger boxes in the bottom row list specific problems to target for treatment.**
Social and Peer Interactions

Friendships, peer relationships, and social skills are another area of difficulty for many individuals with WS. This is despite the fact that most individuals with WS are highly socially oriented, making more eye contact than is typical for instance, even as infants. Individuals with WS demonstrate developmental delays in aspects that reflect key components of successful social functioning including language processing, language formulation, pragmatic language, and nonverbal communication skills. Additional problems with processing of subtle social cues, cognition and mental health issues such as anxiety, ADHD and specific phobias, all adversely impact successful social functioning. Further, there are several medical issues that can interfere with social functioning. For example, in younger children, oromotor problems can make speech less intelligible; this combined with hypotonia and/or malocclusion results in drooling, which can be socially stigmatizing. Other medical issues presenting as diminished social interactions are overall sleepiness that may be present secondary to sleep apnea, or hearing loss that may impact responsiveness to language, and should be considered. Additionally, in adolescence and adulthood where more independence is expected and peers are more aware of appearances, problems with motor planning, organization, attention, and visual spatial skills as well as possibly also diminished and/or increased sensory sensitivities, can interfere with processes involved in maintaining socially acceptable personal appearance (eg, having clothing adjusted correctly, caring for hair appropriately, etc.) and have a resultant negative impact on peer perception. This combination of being very socially oriented but lacking in many social skill components can lead to an undesirable state of social failures and isolation, with secondary depression and/or behavior problems. Patients of all ages presenting with “social problems” are likely to benefit from support and remediation in any or several of the domains above (see Figure 4, page 460). The pediatrician will want to consider each of these pathways to determine the best course(s) for evaluation and treatment. Once it is determined which factors are contributing most substantially to social difficulties, treatment modalities become clearer.

TRANSITION AND THE PEDIATRICIAN

Maintaining this multidisciplinary mindset benefits the patient in other areas of care as well. As individuals with WS get older, it is necessary to transfer their medical care from pediatric to adult health providers as well as to prepare for other areas of transition in their lives. Although transition to adulthood has traditionally been addressed separately in the school and healthcare systems, the process ideally should be more integrated, focusing on the individual’s and family’s wishes with input from other areas including healthcare, education, employment, and the community. Because individuals with WS have many health concerns that may impact transition planning, the pediatrician is in an excellent position to help facilitate and contribute to this process.

Identifying Key Issues in Transition

Transition is a complex, ongoing, developmental process for everyone but even more so for individuals with WS or other special healthcare needs. Although several pieces of legislation such as the Individuals with Disabilities Education Act (IDEA) and the Americans with Disabilities Act (ADA), as well as the 2000 and 2002 policy statements by the American Academy of Pediatrics (AAP), promote transition preparations, there are many barriers arising between medical care providers and their patients/families which impede successful transition. These include lack of communication, avoidance of sensitive issues, and unfamiliarity with available resources. The first step in transition planning for an adolescent with WS is recognizing the key issues.

Some issues that arise during transition are common to all patients, such as establishing a level of independence compatible with their capabilities, building interests with less of an academic focus, gaining self-confidence, being comfortable with daily living skills/vocation, developing relationships and social opportunities, discovering sexuality, taking as much responsibility for their own medical care as possible, continuing exercise and good nutrition, and reaching self-determination. In addition, it has long been recognized that there are several differences between pediatric and adult care. For example, adult care is often more fragmented with less coordination, which increases the likelihood of gaps in care that could be detrimental to the patient.

Some issues at the time of transition may be more specific to WS. For instance, many medical problems can potentially develop or worsen as individuals with WS age including hypertension, progressive joint limitations, and gastrointestinal problems such as diverticulitis disease. Studies have shown effective transition programs take advantage of written plans or protocols to guide care. For WS, a set of guidelines that can help anticipate some of these problems has been published by the AAP; similarly a set of guidelines for medical monitoring in adults with WS has also been published.

Communication

In addition to identifying each patient’s specific transition-related issues, there should be communication about the process with all parties involved.
Schrander-Stumpel et al suggested that in an ideal situation a coordinated visit should take place with both the pediatrician and the new adult provider. If this is not possible, then the pediatrician can assist with referrals to appropriate adult care providers. To ensure that important medical information is transferred, a medical summary sheet should be created and shared by everyone involved in the transition process. A newer option consists of Web-based electronic medical records. Not only would pertinent medical records be available, but published guidelines regarding care of individuals with WS could be uploaded and also be accessible. A good resource for developing personal health records and links for companies providing such services can be found on the American Health Information Management Association Web site. Discussions with the family about their concerns for their child are also important as families promote advocacy and empowerment for their children. For individuals with WS, it is helpful to have these conversations before the patient reaches the legal age of consent. In the absence of a formal evaluation of competency, most individuals with WS are de facto their own legal guardians, but a parent or sibling almost always assists in medical decision making; delineating these roles early on will facilitate the transition. Determination of competency, especially for individuals with WS, must take into account more than IQ score alone; a global assessment including capacity for decision making and level of function in daily activities must be made.

**Anticipatory Guidance**

Closely related to communication is the role of education, where again the pediatrician plays an important role in informing others about the patient’s needs. By educating other medical specialists, schools, and communities, the transition process becomes more effective and coordinated. Adult physicians have specialized training in adult-related issues. However, they are less likely than the pediatrician to be familiar with the generic medical and cognitive problems that typify WS, and would particularly benefit from pediatrician input in the immediate transition period to enhance continuity for a patient and his/her specific needs. A family practitioner or physician with training in general medicine and pediatrics might not require as much additional education from the pediatrician.

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For individuals with WS, sex education is particularly important. It is an area in which education and guidance are often overlooked but based on our conversations with many WS adults, sexual thoughts figure prominently in their minds and furthermore, many individuals engage in exploratory sexual activity, even relations. Unfortunately, persons with WS (potentially even more so than other individuals with special needs due to their distinct personality described above) can fall prey to inappropriate or abusive sexual advances, making the need for instruction even more paramount. Murphy and Elias suggest frequent conversations about sexuality beginning at an early age will help the individual and family become more comfortable discussing the topic and also facilitate processing of this information by both the family and the individual with special needs. They also suggest exploring parents’ expectations of sex education for their child and providing factual information for both the parent and child. In most cases, sex education must be tailored to the special needs and level of understanding of each individual with WS. Many care providers and families feel reluctant to address this important topic but resources are available to help, including AAP guidelines for pediatricians to discuss sexuality with individuals and disabilities, as well as information available from the National Information Center for Children and Youth with Disabilities (NICCY, www.nichcy.org) and Planned Parenthood Federation of America (www.plannedparenthood.org).

Although it is not practical for the clinician to be involved in every aspect of transition, it is important to encourage a comprehensive approach. A helpful method to guide and augment appropriate transition preparations is the creation of a “transition worksheet” developed by the family and the pediatrician for both healthcare and school settings. The medical summary sheet could be a subset of this but it would also provide guidelines and/or a list of what needs to be done to prepare for a successful transition. The Full Life Ahead Planning Workbook (www.full-lifeahead.org) and the Making Action Plans (MAPs) person-center planning process are two models used predominantly in the school setting that could be adapted to fit both medical and educational transition needs. By extending past the boundaries of strictly medical concerns, a more effective medical home, or system of coordinated care that meets the full range needs for an individual can be provided.

Comprehensive care of individuals with WS or any other special healthcare needs is complicated and potentially requires input from many disciplines. The pediatrician plays a particularly important role in helping patients and their families by recognizing the potential complexity and multifactorial nature of presenting problems. Although this article uses WS as a model for the multidisciplinary mindset, it can truly be applied to any complex condition. With knowledge of common complications and risk factors associated with a complex condition, plus a team of designated specialists for referral and collabora-
tion, the pediatrician is in the best position to interpret and integrate findings and ultimately improve the quality of life for the individual with special health care needs like WS and their family.

REFERENCES