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REVIEW

Description of Common Musculoskeletal Findings in Williams Syndrome and Implications for Therapies

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Williams syndrome (WS), also referred to as Williams-Beuren syndrome (WBS), is a relatively rare genetic disorder affecting ~1/10,000 persons. Since the disorder is caused by a micro-deletion of ~1.5 Mb, it is not surprising that the manifestations of WS are extremely broad, involving most body systems. In this paper, we primarily focus on the musculoskeletal aspects of WS as these findings have not been the subject of a comprehensive review. We review the MSK features commonly seen in individuals with WS, along with related sensory and neurological issues interacting with and compounding underlying MSK abnormalities. We end by providing perspective, particularly from the vantage point of a physical therapist, on therapeutic interventions to address the most common MSK and related features seen in WS. Clin. Anat. 00:000–000, 2016.

Key words: Williams Syndrome; musculoskeletal; physical therapy

INTRODUCTION AND BACKGROUND

Williams syndrome (WS), also referred to as Williams-Beuren syndrome (WBS), is a relatively rare genetic disorder affecting ~1/10,000 persons. The disorder was first recognized as a distinct clinical entity in isolated case reports published in the 1950s. A decade later Dr. JCP Williams and Dr. Alois Bueren each published small case series highlighting some of the disorder's core features (Williams et al., 1961; Beuren et al., 1962). Today, we recognize that the manifestations of WS are extremely broad, involving most body systems. In this chapter, we will primarily focus on the musculoskeletal aspects of WS as these findings have not been the subject of a comprehensive review. We will begin, however, with an overview of common nonmusculoskeletal features of WS in order to provide the reader a better appreciation of the complexity of the disorder. The current understanding of the genetic basis underlying WS will be presented as well.

Common Medical Features in WS

Though every organ system can potentially to be impacted in WS, no single individual displays or develops all of the possible problems shown in Table 1. With timely medical monitoring, and interventions as needed, most individuals experience relatively good medical health. However, involvement of the cardiovascular system merits being singled out as it is one of the cardinal features of WS. The most characteristic lesion, vascular

Additional Supporting Information may be found in the online version of this article.

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TABLE 1. Common Medical Problems and Physical Features in WS[a]

Organ system (alphabetical)	Potential problems (listed in descending order of likelihood)	Natural history
Auditory/ENT	Auditory aversions	Sensitivity to sounds
	SNHL	Mild to moderate loss (but w/o impacting daily life in most)
	Recurrent ear infections	Common in childhood; PE tubes needed in a subset
Cardiovascular	Vascular stenosis (SVAS most common)	Can remain stable or worsen over time
	Hypertension	~50% develop
	Prolonged QTc	~10% in 1 series
	Stroke	Sequelae location dependent
Dental	Small/unusually shaped teeth	↓1° teeth size → ↑ interdental spacing; slightly small 2° teeth
	Malocclusion	Anterior crossbite common
	Absent teeth	↑frequency in 1° & 2° dentition
Endocrine	Early puberty	Averages ~2 yrs early
	Glucose intolerance/diabetes	50 – 70% adults have abnormal OGTT
	Subclinical hypothyroidism	Elevated TSH is common in childhood; actual hypothyroidism is rare
	Hypercalcemia	Documented in minority of pts; if present, most likely in childhood
GI/Growth	Difficulty feeding	Colic during infancy; difficulty transitioning to textured food
	Impaired growth	Slow rate of growth, even FTT during infancy/childhood. Variably short adult stature.
	Excess weight gain	Obesity with "pear-shaped" accumulation of weight in adults
	Abnormal bowel movements	Constipation (& constipation alternating with diarrhea in some)
	GE reflux	Common; precise frequency not documented in any systematic series
	Diverticulitis	Observed even in young adults
	Celiac disease	Uncommon but increased frequency vs general population
Neurologic	Hypotonia	Nearly universal in infancy
	Transition to hypertonia	Increased tone, esp in LE, in older children & adults
	Cerebellar findings	Poor balance, tremor
	Chiari Type I	Occasional incidental finding on MRI scan; surgery infrequently indicated
Ophthalmologic	Strabismus	Present in ~50%
	Hyperopia	Most common but myopia occurs too
	Poor depth perception	Present in ~35%
	Lacrimal stenosis	Duct growth commensurate with child; dilation sometimes needed
Pulmonary	Sleep apnea	Obstructive sleep apnea not uncommon (but exact frequency currently not known)
	Emphysema	Extremely uncommon (but at risk due to elastin gene deletion; smoking should be strongly discouraged)
Skin/ Integument	Soft skin	Very common ("baby soft" skin)
	Hernias	Inguinal & epigastric hernias
	Premature graying of hair	Graying can start in late childhood; etiology unknown
	Small subset show splaying of skin as part of wound healing	Many show normal wound healing but minority do not
Urinary tract	Various structural anomalies	Renal anomalies in ~15% (solitary kidney, horseshoe kidney, etc). Bladder diverticuli commonly seen in adults. Nephrocalcinosis 2° to hypercalcemia can occur.
	Functional anomalies	Delayed toilet training (day & night); urinary frequency & urgency once trained

[a]See Review articles Morris (1999), Committee on Genetics (2001), Schubert (2009), and Pober (2010) for further details. ENT, Ear, Nose, Throat; FTT, failure to thrive; GE, gastroesophageal; HTN, hypertension; LE, lower extremities; OGTT, oral glucose tolerance test; PE, pressure equalizing tubes; QTc, interval between start of Q wave and end of the T wave, corrected for rate; SNHL, sensorineural hearing loss; SVAS, supravalvar aortic stenosis; TSH, thyroid stimulating hormone.

stenosis, is present in ~80% of patients. The degree of narrowing can be stable or can progressively worsen over time. Interventions to relieve narrowing of the aorta or aortic branches generally require surgery, while narrowing of the pulmonary vasculature may resolve on its own or be amenable to balloon dilation or stenting. Approximately 50% of individuals with WS develop high blood pressure during their lifetime and that hypertension can start in young childhood. Finally, mortality due to cardiovascular disease is increased 25 – 50x compared to the general population and often (though not always) occurs in the setting of anesthesia use (Pober et al., 2008).

A detailed discussion of additional medical problems is beyond the scope of this article and the interested reader is referred to several comprehensive reviews (Morris, 1999; Committee on Genetics, 2001; Schubert, 2009; Pober, 2010).

Characteristic Neurodevelopmental Profile and Personality in WS

Individuals with WS display a unique cognitive profile and personality. In terms of the former, some degree of intellectual disability is a core feature of the disorder. The mean full scale IQ is ~55–60, with a broad range from 40 to 100. However, a full scale IQ score fails to reflect the characteristic pattern of cognitive strengths and weaknesses that typify individuals with WS. Specifically, relative strengths in selected language skills, along with marked weaknesses in specific visuospatial skills, coexist in most persons with WS. This profile of uneven abilities, almost always occurring along with a shortened attention span and distractibility, means that classroom placement, extent of special education support, and the therapies that are offered must be thoughtfully and individually tailored to each person with WS (Meyer-Lindenberg et al., 2006; Mervis and John, 2010). The ability to learn is lifelong in WS.

Individuals with WS also display a highly distinctive, if not unique, personality. They greatly enjoy other people (e.g., are quite social). In fact, they can be described as hypersocial and display features including but not restricted to difficulty maintaining interpersonal boundaries and the propensity to approach, even wander off, with strangers. Along with their affiliative nature comes a high degree of anxiety disorders, specific phobias, and Attention Deficit Hyperactivity Disorder (ADHD). The former can adversely impact quality of life, especially in adults.

Genetic Basis of WS

WS is a micro-deletion disorder, caused by deletion (e.g., loss) of a segment of DNA referred to as the WS critical interval. This interval on chromosome 7q11.23 extends for ~1.5 – 1.8 million base pairs and contains ~26–28 genes. Thus, persons with WS have only a single copy of these 26–28 genes, as opposed to typically developing persons who carry two copies of each of these genes. Deletion of the WS critical interval causes the constellation of features we recognize as WS. Despite considerable variability in the extent of medical and cognitive involvement, the deletion size is comparable across almost all persons with WS. This is because repetitive DNA segments, called duplicons, flank the WS interval; these duplicons, in turn, predispose the chromosome 7 pair to mispairing during meiosis. Thus, WS arises from the nature of the genetic material on chromosome 7q11.23 and is not due to parental factors such as age or environmental exposures. A depiction of genes deleted in persons with WS is shown (Supporting Information Figure S1); additional information about each gene can be found at https://decipher.sanger.ac.uk/syndrome/3#genotype/cnv/14/genes. The cardiovascular features of WS (described above) are primarily due to deletion of a copy of the elastin gene, which may also play a role in the development and/or progression of certain musculoskeletal features.

The most widely used genetic tests to establish the diagnosis of WS are either fluorescent-in-situ hybridization (FISH) or chromosomal microarray (CMA, also referred to as comparative genomic hybridization, CGH; see Fig. 1).

OVERVIEW AND LITERATURE REVIEW OF MUSCULOSKELETAL FEATURES IN WS

A common pattern of MSK findings occurs in many, though certainly not all, individuals with WS. In this article, component features of the pattern described in the medical literature will be presented (see Supporting Information Table S1) followed by a discussion of their impact on day-to-day function, as assessed clinically by physicians and physical therapists; we then conclude with available strategies and options for intervention. Since there exists no single published overview of MSK changes over lifespan, we will highlight changes that occur between childhood and adulthood. It should be noted that in much of the literature we cite, the presence or absence of joint laxity, contractures, lordosis, and other MSK alterations are not objectively "defined". Rather, most of the data currently in the literature derive from clinical assessments or a doctor's clinical impressions. In addition, the etiology (or etiologies) underlying most of the MSK abnormalities seen in WS are not known, although the mutation/deletion of the elastin gene has been hypothesized to have broad effects on the musculoskeletal system (Damasceno et al., 2014). In all likelihood many of the findings we describe have complex origins, due to as yet unknown interactions between loss of one or more of the genes responsible for WS which, in turn, variously perturbs development and/or function of the neurological, skeletal, connective tissue, and muscular systems.

Range of Motion Abnormalities

Alteration in joint range of motion is a principal musculoskeletal feature present in nearly all patients with WS. Many patients present as infants or small children with low muscle tone (hypotonia), often accompanied by joint laxity (Chapman et al., 1996; Taeusch et al., 2004). Chapman et al. documented hypotonia in seven of 17 children ages 2–8 years

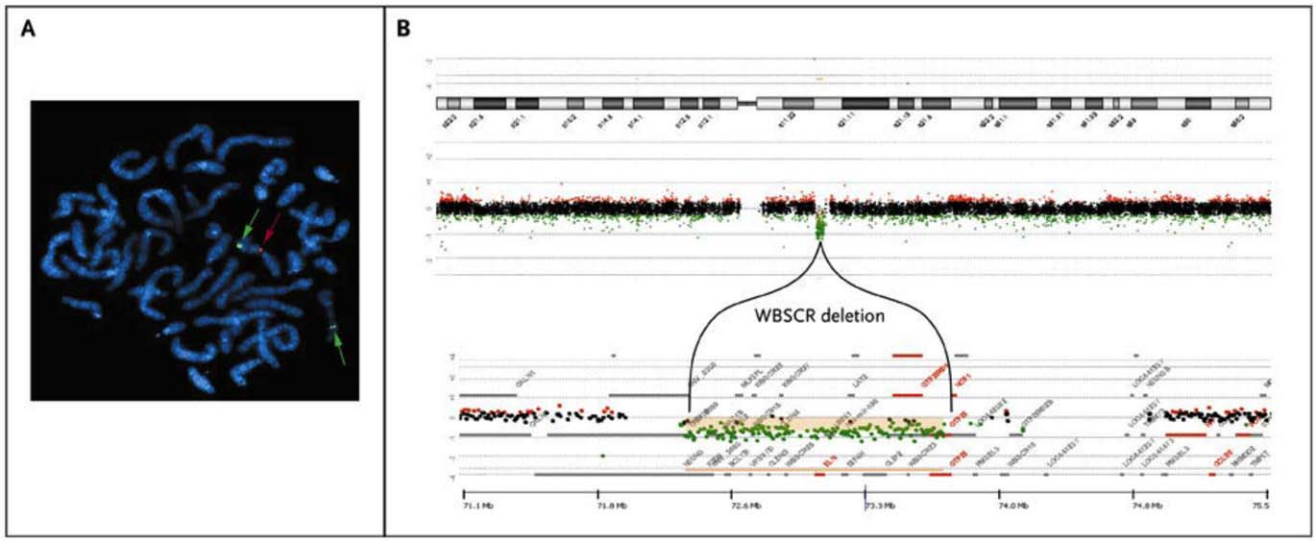

Fig. 1. Common laboratory methods fluorescent-in-situ-hybridization (FISH) [panel A] and chromosomal microarray (CMA) [panel b] for diagnosing Williams-Beuren syndrome. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(41%). Hypotonia may impact infant feeding, as low tone in the facial musculature can weaken suckling (Taeusch et al., 2004). Persistent joint laxity may contribute to the infrequent reports of joint dislocation in the WS population (up to 2%; Morris et al., 2010).

While hypotonia and joint laxity predominate among infants and young children, with increasing age, contractures and hypertonia become more prevalent (Chapman et al., 1996; Morris et al., 1988; Cherniske et al., 2004). Contractures in the upper limb tend to be concentrated in the distal joints (metacarpal, phalangeal, and interphalangeal) (Kaplan et al., 1989). Overall, however, lower limb contractures, which can affect the knees and ankles (Kaplan et al., 1989), seem more prevalent than contractures affecting the upper limb. While most researchers have noted a progression in symptoms from joint laxity among infants and children to contractures in older children and adults, particularly in the lower extremities (Chapman et al., 1996; Morris et al., 1988; Cherniske et al., 2004), Kaplan et al. (1989) documented contractures in 10 of 20 patients (50%) aged 2–24, noting an onset of infancy or childhood for most, but also commenting that none were progressive. Similarly, Elison et al. (2010) reported little change in joint pain and stiffness in either a cross-sectional cohort comparing adolescents and young adults to adults over 30, or within a 12-year follow-up in a subsample of the same group. Further study is needed to accurately define the progression of joint contractures over time.

Toe walking is a commonly seen gait deviation (Cherniske et al., 2004; Pober and Filiano, 1995). However, the etiology of toe walking has not been fully clarified. Potential etiologies include neurologic disorders that lead to increased tone (hypertonicity with or without spasticity) in the lower extremities, sensory aversion (such as tactile hypersensitivity) in which the patient avoids placing his or her entire foot on the floor, and repetitive vertical movement as a sensory seeking behavior (Ermer and Dunn, 1997). Repetitive toe walking can result in shortened heel cords (gastrocsoleus tendon) limiting the possibility of flat footed gait. Other gait alterations reported for individuals with WS include decreased speed and stride length and a broader base of support relative to controls (Hocking et al., 2009).

We hypothesize that gait deviations described in the literature and noted by clinicians (such as decreased speed, broader base of support, lack of reciprocal arm swing, and toe walking) could occur as compensations for decreased postural control. Weakened postural musculature and poor core activation could lead to poor balance, which when accompanied by decreased sensory function such as poor proprioception may manifest as any of the various gait deviations (Roden-Reynolds et al., 2015). Testing this hypothesis will require additional studies examining the entire body's participation in locomotor behavior, rather than solely focusing on the role of the foot in WS gait deviations.

A finding of radioulnar synostosis (RUS) has been reported in 12% of an infant WS population (Martin et al., 1984), although the method of detection was not noted, and in 26% of a WS population of unknown age (Charvat et al., 1991), confirmed radiologically. Additionally, reduced elbow extension and supination, possibly due to RUS (although not confirmed radiologically), was reported in 55% of an adult WS population (Cherniske et al., 2004). RUS is presumed present since birth since the defect stems from failure of segmentation between the radius and ulnar; thus, the degree of impaired supination is stable and therefore does not progress across the lifespan.

TABLE 2. Physical Therapist's ICF-Based Assessment of Potential Musculoskeletal Problems in Williams Syndrome Across the Lifespan

Dimensions	Body structures	Body functions	Presentation in infancy to young child	Presentation in school-aged to adolescent	Presentation in adulthood
Body Structures and Functions	Musculoskeletal (MSK) system	Strength	Decreased strength throughout	Decreased strength particularly in core muscles	Decreased strength extending from core to proximal muscles
		Range of Motion (ROM)	Excessive ROM throughout	Tightness in gastrocsoleus (heel cords)	Limitations & contractures in hamstrings, hip flexors, gastrocsoleus
			Torticollis sometimes found	Decreased trunk and pelvis mobility	Decreased mobility, joint stiffness throughout
		Bony alignment and composition	Ribcage flaring/elevation	Scoliosis (often functional but sometimes structural) & development of asymmetries	Spinal limitations: scoliosis, kyphotic or lordotic postures
			RU synostosis		Osteopenia/Osteoporosis
	Neuromuscular (NM) system	Hypotonicity (reduced active movement against gravity)	Hypotonicity throughout	Hypotonicity primarily affecting posture	Hypotonicity primarily affecting posture with distal stiffness also present
		Hypertonicity (stiffness/ excessive motor firing)	Infrequently see stiffness in extremities	May show distal stiffness	Hypertonicity generally present distally
		Spasticity (Resistance to quick stretch, e.g., clonus)	Spasticity rarely present	Spasticity sometimes present	Spasticity sometimes present
		Grading and control (contextual movement control)	Movement likely to be undergraded	Movement may either be slightly undergraded or over-graded	Movement may become over-graded
		Coactivation (muscles working cooperatively across joints or body segments)	Decreased coactivation	Coactivation occurs without dynamic control (control to match the context of movement)	Coactivation may be decreased or excessive
Body Structures and Functions	Sensory or Sensory-Motor (SM)	Sensory Reactivity	Auditory hypersensitivy	Auditory hypersensitivy	Self-selects environments (seeks or avoids environments based on past experiences)
			Over- or under-responsive to sensory input	Avoids or seeks sensory input	
			Tactile sensitivities	Tactile/vestibular sensititivies	
				Visual-spatial difficulty	
				Decreased proprioceptive awareness	
	Regulatory	Arousal	Easily overwhelmed, withdraws	Poor modulation of emotion and attention	Ability to regulate varies (i.e. seeks or avoids crowds and excitement; engages in conversations actively)

TABLE 2. *Continued*

Dimensions	Body structures	Body functions	Presentation in infancy to young child	Presentation in school-aged to adolescent	Presentation in adulthood
			Inconsistent emotional and attentional responses Fleeting attention		
	Short attention span Cognitive	Executive Functions	Global delays Latent responses (processing delays)	Varying degree of intellectual disability	
Limited problem solving and play			Limited ideation and poor motor planning		
Body Structures and Functions	Multisystem Functions	Postural Alignment and Control: Related to MSK/NM/SM	Delayed development of motor patterns (seeking upright positions)	Postural compensations become consistent	Postural compensations: gravity has greater effect
			Splayed with excessive abduction at shoulders/hip	Compensatory postural alignment to balance Center of Mass (COM)	
			Wide base of support in all positions	Forward head/lateral tilt	Rounded shoulders, kyphotic posture, posterior pelvis/hip external rotation, knee flexion, out-toeing, pronation
			Poor antigravity movement	Either thoracic kyphosis and posterior pelvis, or lumbar lordosis and anterior pelvis	
			Increased contact with support surface	Either hip external rotation, out-toeing, foot pronation, or knee valgus, intoeing, plantarflexion	
			Compensates with stiffness	Tends to lean or sit	
			Extends away from gravity	Rarely jumps or leaves the support surface	
			Single plane movement in sagittal (rarely in lateral or rotational planes of movement)	Poor use of lateral or rotational planes of movement	
Body Structures and Functions	Multisystem Functions	Balance: Related to NM/MSK/SM systems	Difficulty engaging muscles across segments to co-activate and stabilize	Poor unilateral or sustained tandem stance	Occasional reports of falling and unsteadiness
			Difficulty identifying change in COM to respond to contextual needs	Increased lateral sway	Contributes to slow pace
				Brings COM toward the surface	
		Coordination: related to NM/SM systems	Decreased bilateral coordination		Difficulty with manipulation and bilateral coordination

TABLE 2. *Continued*

Dimensions	Body structures	Body functions	Presentation in infancy to young child	Presentation in school-aged to adolescent	Presentation in adulthood
			Poor manipulative skills	Prolonged use of UEs for support: decreased practice for bilateral use	
			Use of extremities to stabilize Infrequent use of bilateral upper/lower extremities with reciprocal sequences		
		Gait: related to MSK/NM/SM	Wide based, pronated feet, slight out-toeing; crouched (increased flexion at hips/knees/upper body/trunk	Hypotonia: Wide-based, out-toeing, slightly crouched	Out-toeing
			COM closer to the support surface	Hypertonia and Spasticity: toe-walking, forward lurch, poor balance and control	Shorter step length
				Decreased endurance and speed	
			Mild asymmetries in alignment and weight bearing		
Activity		Multi-system Functions used in context	Delayed milestones: rolling, sitting, standing, walking	Slow/poor endurance with running, jumping, climbing	Escalating need for assistance with some skills (e.g., self-care and activities of daily living; transportation/travel; exercise)
			Delayed play skills	Decreased ball skills (e.g., poor accuracy in throwing, catching, aiming, kicking)	Specific motor task difficulties involving: balance, speed, coordination
			Delayed language	Exchange mostly pleasantries, limited depth of conversation and exchange	
			Feeding difficulties		
Participation		Venues in which people with WS have difficulty participating or accessing	Daycare/childcare	Playground	Gym and other physical activities
			Family gatherings	Recreational sports	Impaired mobility interferes with getting to and participating in jobs and social activities
			Gymboree	Community programs (classes)	
			Mommy and Me Playground Pre-school	Amusement parks	

Spinal Curvature Abnormalities

Atypical posture and exaggerated or abnormal spinal curvatures are also a common finding in patients with WS. Based on general physical examination: kyphosis has been reported in 10–21% of infants and young children (Kaplan et al., 1989; Martin et al., 1984; Morris et al., 1988); lordosis was described in 38% of infants and 90% of adolescents and young adults by Morris et al. (1988), and in 30% of adults by Cherniske et al. (2004); and scoliosis was reported in 12% (Morris et al., 1988)% to 20% (Kaplan et al., 1989) of infants and 20% of adults (Cherniske et al., 2004).

In a single recent study, all patients were examined by an orthopedist (Damasceno et al., 2014). These authors identified scoliosis in 14 of 41 (34%) patients with WS in Brazil, noting that the severity of the condition ranged from flexible and simple curves among younger patients to double and triple curves in adults. However, the study failed to reveal statistically significant relationships between scoliosis and age or sex, possibly due to small sample sizes.

Bone Mineral Density

There are few studies assessing bone mineral density (BMD) in persons with WS. In one systematic series, 20 adults (10 males and 10 females) over the age of 30 underwent dual-energy X-ray absorptiometry (DEXA) scanning. The results were as follows: seven had normal BMD at both the femoral neck and lumbar spine; nine (four females and five males) had reduced BMD (either osteopenia or osteoporosis) at both sites; and the remaining four had osteopenia at the femoral neck or lumbar spine (Cherniske et al., 2004). One case report of a 50 year old male with long standing mild hypercalcemia mentions DEXA results that were "normal" (Letavernier et al., 2012). In clinical practice, symptomatic bone fractures in the absence of trauma are not seen but similar to the findings reported by Cherniske et al. decreased BMD affects WS adult males as well as adult females.

PHYSICAL THERAPY ASSESSMENT OF MUSCULOSKELETAL FEATURES

As is evident from the literature on MSK findings summarized above, assessment of MSK features is generally performed as one component of a global evaluation. Furthermore, discussion of therapy or intervention is absent. In an effort to overcome this void, perspectives on MSK features are provided below including their (a) progression; (b) assessment; (c) impact on function; and suggested interventions, particularly from the vantage point of a physical therapist evaluating and working with individuals with WS (see also Table 2).

People with WS have a recognizable physical presentation that tends to aid in diagnosis. Though each individual is unique, their posture and movement will likely present with predictable features. The progression of physical attributes associated with the disorder follows certain anticipated, though not invariant, trends. Patients should be monitored by a provider who has familiarized him- or herself with the typical trends of WS; ideally this would be a physical therapist practicing as part of an interdisciplinary healthcare team.

During infancy, decreased strength, hyperextensibility/mobility, and hypotonia are commonly observed as extremity splaying during supine and prone positioning, and as poor anti-gravity muscle activation. The movement patterns used to overcome gravity and for transitioning to upright positions in WS toddlers are likely to show compensations that persist into childhood. If hypotonia is present throughout the body (including low postural tone), the toddler with WS may continue to sink into gravity, unable to counteract its pull, remaining wide based with excessive mobility and in greater contact with the support surface (Martin and Kessler, 2016). Once attaining upright positions, the poor postural control of toddlers with WS leads to positions that bring the center of mass (COM) closer to the support surface such as forward head, rounded shoulders/pelvis, hip/knee flexion, genu valgum, and foot pronation. Out-toeing creates a widened base of support. Hands and other parts of the body are often used for added support by holding or leaning.

A second possible compensation for hypotonia involves development of excessively sustained activation (hypertonia or stiffness) across joints and between body segments, serving as an anti-gravity strategy (Sanger et al., 2003). When hypertonia is present, postural adjustments during movement are compromised (poor dynamic stability) and result in upper extremities held in high guard, hyperextension of the head/neck, and elevation of the shoulders to enhance upper body stability. The trunk is in lumbar lordosis, and pelvis tilted anteriorly, balancing the COM. Varied hip/knee positions are seen with plantarflexion (up on toes). Though this postural strategy counteracts gravity and allows upright positions (e.g., standing, walking), stability and balance are simultaneously compromised due to a narrowing of the base of support. Hypertonicity as a compensation leads to the inability to sustain upright positions. Accordingly, the individual is constantly moving, displaying a lurching forward gait, or holding onto or leaning for support.

As children with WS grow up, their muscular weakness and low postural tone continues, though it is more centralized in the trunk and pelvis. Postural malalignment may become more pronounced with rounding into gravity or stiffening away from it. Lateral flexion of the head and/or trunk can add asymmetrical forces on the spine during growth and development. Range of motion limitations emerge secondary to tightness and progressive contracture development. As previously mentioned, these range of motion changes are commented upon in the literature, but there is little specificity as to the etiology of this progression. Furthermore, the studies reviewed do not provide information on the methods or tools used to assess range of motion or muscle tone. And though there is controversy as to the use of poorly defined or disputed terms such as spasticity and hypertonia, these terms are consistently present in literature describing persons with Williams syndrome (Morris et al., 1988; Chapman et al., 1996;

Cherniske et al., 2004) and are often used interchangeably despite their nuanced differences (Sanger et al., 2003; Bakheit et al., 2011; Beverly Cusick, personal communication). Even so, hypertonia and spasticity prompt similar postural compensations of poor contact with the support surface and plantarflexion (toe walking).

As people age, their gross motor function is expected to become more complex, but many WS patients are unable to maintain pace with their peers' development. Overall, their motor behavior can be described as overgraded, which appears as slow speed of movement, due to deficits in motor planning and motor control (Martin and Kessler, 2016). Persons with WS also show poor endurance with frequent requests to sit, constant leaning for support, and complaints or refusal to walk for long distances.

Motor behaviors require the cooperation of the sensory, musculoskeletal, and neuromuscular systems (Martin and Kessler, 2016), and all play a role in postural control, balance, and coordination. Along with the musculoskeletal challenges discussed above, WS patients also show sensory sensitivities and over- or under-responsiveness to noisy, busy, and/or medical environments. The combination of these traits and challenges are likely contributors to the highly prevalent behavioral phenotype of anxiety and phobias, which in turn, can limit activity and participation at school, home, and in the community.

As adolescents mature into adults, low postural tone may revert to more generalized underlying hypotonicity in a subset. This manifests as muscular weakness, poor postural alignment, a widened base of support and lowered COM; notable features seen in sitting and standing, and walking are rounded shoulders and thoracic kyphosis, rounded (posterior) pelvis with hip external rotation, and out-toeing gait with pronation. Some adults report joint stiffness in hands, shoulders, hips, and knees, though upper extremity joint laxity can also persist. A predominantly sedentary lifestyle, commonly accompanied by weight gain and increased lower body girth, is seen in many adults. The etiology of this is likely multifactorial and joint stiffness could be a contributing factor.

The International Classification of Function, Disability, and Health Enablement Model

Patients with Williams Syndrome show widespread deficits that span MSK and physical areas of function and that can last throughout their lifetime. This discussion of WS expands from medical description of common MSK problems to their impact on daily life across the lifespan and thus requires a holistic view. The International Classification of Function, Disability and Health (ICF) Enablement Model (WHO, 2002) provides this holistic view. The ICF model considers how body systems (body structure and function) interact with the global features of a disorder, and relates impairments to functional limitations, acknowledging that environmental and personal factors also affect an individual's participation in desired activities (Fig. 2).

IMPACT ON FUNCTION

The role of pediatric physical therapists (PTs) is to work with children and their families to assist each child in reaching their maximum potential to function independently and to promote active participation in home, school, and community environments. Physical therapists use their expertise in movement and apply clinical reasoning through the process of examination, evaluation, diagnosis, and intervention to promote independence, increase participation, facilitate motor development and function, and improve strength and endurance with the goal of enhancing learning.

An evaluation performed by a PT begins with a parent (and patient) interview to identify primary concerns and priorities while collecting information on a family's or patient's daily routines and physical performance within the context of their everyday environments. A thorough clinical assessment includes examination of the individual, and the status of each body system obtained as objectively as possible. Standardized tests and measures are used to determine level of developmental delay or disability based primarily on age (such as Alberta Infant Motor Scale [AIMS] for 0–18 months, Peabody Developmental Motor Scale-second edition [PDMS-2] for 0–60 months, Movement Assessment Battery for Children-2 [MABC-2] for 3–17 years, Bruininks-Oseretsky Test of Motor Proficiency-2 [BOT-2] for 5–17 years, Pediatric Evaluation of Disability Index [PEDI] for 6 months−7 years, or Functional Independence Measure & Pediatric Version [FIM & WeeFIM] for 6 months−21 years for persons with Developmental Delays). The evaluation process is customized for each individual, largely guided by diagnosis and expectations of that condition or disorder. The ICF-based assessment chart (Fig. 2) provides a list of key impairments, and barriers to activities (functional limitations) and participation as outlined by the ICF model.

Findings from appropriately chosen assessment tools are synthesized to: (a) provide a comprehensive view of the individual's abilities to participate in home, school/work and community activities; and (b) identify which activities are impacted by the physical (along with social and cognitive) attributes of the disorder. The completed evaluation broadly describes the individual's mobility, strength and endurance, muscle and joint function, sensory and neuromotor development, posture and balance, and other multisystem behaviors related to movement and participation and informs the plan of care and intervention approach.

Intervention planning considers the patient and family's priorities, as well as expectations based on typical milestones and developmental benchmarks. Strategies that we suggest for intervention do not, unfortunately, derive from empiric evidence of success in WS (as this is a notable void in both research and clinical data). Rather, the suggested strategies have been generalized from similar or related developmental disorders where they have been shown to be effective.

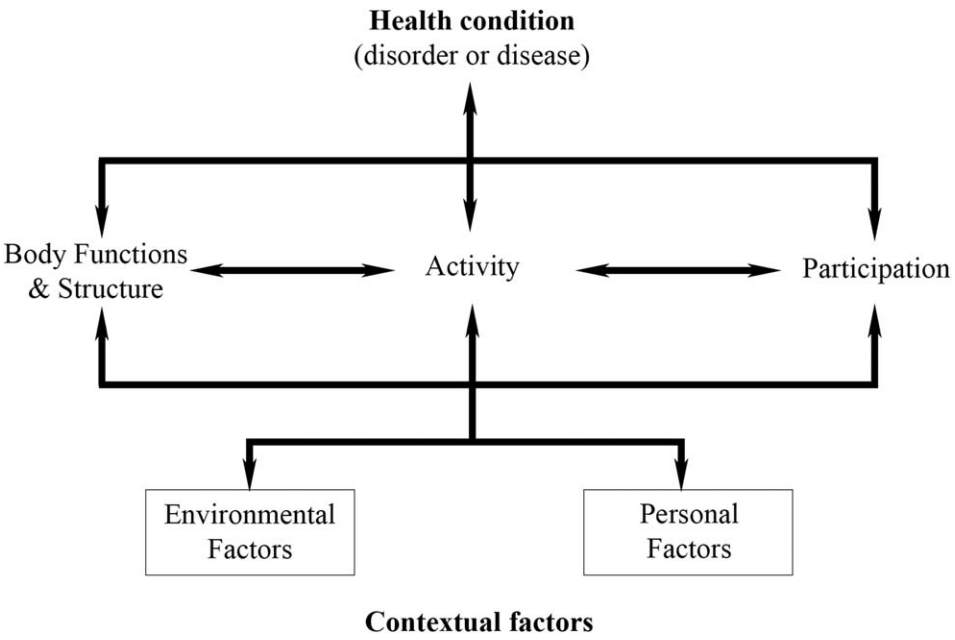

Fig. 2. The International Classification of Function framework uses this *biopsychosocial* model to illustrate the dynamic interaction between the individual's health condition (diagnosis), domains of functioning (body functions and structures, activity, and participation) and contextual factors (environmental and personal factors) using these definitions: **Health Condition** Diseases, disorders and injuries. **Body Functions** Physiological and psychological functions of body systems. **Body Structures** Anatomical parts of the body (including organs, limbs, and their components). **Activity** The execution of a task or action by an individual. **Participation** Involvement in a life situation. **Environmental factors** Characteristics of the psychosocial environment such as societal attitudes, architectural or physical characteristics. **Personal Factors** Age, gender, socioeconomic background, coping styles, vocation, education, behaviors, personality/character. **Contextual Factors**: Impact and/or influence how disability is experienced and perceived [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In order to devise and execute the most effective interventions and strategies, providers should be familiar with the many strengths and motivations typically are present in people with Williams, such as focal interest in music, physical independence, friendliness, a willingness to engage with others, and a strong desire to please others.

INTERVENTIONS

Musculoskeletal impairments impede physical (gross motor and mobility), occupational (fine motor, activities of daily living, and adaptive skills) and speech (language and oral-motor) based function. A focus on physical therapy will be provided here as an example of intervention strategies and how they are applied, although patients with WS are often simultaneously treated by occupational and/or speech therapists.

Physical therapy for people with developmental disabilities focuses on development of efficient movement patterns while minimizing compensations, in an effort to prevent development of more complex motor issues.

Since virtually all infants and young children with WS show delayed achievement of gross motor milestones (including rolling, sitting, standing, and walking) with concomitant sensory and social difficulties, their participation in typical age related activities such as mommy and me class, playground activities, community, and pre-school programming, and family gatherings is frequently negatively impacted. Building proper movement patterns in infancy through young childhood can be accomplished by eliciting and facilitating use of transitional movements, with gravity and bodyweight as resistance and the use of repetition to build muscle strength throughout the range of motion in a variety of planes of movement. Play is the primary motivator, and toy choices are guided by the individual's personal factors and preferences. The therapeutic environment is deliberately designed through toy or equipment choice and placement. Caregivers and families should be included in therapy sessions so that carrying, positioning, and play skills that support developmental progress are carried over into daily routines. Therapy approaches and frameworks vary, though evidence shows context-based intervention in the natural environment using functionally pertinent activities enhances acquisition of developmental motor skills. Best practice suggests therapy sessions take place in a patient's home and utilize objects and materials they have readily available to maximize carryover of the learned skills to everyday life.

Children with WS who are school age and maturing toward adolescence are surrounded by peers who are comfortable in venues that require interaction and cooperation such as playgrounds, recreational sports, and amusement parks. Children with WS are typically less comfortable in such unpredictable settings that often include long distance walking, agile running, navigation of multi-sensory and multi-level surfaces, climbing and vestibular movement, and ball skills of throwing, aiming, and catching. Concomitantly, as patients with WS age, context-based intervention that incorporates the gross motor aspects of age-appropriate challenges become more difficult to deliberately incorporate in therapy venues. For example, many children with WS have auditory hyperacuity (see Table 1), which may cause them to be overwhelmed when attempting to participate on a T-ball team due to the distraction of cheering teammates and spectators. Covering their ears to muffle the sounds is incompatible with catching or batting. Such a sensory modulation disorder (SMD) is also frequently seen in children on the autism spectrum (Miller et al., 2007). A therapist cannot recreate an entire T-ball game, but can work on a child's ball skills in a closed and quiet environment first, adding in additional sensory input as the child shows the ability to regulate his or her responses. Additionally, use of strong motivators such as music, or favorite themes (video game and cartoon characters, superheroes, and famous singers) are useful tools to motivate participation specifically in therapy but also in other activities.

In late adolescence and adulthood, patients with Williams typically become less active settling into a sedentary lifestyle and identification of therapy resources becomes increasingly challenging. Logistics of travel become a barrier to access and to acquiring therapy due to continued dependence on social supports to navigate most environments, and access to gyms or other exercise venues. Adults with WS infrequently develop the independence to participate in activities of lifelong health and wellness such as bicycling, swimming, or taking classes at their local recreational programs. Due to their need for guidance in navigating novel settings, their opportunities to engage in social outings such as bowling or dancing are influenced by the level and availability of caregiver assistance. Potential strategies for increasing participation in physical activity include encouraging social exercise classes (yoga, zumba) or working with a personal trainer.

For certain of the MSK abnormalities that can complicate WS, the physical therapist works in conjunction with other medical specialists (such as orthopedists, physiatrists, and orthotists) to offer "standard" therapies widely used in the general population and in children with other developmental disabilities. However, there are no evidence-based studies specific to WS that have evaluated the efficacy of these various standard treatments. Based on our clinical experience, rates of success appear comparable to those seen in other disorders. For example, bracing strategies can minimize alignment issues such as excessive pronation or plantarflexion (toe walking). In the presence of more severe hypertonicity or spasticity of the heel cords, botulinum toxin (botox) may be used to weaken the gastrocsoleus, to enable practice of movements such as full contact of the foot surface during gait. In the most serious case of toe-walking when contractures develop, serial casting or surgery may be required to address the range of motion impairment. Treatment of late childhood or adolescent onset scoliosis in WS also follows standard paradigms with bracing first being used in an effort to stabilize a curve of $<30^{\circ}$, but then proceeding to surgical correction for progressive or more severe curves.

CONCLUSION

As summarized in this review, MSK problems commonly occur in WS. The individual problems are not unique to WS; rather they are of the type seen in the general population. Their impact, however, has been insufficiently appreciated because it extends far beyond physical limitations (see Table 2). Accordingly, we argue that the MSK issues of WS need to be evaluated and treated using a holistic perspective. Strategies for interventions, particularly those administered by physical therapists, are provided.

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