ARTICLE

Diagnosis and Management of Medical Problems in Adults With Williams–Beuren Syndrome

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Williams–Beuren syndrome (WBS) is a multi-system disorder that requires ongoing management by a primary care physician familiar with the natural history and common medical problems associated with the condition. Some abnormalities are unique to WBS, such as the elastin arteriopathy that often manifests as supravalvar aortic stenosis and hypertension. Still other features, such as diverticulosis, are seen in the general population but tend to present earlier in WBS. Life long monitoring of the cardiovascular and endocrine systems is essential to the clinical management of individuals with Williams–Beuren syndrome. Constipation should be aggressively managed, and symptoms of abdominal pain should prompt an evaluation for diverticulosis/diverticulitis. While the mean IQ of WBS is in the mild mental retardation range, difficulties with attention and anxiety are more likely to negatively impact independent functioning in the adult with WBS. There is no evidence for decline in cognitive ability over time, but adaptive functioning may be improved with treatment of anxiety by both behavior and medical modalities.

KEY WORDS: Williams syndrome; medical management in adults with mental retardation

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INTRODUCTION

Knowledge of medical, cognitive and behavioral problems found in patients with Williams–Beuren syndrome (WBS, OMIM 194050) has grown dramatically over the past 45 years. First reported as a distinct clinical entity in Williams et al. [1961] and Beuren et al. [1962], WBS is now recognized to be a multi-system disorder with particularly prominent cardiovascular, endocrine, and neurological problems. Information on the evolution of problems during the WBS life cycle has likewise grown during the past four decades, but continues to be rather limited compromising our ability to prognosticate, manage, treat, and implement preventative strategies for adults with WBS.

Prior to 1993 the diagnosis of WBS was established using clinical criteria, which were applied by an experienced diagnostician such as a medical geneticist. The discovery that WBS was a chromosome microdeletion disorder that could be confirmed by FISH [Ewart et al., 1993] allowed both primary care physicians and specialists to establish the diagnosis. This wider availability of diagnostic testing has revealed a broader phenotype of WBS particularly in adulthood. Case summaries from adults diagnosed with WBS will serve to set the stage for the discussion that ensues on the diagnosis, management, and prevention (if available) of some of the important problems facing adults with WBS.

Case 1

An 82-year-old female was recently diagnosed with WBS (K Rodgers & BR Pober, manuscript in preparation). The patient was born in a rural community, experienced good health during childhood, and received limited formal education. Starting after her 4th decade, she developed numerous problems including: obesity, diverticular disease, hypertension, diabetes, lipoedema/ lymphedema, hypothyroidism, and atrial fibrillation. She has not lived independently nor achieved competitive employment. All but her atrial fibrillation are characteristic of WBS but the diagnosis was *not* suggested by any of her physicians or care providers. Rather it was raised by a niece working in special education who noted similarities between her aunt and a youngster with WBS in her school system.

Case 2

A 30-year-old man diagnosed with WBS as an adolescent complained of

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abdominal pain and was diagnosed with diverticulitis of the colon after undergoing surgery for presumed appendicitis. He had required special education, and turned a fascination with lawn mowers into a job repairing them and mowing lawns in his neighborhood when in high school. After training with a job coach, he was able to obtain full time competitive employment in landscaping. He briefly lived in a supervised apartment but moved back with his parents at his request. He has not had any significant cardiovascular disease. He does have an awkward gait and has mild contractures of the hamstrings.

OVERVIEW OF DIAGNOSIS AND MEDICAL CARE FOR ADULTS WITH WBS

Initial consideration of the diagnosis of WBS always begins with the astute clinician. Recognition of the phenotype during infancy or childhood is usually prompted by the presence of one or more "classic" WBS findings such as typical cardiovascular lesions (e.g., supravalvar aortic stenosis), hypercalcemia, and/or developmental delay. A different constellation of features typifies WBS when the diagnosis is first established during adulthood. Among elderly previously undiagnosed WBS patients the presenting features most often are mild intellectual handicap, anxiety, other psychiatric disorders or emotional problems (such as depression, obsessive-compulsive symptoms, post-traumatic stress disorder), gastrointestinal problems (such as diverticular disease), intra-cardiac lesions (such as mitral valve prolapse), and hypertension (personal observations).

Among elderly previously undiagnosed WBS patients the presenting features most often are mild intellectual handicap, anxiety, other psychiatric disorders or emotional problems (such as depression, obsessive-compulsive symptoms, post-traumatic stress disorder), gastrointestinal problems (such as diverticular disease), intra-cardiac lesions (such as mitral valve prolapse), and hypertension (personal observations).

Individuals who escape early diagnosis tend to have fewer of the "classic" medical problems that raise suspicion of WBS among pediatricians, and also may have had relatively limited access to medical care during childhood. Additionally, individuals diagnosed late in life typically reside in non-independent living situations, and are unemployed or employed in non-competitive jobs.

Another challenge to diagnosing WBS during adulthood, especially in senior citizens, is that the same medical problems can be found among the elderly in the general population. For example, diverticular disease occurs in both the general population and in WBS adults (though can have a much earlier age of onset in WBS) [Parks, 1975; Partsch et al., 2005]. Likewise, MVP is found in as many as 1–2% of adults in the general population [Hepner et al., 2007] and also occurs in adults with WBS but at a much higher frequency. In spite of the existence of overlapping medical problems in both WBS and adults in the general population, both the pattern and the total number of medical problems should suggest the presence of an underlying genetic syndrome.

Finally, adults with WBS often receive problem-specific care, rather than global care that addresses each medical problem in the context of an underlying disorder. Patients may not receive screening for high-risk problems due to absence of the correct diagnosis or lack of familiarity with the adult spectrum of the disorder. The degree of intellectual handicap in most adults with WBS prevents them from coordinating care of their complicated needs so that the burden falls to family members or group home staff. Collectively, these difficulties lead to superficial and fragmented care for most adults with WBS. In order to combat these challenges, efforts must be made to increase awareness among adult care providers about WBS diagnostic features and medical complications.

ADULT WBS PREVALENCE AND LIFE EXPECTANCY

Published prevalence estimates for WBS range from a high of ~1/7,500 [Stromme et al., 2002] to a low of ~1/20,000 [Morris et al., 1988; Yau et al., 2004]. In all likelihood, this threefold variation is caused by methodological differences between studies, including which criteria are used for establishing the diagnosis of WBS. No formal studies of life expectancy in WBS have been published to date, so we cannot estimate adult WBS prevalence with any certainty. However, we anticipate that compared to the general population, life expectancy is mildly shortened due to mortality from chronic conditions (such as cardiovascular and gastrointestinal complications) as well as the rare but well-documented occurrences of sudden death [Bird et al., 1996; Imashuku et al., 2000; Wessel et al., 2004].

MEDICAL PROBLEMS IN ADULTS WITH WBS

The most *common* medical problems facing adults with WBS are listed by organ system below. Suggestions for medical monitoring are presented in the Table I (reprinted with permission from Cherniske et al. [2004]).

Cardiovascular Disease

In individuals with WBS the hallmark cardiovascular problems are vascular stenoses, especially of the following sites: supravalvar aortic stenosis (SVAS), supravalvar pulmonary stenosis (SVPS), peripheral pulmonary stenosis (PPS), and/or branch pulmonary stenosis. Structural intra-cardiac malformations

TABLE I. Recommendations for Medical Monitoring of Adults With Williams Syndrome (from Cherniske et al. [2004])

The recommendations listed below are intended to assist in the ongoing management of adults with WS. Recommendations for the initial medical assessment of the newly diagnosed patient with WS have been recently published elsewhere [2001]. We have expanded on these recommendations, especially those specific to adults over the age of 30 years

General
- Comprehensive annual medical evaluation, preferably by a physician with expertise in WS

General well-being and nutrition
- Nutrition education focused on preventing excess weight gain
- Calcium and Vitamin D intake not to exceed RDA
- ADA diet if needed (see endocrine section below)
- Encourage active lifestyle and focused exercise regimen assuming there are no cardiovascular contraindications

Ophthalmologic
- Annual vision evaluation to monitor for strabismus, refractive errors, and cataracts

ENT/audiologic
- Baseline audiologic evaluation at 30 years of age to rule out sensorineural hearing loss
- Audiologic evaluation every 5 years or more frequently until existing hearing loss stabilizes
- Prevent ear wax build-up with softening drops and cleanouts as needed

Dental
- Supervision of brushing and flossing
- Consider use of an electric toothbrush
- Comprehensive dental cleaning every 3–4 months
- Consider use of a short acting oral anxiolytic prior to dental cleanings and procedures

Cardiovascular
- Cardiology evaluation every 3–5 years, even in the presence of stable cardiovascular disease
- Annual auscultation of abdomen to screen for bruit
- Evaluation of bruit by Doppler ultrasound and/or non-invasive imaging

Blood pressure monitoring
- a. If normotensive—biannual blood pressure determination
- b. If hypertensive—evaluate for stenoses, renal disease, and hypercalcemia. No preferred pharmacologic treatment for idiopathic hypertension yet identified
- Evaluate for stroke only if symptomatic

Gastrointestinal
- Medically treat documented reflux
- Monitor for constipation, rectal prolapse, and/or hemorrhoids
- Prevent constipation with dietary manipulation or medical management if needed
- Prompt evaluation of severe or recurrent abdominal pain (to rule out diverticular disease)

Genitourinary
- Annual BUN, creatinine and urinalysis
- Renal and bladder ultrasound for symptomatology, or every decade for ongoing monitoring
- Increased vigilance for urinary tract infections
- Routine gynecologic care and prostate screening

Endocrine
- Blood calcium determination every 1–2 years (but more frequently if abnormal)
- Spot urine calcium to creatinine ratio annually
- For documented hypercalcemia and/or persistent hypercalciuria
  - a. Three day diet history to calculate calcium and vitamin D intake; if intake exceeds RDA then decrease to 80% of the RDA and retest
  - b. Twenty-four hour urine for calcium to creatinine ratio (normal adult ratio 0.22; normal adult calcium excretion <0.4 mg/kg/24 hr)
  - c. Renal ultrasound to assess for nephrocalcinosis
  - d. Fasting determinations of biointact PTH, 1,25 $(OH)_2$ and 25-OH vitamin D
  - e. DEXA scan to assess bone mass
  - f. Referral to endocrinologist if hypercalcemia and/or hypercalciuria persist, or if regulatory hormone levels are abnormal

(*Continued*)

TABLE I. (*Continued*)

- Baseline DEXA scan
  - a. If normal repeat in 5 years; repeat sooner if fractures occur
  - b. For mild osteopenia (bone mineral density T-score between −1.5 and −1.8 SD below the mean) *and* no other risk factors for a bone fracture
    - i. Check urinary markers of bone turnover
    - ii. Check 24 hr urine calcium, creatinine, and sodium excretion
    - iii. Check 25-OH vitamin D level
    - iv. If these studies are normal, repeat DEXA in 1 year
    - v. Do *not* begin calcium supplementation
  - c. For more severe bone loss (bone mineral density T-score −1.8 or −2.0 SD below the mean)
    - i. Evaluate for secondary causes of bone loss such as hyperparathyroidism, hyper- or hypo-thyroidism, hypogonadism, Cushings disease, etc.
    - ii. Consider treatment with a bisphosphonate
- Monitor carefully for gastroesophageal reflux if using a bisphosphonate
- Thyroid function tests and thyroid stimulating hormone (TSH) level every 3 years
  - a. If abnormal obtain anti-thyroid antibodies
  - b. For compensated hypothyroidism, check TFTs and TSH annually and consider thyroid hormone replacement if TSH >10
- Baseline 2 hr oral glucose tolerance test (OGTT) at 30 years
  - a. Repeat OGTT every 5 years or sooner if rapid weight gain
  - b. Hemoglobin A1C is not a good screening tool in WS adults
  - c. Control impaired glucose tolerance with exercise and diet
  - d. Manage silent diabetes with exercise, diet, and consider medication
  - e. Patients with clinical diabetes should be managed like adults in the general population with diabetes
- Routine gynecologic care and mammography
  - a. Consider use of a short acting oral anxiolytic prior to pelvic examination
  - b. Use pediatric speculum
- Musculoskeletal/integument
- Physical therapy consultation to assess for contractures and/or scoliosis
- Limited exercise regimen to maintain joint range of motion and posture
- Seek specialist assessment for lower extremity lipedema; consider treatment with compressive stockings and wraps
- Neurologic
- Acute neurological symptoms, asymmetry on neurological exam, and/or worsening of chronic low grade neurological problems require prompt evaluation by a neurologist as well as neuroimaging
- Baseline neuroimaging, without any clinical indication, is not recommended
- Cancer Screening
- Routine cancer surveillance, including mammography, prostate, testicular, and colon cancer screening should be performed as dictated by age and family history
- Psychiatry
- Low threshold for psychiatric intervention given prevalence of anxiety disorders as well as increased frequency of other psychopathology including depression
- Begin with low doses of medication as patients seem to have an increased sensitivity to standard adult doses
- Caution against diagnosis of psychotic disorder without careful and longitudinal mental status assessment
- Social and vocational
- Tailor residential placement to maximize independence while taking into consideration the strengths and weaknesses of WS cognitive functioning
- Encourage vocational opportunities, even volunteer positions
- Foster social outings and networking

such as VSD or ASD are uncommon, found in <5%. The study of Eronen et al. [2002] is instructive, despite their small WBS adult cohort. Among 75 patients studied retrospectively, 14/23 (60%) of the infant-diagnosed group required intervention or surgery for their cardiovascular disease, 3/14 (11%) of the child-diagnosed group, but 0/7 (0%) of the adult-diagnosed group required such care. In several series of adults in whom the diagnosis of WBS had already been

established, the frequencies of vascular disease were 70% [Cherniske et al., 2004], 76% [Morris et al., 1988], and 100% [Lopez-Rangel et al., 1992]. Similar to studies of children with WBS, the most common lesions in these adults were SVAS and other vascular stenoses, though isolated mitral valve prolapse or regurgitation was found in 10–30% of the adults in two of these cohorts. The vascular stenoses are secondary to the generalized elastin arteriopathy associated with hemizygosity for the *elastin* gene [Keating, 1995]. Arterial walls in WBS have a diffusely thickened media [Rein et al., 1993], but clinically significant narrowing is most likely to occur at arterial origins [Stamm et al., 2001]. Peripheral arterial stenosis rarely requires surgical intervention.

Hypertension is common in individuals with WBS, reported in 10–60% [Hallidie-Smith and Karas, 1988; Morris et al., 1988; Ingelfinger and Newburger, 1991]; differing study designs may account for this extremely broad range.

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Two studies, using 24 hr ambulatory blood pressure monitoring, showed a hypertension frequency of 40% without evidence of age effects in cohorts comprised of individuals 1–23 years of age [Wessel et al., 1997] and 11–44 years of age [Broder et al., 1999]. Although some authors suggest that hypertension is found more commonly in teenagers and adults than in younger children, the ambulatory blood pressure data refute this. Hypertension, endemic in the general adult population with an estimated prevalence as high as 25% [Williams, 2006], is even more prevalent in individuals with WBS, and dramatically so in WBS children and adolescents. The etiology of hypertension in WBS is likely to be multi-factorial possibly due to elastin haploinsufficiency [Faury et al., 2003], *NCF1* hemizygosity [Del Campo et al., 2006], and/or renovascular disease [Radford and Pohlner, 2000].

Cerebral infarction has been reported in a few children and adults with WBS; underlying intracranial vascular stenosis is the major (though not sole) risk factor in these patients [Kawai et al., 1993; Ardinger et al., 1994; Kaplan et al., 1995; Soper et al., 1995; Wollack et al., 1996]. The frequency of stroke does not appear to be age-related but limited data are available to address this issue.

Since cardiovascular problems are present in most adults with WS, and may progressively worsen over time, ongoing monitoring by a primary care physician, preferably in conjunction with a cardiologist, is essential. No specific treatments have yet been identified for these conditions in WBS, for example, antihypertensive pharmacotherapy should be *individually* tailored to maximize efficacy and compliance while minimizing side effects. WBS-targeted preventive therapies to minimize or ameliorate cardiovascular disease do not currently exist. Additional recommendations for cardiovascular monitoring are outlined in Table I (reprinted with permission from Cherniske et al. [2004]).

Endocrine Abnormalities

The most commonly discussed endocrine abnormality in WBS is hypercalcemia, though it is documented in only ~15% of infants and young children. Both the etiology and true frequency of hypercalcemia remain unknown, the latter because blood calcium levels may not be routinely checked in patients with an established diagnosis of WBS and are rarely, if ever, obtained in undiagnosed individuals. Although blood calcium elevations are reported most often among infants and young children, hypercalcemia can occur during adulthood as can nephrocalcinosis, calcification of the vascular wall, and hypercalciuria [Morris et al., 1990].

A far more common endocrine abnormality, especially in WBS adults, is diabetes mellitus or the pre-diabetic condition referred to as impaired glucose tolerance. In one cohort of WBS adults over 30 years of age, 75% met diagnostic criteria for abnormal glucose tolerance, either diabetes or pre-diabetes, on a standard two-hour oral glucose tolerance test (GTT) [Cherniske et al., 2004].

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Additionally, several reports of adults with overt manifestations of diabetes have been published [Morris et al., 1988; Lopez-Rangel et al., 1992; Imashuku et al., 2000; Nakaji et al., 2001]. The work of Cherniske and colleagues suggests this problem may start early in life, given that a few children and adolescents had impaired glucose tolerance on GTT, but the prevalence and severity of this problem is far greater among adults. It is likely that hemizygosity for a gene in the WBS critical region, possibly syntaxin-1A, confers risk for diabetes though the underlying mechanism of insulin dysregulation (e.g., insulin secretory defect or insulin resistance) remains unknown.

There have been recent reports of thyroid abnormalities in WBS, though the data contained therein primarily focus on children. Subclinical (e.g. compensated) hypothyroidism is far more common in these reports than bona fide hypothyroidism which requires thyroid hormone supplementation, a finding similar to the only study that examined this issue in adults [Cherniske et al., 2004; Stagi et al., 2005; Cambiaso et al., 2007]. Diminished thyroid volume has been implicated as the cause, or at least a contributing factor, to this phenomenon.

Dental Findings

Our experience reveals that caries and gum disease are common in adults with WBS, prompting restorative care and even extractions in some cases. These problems are likely due to poor visual spatial skills that preclude maintenance of proper dental hygiene, rather than intrinsic deficiencies of tooth integrity. Several morphological abnormalities of the secondary dentition have been reported including tooth aplasia, tooth hypoplasia, and aberrant crown shape [Hertzberg et al., 1994; Axelsson, 2005]. SBE prophylaxis is indicated in individuals with WBS who have aortic abnormalities.

ENT/Audiologic Problems

Most persons with WBS manifest hypersensitivity and distress in response to selected sounds (so-called hyperacusis and phonophobia, respectively), though the intensity of the adverse response is diminished in adults compared to children. Recurrent otitis media, a particularly common childhood complication, is infrequently diagnosed in adults. The voice is typically described as hoarse and/or low pitch, another finding presumably attributed to elastin deficiency (specifically of the vocal cords in this instance) [Vaux et al., 2003].

Recent work demonstrates that mild to moderate high frequency sensorineural hearing loss is present in the majority of individuals with WBS, possibly caused by cochlear dysfunction [Cherniske et al., 2004; Marler et al., 2005; Gothelf et al., 2006].

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Since all studies performed have only analyzed cross-sectional data, it is not yet known whether loss can progressively worsen over time (though the study by Marler and colleagues suggest this might be so). Most adults do not demonstrate obvious clinical sequelae as the degree of loss does not interfere with social conversation, though a few have benefited from use of a hearing aid (personal observations). Excess wax build-up is commonly observed among adults with WBS [Cherniske et al., 2004].

Neurological Abnormalities

A characteristic constellation of findings on neurological examination in adults with WBS include hyper-reflexia, hypertonia, as well as signs of cerebellar dysfunction such as ataxia and dysmetria [Trauner et al., 1989; Chapman et al., 1996; Cherniske et al., 2004; Pober, 2006]. Young children with WBS are typically hypotonic and the mechanisms underlying progression to hypertonia with advancing age are not known. The precise basis of all the neurological pathologies of WBS is not known but work drawing brain structure–function relationships is increasingly underway (see review by Meyer-Lindenberg et al. [2006]). Brain malformations are relatively infrequent in the WBS population as a whole but one condition that can be diagnosed during the adult years is Type I Chiari malformation, presenting either with acute symptoms due to obstructed CSF flow or with upper extremity weakness, muscle atrophy and parasthesias secondary to chronic posterior fossa compression [Pober and Filiano, 1995] (and personal observations).

Musculoskeletal Problems

Infants with WBS have significant hypotonia, and also have lax joints probably related to elastin haploinsufficiency. This is one of several factors contributing to delayed ambulation in WBS. Young children with WBS are often afraid to walk independently, likely related to poor stereo acuity, mild cerebellar dysfunction that affects balance, and the loose joints that make maintaining a normal posture difficult. To improve stability, children with WBS typically adopt a bent-knee, flexed-hip stance accompanied by a lordotic posture, and kyphosis soon follows. Over time, hyper-reflexia of the lower extremities will develop as will contractures of the hamstrings and Achilles tendons [Morris et al., 1988; Kaplan et al., 1989; Morris and Carey, 1990; Cherniske et al., 2004]. These contractures typically worsen without physical therapy. Regular stretching range of motion exercises should be part of the daily regimen for a person with WBS. It is likely that the spine and joint problems associated with WBS result from interactions between reduced muscle tone combined with ligamentous laxity. Individuals with connective tissue disorders may be more likely to have Chiari I malformation (see above) [McDonnell et al., 2006]. The gait may become increasingly stiff and awkward over time. Individuals with WBS will often complain of leg cramps at night, especially after a day of a high level of exercise. The adult with WBS may have fixed contractures if not treated with physical therapy. With aging and growth, the neck appears long, and is accentuated by the sloping shoulders. Adults with WBS often have diminished strength around the shoulder girdle. They are often easily fatigued, which may be multi-factorial in origin stemming in part from expenditure of extra energy required due to the gait disturbance.

There are few reports regarding bone mineral density in adults with WBS. Cherniske et al. [2004] demonstrated osteopenia or osteoporosis in at least one site (femoral neck or lumbar spine) using DEXA scans in 14/20 adults aged 30–52 years. It is unclear whether diminished bone mass in WBS is secondary to abnormalities in calcium metabolism or simply a non-specific manifestation of decreased activity commonly found in adults with intellectual disabilities.

Gastrointestinal Disorders

Chronic abdominal pain is common in adults with WBS and can arise from multiple physiologic causes. Although "functional" abdominal pain related to

anxiety does occur, it should always be a diagnosis of exclusion. Gastroesophageal reflux, found in all age groups, occurs in 25% of adults [Cherniske et al., 2004], and does respond to typical medical treatment. Some rare individuals have had episodic abdominal pain related to discrete arterial stenosis resulting in bowel ischemia (personal observations). Half of adults with WBS have chronic constipation that may cause discomfort and should be treated aggressively [Morris et al., 1988]. Individuals with WBS are more likely to develop diverticulosis at a young age, presumably due to haploinsuffiency of elastin. One of the earliest reports of diverticular disease in WBS described an adult male, age 42, who died following rupture of the sigmoid related to diverticulitis [Dupont et al., 1970; Jensen et al., 1976]. One quarter of adults with WBS were reported to have diverticular disease in one series [Morris et al., 1990]. Partsch et al. [2005] reviewed clinical findings in 128 German adults with WBS aged 18–62 years, and found diverticular disease of the sigmoid colon in 14 (11%).

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The authors noted that diverticular disease in individuals with WBS under age 40 years is 3–4 times more common than in the general population. In a US cohort of 20 adults over age 30 years, diverticular disease was present in 40%, with 75% of them requiring surgery [Cherniske et al., 2004]. From published reports, there is a trend suggesting that the diverticular disease is more severe and has an earlier onset in males with WBS. Adults complaining of abdominal pain should be evaluated for diverticular disease. In all of these series, the diagnosis of diverticular disease was established after symptoms appeared. Therefore, the prevalence of diverticulosis may be much higher in individuals with WBS, but has not been studied. Rectal prolapse, hemorrhoids, and cholecystitis are other reported gastrointestinal complications in WBS.

Genitourinary Problems

Urinary frequency is a common problem at all ages in WBS. The prevalence of structural abnormalities of the urinary tract detected with renal ultrasonography ranges from 20 to 35% [Pober et al., 1993; Pankau et al., 1996; Sforzini et al., 2002]. Adult females with WBS have increased frequency of urinary tract infections [Morris et al., 1990; Lopez-Rangel et al., 1992; Cherniske et al., 2004]. Bladder diverticula, possibly due to the elastin deficiency, have been reported in adults [Morris et al., 1990; Schulman et al., 1996; Sammour et al., 2006]. Renal failure appears to be a relatively rare complication [Davies et al., 1997]. Inguinal hernias are repaired in 40% of young children with WBS [Morris et al., 1988], and recurrence is frequent in adults. Little information regarding fertility in WBS is available, though both males and females with WBS have reproduced [Morris et al., 1993; Sadler et al., 1993]. In the past, elective hysterectomy was often performed in women with intellectual disability; currently, use of oral, depot, or transdermal preparations are preferred methods of birth control for females. It is important to advise the use of condoms for STD prevention.

Risk of Cancer

There are four published reports of malignancy occurring in adults with WBS: (1) pancreatic carcinoma discovered at autopsy in a 42-year-old man who died after rupture of sigmoid diverticulitis [Dupont et al., 1970; Jensen et al., 1976]; (2) mucinous cystadenoma of the ovary in a 21-year-old female [Marles et al., 1993]; (3) non-Hodgkins lymphoma in a 29-year-old female [Felice et al., 1994]; and (4) endometrial carcinoma in a 43-year-old female [Cherniske et al., 2004]. We have additionally provided care for two women diagnosed with uterine cancer and ovarian cancer, respectively, and have been informed by the parent support group, The Williams Syndrome Association, about a few other adults treated for cancer, including two women have been successfully treated for postmenopausal breast cancer. Although there are no formal estimates of the frequency of cancer among adults with WBS, there is no evidence to suggest that WBS is a syndrome that inherently confers cancer risk.

Facial Features in WBS and Diagnosis

The distinctive facial features in infants and children with WBS often assist the pediatrician in recognizing the syndrome in a child with short stature and developmental delay. There is typically a broad forehead, bitemporal narrowing, periorbital fullness, epicanthal folds, low nasal root, flat malar region, full nasal tip, long philtrum, wide mouth, full lips, full cheeks, small jaw, small widely spaced teeth, and prominent ear lobes (Fig. 1). In blue-eyed individuals with WBS a stellate or lacy pattern of the irides is usually present; this manifestation of hypoplasia of the iris stroma is evident on slit lamp examination of brown-eyed individuals. During childhood, facial asymmetry may be noted, and the full cheeks of infancy gradually resolve. With growth, the face often appears gaunt which may be accentuated by the long neck and sloping shoulders. The supraorbital ridge may be prominent, the narrow nasal root is normal height, dental malocclusion is typical, and the mandibular angle is increased. The wide mouth and prominent lips are the most distinguishing facial features in the adult with WBS, as demonstrated by three-dimensional imaging of the face surface [Hammond et al., 2005]. While the young child may appear to be younger than chronologic age, the adult

Figure 1. Facial features over time in a female with Williams syndrome: from left to right, top row, age 2 years, 8 years, 29 years and bottom row, 34 years, 46 years, 46 years.

with WBS may appear to be older, due to premature graying of the hair, and a somewhat "coarse" appearance to the face in some individuals. In some adults, sagging facial tissue may contribute to an aged appearance, an identical phenotype to autosomal dominant cutis laxa [OMIM 123700], which is caused by a mutation in the elastin gene. Premature graying of the hair is very common in WBS.

The differential diagnosis for WBS includes syndromes that are associated with short stature relative to the family background, mild mental retardation, cardiovascular disease, behavior problems, and dysmorphic facial features [Morris, 2005]. FISH studies are clinically available to confirm or rule out a diagnosis of WBS. Newer molecular techniques, such as high-resolution chromosomal microarray techniques, will likely reveal heretofore undescribed microdeletions or microduplications of other chromosomes in those individuals who also have dysmorphic facial features different from the family background. Sometimes, the diagnosis of WBS is considered in adults who have the least specific features overlapping the WBS phenotype, such as mental retardation, anxiety, ADHD, a friendly personality, and a love of music. A normal FISH or microarray test can easily exclude the diagnosis of WBS, because virtually all individuals with WBS have a deletion of 7q11.23 demonstrable by molecular cytogenetic techniques (personal observations).

Cognitive Impairment

The mean IQ for WBS falls in the range of mild mental retardation, as measured by multiple standardized tests in several cross-sectional studies. The range of cognitive ability is broad, from severe mental retardation to normal IQ. When the data on adults are analyzed, it appears that the cognitive ability is stable [Mervis et al., 1999]. One primarily cross-sectional study of 80 adults with WBS between ages 17 and 52 years showed no difference in the full scale IQ across ages; furthermore, four of these adults who had been studied longitudinally over a 9-year interval showed no decrease in IQ scores [Searcy et al., 2004]. Udwin et al. [1996] showed stable IQ scores in a cohort of 23 individuals aged 10–15 years at initial evaluation who had no decline in IQ scores when retested at ages 19–25 years. There is some evidence to suggest an age-related decline in certain memory processes in older individuals with WBS [Devenny et al., 2004]. In one small study, 12 adults with WBS (age range 30–78) were compared to a group with unspecified mental retardation using a list learning task to evaluate explicit memory; performance was affected by IQ in both groups, but an age effect was demonstrated only in the WBS group [Krinsky-McHale et al., 2005].

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While overall cognitive ability is diminished in WBS, the syndrome is characterized by a specific profile of strengths and weaknesses with relative strengths in verbal short-term memory and language, but profound weakness in visuospatial constructive abilities.

The cognitive profile (WSCP), which is independent of overall cognitive ability, persists in adulthood as demonstrated in a group of 33 adults aged 18–47 [Mervis, 2006]. The specific deficit is in the function of the dorsal stream of visual processing ("where") versus the ventral stream ("what"). Adults with WBS were found to have difficulty with visual-motor tasks but had preservation of object recognition, an identical pattern to that seen in children with WBS [Atkinson et al., 2006]. The visual processing deficit demonstrated

in functional MRI experiments correlates with reduced gray matter volume in the intraparietal sulcus identified using voxel based morphometry [Meyer-Lindenberg et al., 2004; Eckert et al., 2005; Boddaert et al., 2006]. Hippocampal dysfunction is thought to contribute to difficulties in spatial navigation and long-term memory in WBS [Meyer-Lindenberg et al., 2005]. Most adults with WBS are able to read, but have significant difficulty with math, making it difficult to tell time, make correct change, or manage personal finances.

Social Cognition and Behavior

Individuals with WBS have a unique behavioral profile characterized by hypersociability, heightened empathy, attention deficit, and anxiety. In a cohort of 119 individuals aged 4–16 years, Leyfer et al. [2006] demonstrated attention deficit disorder in 65% and specific phobia in 54%. The diagnosis of generalized anxiety disorder was more common in the 35 individuals aged 11–16 years, occurring in 23% versus the 14% prevalence in the 7–10 year olds (N = 44). Prevalence of specific phobia was 34% and generalized anxiety disorder was 16% in a WBS group (N = 51) aged 5–49 years [Dykens, 2003]. In an adult cohort of 18, nine were diagnosed with specific phobia, virtually all met threshold or sub-threshold criteria for anxiety disorder, and half were being treated medically for psychiatric symptoms [Cherniske et al., 2004]. Self-calming techniques, including deep breathing, "self talk", and yoga exercises can be taught to individuals with WBS, and anecdotally appear to have the greatest benefit if they become part of the family routine prior to adolescence. While externalizing behaviors become less prominent with age in WBS, distractibility is still common (90% in one series of adults) [Davies et al., 1998; Dykens and Rosner, 2006]. Attention problems continue to impact performance in adults, and our own experiences confirm that many require medical treatment for anxiety or depression (personal observations). The neurobiological basis for the behavioral profile of WBS is thought to be related to diminished volume of gray matter in the orbital frontal cortex leading to abnormal regulation of the amygdala and thus to the social disinhibition common in individuals with WBS [Meyer-Lindenberg et al., 2006].

Sleep problems are common in individuals with WBS at all ages, and may be related to periodic limb movements in sleep or obstructive sleep apnea in some individuals [Mason and Arens, 2006]. Some adults complain of difficulty initiating sleep due to worries, while others note night waking due to physical discomfort, such as leg cramps, a full bladder, or pain related to gastroesophageal reflux (personal observations). Sleep disturbance may result in fatigue, irritability, and diminished performance.

Howlin and Udwin [2006] surveyed 239 families of adults with WBS in the United Kingdom to learn about medical and adaptive problems in adulthood. The adults' mean age was 30 years, with a range 19–56 years. Half reported depression and anxiety, and only 16% were living independently. The 38% that had employment were in part time jobs or sheltered settings. While most adults could take care of basic needs, few could handle their own finances. Parents noted that it was difficult to obtain coordinated medical or mental health services and opportunities for employment were limited. In their study of 20 older adults (ages 30–51 years), Cherniske et al. [2004] found that measures of adaptive behavior were lower than would be expected based on cognitive ability. While 70% had some form of part time employment, only one was in a competitive position.

Management Issues

An increased number of visits to the pediatrician is well-documented for youngsters with WBS [Morris et al., 1988]. Although not similarly documented for adults with WBS, our personal practices indicate this to be true for WBS adults, especially those over 30 years of age. There is an increased frequency of age-related problems, many of which are either specific to WBS or are far more common in individuals with WBS than among comparably aged individuals in the general population. Particularly vulnerable organs in adults with WBS include the cardiovascular, gastrointestinal, and endocrine systems. Also, a strikingly high prevalence of psychiatric impairments superimposed on existing cognitive handicaps negatively impact not only emotional well-being, but also the ability to achieve independence in the personal, social and vocational arenas for almost all adults with WBS.

The frequency and diversity of medical problems found in adults with WBS dictates the need for access to high quality medical care that should be provided by physicians knowledgeable about WBS. Unfortunately, this standard of care is not provided for many adults with WBS, attributable to various factors including: (a) limited access to medical care; (b) care that is fragmented (e.g., provided by specialists without having a physician to coordinate and manage the overall medical care); and (c) lack of knowledge about the natural history of WBS. Table I provides multi-organ system medical monitoring guidelines that reflects the information discussed above.

In summary, WBS is a complex multiple congenital anomaly syndrome that is challenging to diagnose in adults. Diagnosis is critically important, given the wide-range of medical, neurologic and psychiatric problems encountered in the adult with WBS that can profoundly impact health and well-being. Awareness of the specific issues should result in improved preventive care and surveillance, as well as provide a basis for care coordination and guidance that will enhance primary care management.

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