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Multisystem Study of 20 Older Adults with Williams Syndrome

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To address the natural history of Williams syndrome (WS), we performed multisystem assessments on 20 adults with WS over 30 years of age and documented a high frequency of problems in multiple organ systems. The most striking and consistent findings were: abnormal body habitus; mild–moderate high frequency sensorineural hearing loss; cardiovascular disease and hypertension; gastrointestinal symptoms including diverticular disease; diabetes and abnormal glucose tolerance on standard oral glucose tolerance testing; subclinical hypothyroidism; decreased bone mineral density on DEXA scanning; and a high frequency of psychiatric symptoms, most notably anxiety, often requiring multimodal therapy. Review of brain MRI scans did not demonstrate consistent pathology. The adults in our cohort were not living independently and the vast majority were not competitively employed. Our preliminary findings raise concern about the occurrence of mild accelerated aging, which may additionally complicate the long-term natural history of older adults with WS. We provide monitoring guidelines to assist in the comprehensive care of adults with WS. © 2004 Wiley-Liss, Inc.

KEY WORDS: Williams syndrome; adults; diabetes; hearing loss; diverticulitis; obesity; hypercalcemia; bone density; anxiety; aging

INTRODUCTION

Williams syndrome (WS, also known as Williams–Beuren syndrome) [OMIM #194050] is a well recognized multisystem genetic condition affecting at least 1/20,000 individuals [Morris et al., 1988]. The cause of WS is a submicroscopic deletion at 7q11.23 [Ewart et al., 1993]. Research from numerous groups over the past decade delineates the WS critical region to be ~1.6 million base pairs encompassing approximately 20 genes [Osborne, 1999; DeSilva et al., 2002; Merla et al., 2002]. Work on genotype–phenotype correlation provides mounting evidence that the genes at the telomeric end of the critical region, such as *TFII-I*, *TFII-IRD1*, and *Cyln-2*, play a significant role in the cognitive aspects of the WS phenotype [Hoogenraad et al., 2002; Hirota et al., 2003; Morris et al., 2003; Danoff et al., 2004].

While many of the clinical features of WS, including the characteristic facies, the cognitive profile, and vascular disease have been well characterized during childhood, the body of literature devoted to the adult population is small by comparison. The previously published medical and psychological series on adults with WS demonstrate a variety of problems and suggest that WS is a multisystem disorder throughout the lifecycle [Morris et al., 1990; Lopez-Rangel et al., 1992]. However, the mean age of adults in these previous cohorts is less than 29 years of age. To address concerns about aging in older persons with WS, we performed this study exclusively on adults with WS over 30 years of age. Our findings expand the list of medical problems found in the adult WS population and improve our understanding of the natural history of this condition.

METHODS

We performed systematic medical and cognitive assessments on 20 adults with WS who were at least 30 years of age. Subjects were recruited through the Genetics clinic at Yale New Haven Medical Center, the website for the Yale Child Study Center Clinic for Genetic Forms of Developmental Disorders, the Williams Syndrome Association (WSA), and from clinical colleagues. All 20 adults were admitted to the Yale New Haven Medical Center Children's Clinical Research Center (CCRC) where they participated in a multidisciplinary research protocol involving a variety of medical, cognitive, psychiatric, and MRI evaluations. Examples of medical testing that was performed included: audiogram, bone densitometry by DEXA scan, abdominal and carotid Doppler ultrasound, and oral glucose tolerance testing. Detailed physical, neurological and psychiatric examinations were also performed. IQ score was assessed in 19/20 subjects using the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) [Wechsler, 1997] and using the Kaufman Brief Intelligence Test (KBIT) [Kaufman, 1990] in the remaining subject. Vineland Adaptive Behavior Scales [Sparrow et al., 1984] were completed on 18 subjects. Medical history was obtained by direct interview with subjects, parents, and caregivers (i.e., group home staff) supplemented by an Aging Questionnaire designed by the authors, and selective review of the subjects' medical records. A dementia

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questionnaire, The Dementia Questionnaire for Persons with Mental Retardation (DMR), was filled out by parents or caregivers [Evenhuis, 1996]. Since the subjects participated in this study for a variety of reasons, we believe the population represents the range of general medical health in adults with WS. All research was approved by the Yale Human Investigation Committee; study participants and their parents or caregivers consented to participate.

RESULTS

General Findings

The study cohort consisted of 10 females and 10 males. The average age at time of study participation was 38.8 years (range 30–51 years). Seventeen of 20 subjects had an elastin deletion in the WS critical region confirmed by FISH analysis. Although three subjects could not be tested for funding reasons, the diagnosis of WS was clinically confirmed by one of the authors (B.R.P.) in all. The mean age of initial clinical diagnosis of WS was 23 years.

At the time of study participation, average growth parameters were as follows: female height was 153.0 cm (range 148.1–156.3 cm), male height was 167.2 cm (range 155.5–174 cm), female weight was 63.7 kg (range 41–89.7 kg), and male weight was 71.2 kg (range 51–94.2 kg). BMI was calculated for all subjects. A BMI of <20 (very lean) was found in 4/20, 20–25 (lean) in 3/20, 25–30 (overweight) in 9/20, and >30 (obese) in 4/20 subjects. Percent total body fat for 15 subjects was calculated using X-ray absorptiometry with the HOLOGIC 4500 densitometer. Mean total body fat was 30.9% with a range of 15.1 to 50.4%. Three subjects had $<20\%$, five had 20–30%, and seven had $>30\%$ total body fat, respectively. Among the subjects with excess body fat, much of the fat was in a central or pear shaped distribution.

Visual Abnormalities

Information tabulated from medical record review and the Aging Questionnaire showed one or more visual problems in all 20 subjects including: history of strabismus (N = 6), current strabismus (N = 7), hyperopia (N = 6), myopia (N = 4), presbyopia (N = 4), cataracts (N = 4), and chronic conjunctivitis (N = 1). None reported glaucoma. Eye surgery was necessary for seven subjects with five needing strabismus repair, one needing lens implant, and one needing corneal reconstruction. On physical examination, persistence of strabismus was confirmed in seven subjects.

Audiologic Testing

Sixteen of 20 subjects underwent standard audiologic testing at Yale. Based on our study results, only four subjects had normal audiograms. The remaining 75% had a similar pattern of high frequency sensorineural hearing loss (SNHL). Specifically, eight had bilateral mild to moderate high frequency SNHL, one had unilateral mild high frequency SNHL, while the remaining three subjects had high frequency SNHL plus either low frequency SNHL or conductive loss. There was a trend for the hearing loss to exceed age-gender correction [Codes of Federal Regulations FR, 1985] at 4000 Hz that did not meet statistical significance (Spearman's rho = 0.086, 1-tailed).

Dental Health

Dental examination for the purpose of evaluating dental hygiene was performed by one of the authors (B.R.P.). Among the 19 subjects in whom dental hygiene could be assessed two had good hygiene, eight had fair hygiene, and nine had poor hygiene. The effects of poor hygiene included halitosis, dental caries, dental extractions, and gum recession.

Cardiovascular

Cardiovascular abnormalities were reported in 14 subjects; supravalvar aortic stenosis (SVAS) was the single most common diagnosis being present in 13/14 but only three had required surgery. Additional cardiovascular problems included: pulmonic stenosis (N = 3), mitral regurgitation (N = 2), bicuspid aortic valve (N = 2), mitral valve prolapse (N = 1), and VSD (N = 1). Twelve subjects had hypertension and 10 of them were receiving pharmacologic treatment, most commonly with a beta-blocker or calcium channel blocker anti-hypertensive. None reported stroke or were documented to have had a stroke on MRI scan. Ten subjects underwent abdominal Doppler ultrasound studies of their descending aorta, renal arteries, and mesenteric arteries. The indications for these studies were research (N = 7), hypertension (N = 2), and lower extremity edema (N = 1). Isolated branch stenosis of either the SMA or celiac axis was detected in four subjects while a fifth had SMA tortuosity possibly caused by SMA origin stenosis. Neither of the hypertensive subjects had a documented vascular abnormality.

Nine of the subjects underwent a carotid Doppler examination as part of this research study. One of these nine had a carotid bruit. Eight of the studies were normal, including the patient with the carotid bruit; one subject had possible hypoplasia of the left internal carotid artery.

Gastrointestinal

The frequency of gastrointestinal problems was assessed by report from subjects and caregivers as well as by review of medical records. A history of "any" GI problem was present in 15/20 subjects, with several subjects reporting multiple problems including: abdominal pain (N = 8), gastroesophageal reflux (N = 5), constipation (N = 5), diarrhea (N = 4), and both constipation and diarrhea in an additional four. Two had diverticulosis, three had diverticulitis, and an additional three were diagnosed with combined diverticulosis/diverticulitis. Half of the patients with diverticular disease had a history of chronic constipation. Bowel surgery was performed in six of 20 subjects with four undergoing partial colon resection for diverticular disease, while one underwent a hemorrhoidectomy and another a cholecystectomy.

Genitourinary

The single most common GU problem reported was urinary frequency affecting half of the subjects. Two experienced episodes of incontinence, and one required treatment with Ditropan. Four subjects had a history of urinary tract infections; one female with recurrent urinary tract infections was found to have bladder diverticuli, bladder spasm, and interstitial cystitis. Renal function was assessed in 18 subjects by BUN and creatinine determinations. Values were normal in all subjects although two had creatinine levels at the upper limit of normal. Renal ultrasound examinations were performed in 13 subjects and eight demonstrated no abnormalities, four had bladder diverticuli, and one had medullary nephrocalcinosis.

Endocrine

Parents reported prior hypercalcemia in two of 18 subjects. Total blood calcium was measured in all subjects and an 18-hr urine calcium excretion was collected in 17 (see Table I). Most had normal blood and urine calcium levels with only one patient having mild hypercalcemia (10.6 mg/dl), four having mildly decreased calcium levels (8.2–8.7 mg/dl), and one

TABLE I. Selected Findings in Study Subjects

Age	Gender	Blood calcium[a]	Urine Ca/Cre[b]	PTH[c]	Glucose tolerance[d]	Bone mineral density @ femoral neck[e]	Bone mineral density @ lumbar spine[f]
30	F	NL	NL	⇑	NL	NL	NL
30	F	NL	ND	ND	IGT	Osteopenia	Osteopenia
30	M	NL	NL	NL	IGT	Osteopenia	Osteopenia
31	F	NL	NL	⇑	IGT	Osteopenia	NL
32	M	NL	NL	NL	CD	NL	NL
34	M	NL	⇑	NL	NL	Osteopenia	Osteoporosis
35	F	⇓	NL	⇑	SD	NL	NL
36	M	NL	NL	NL	IGT	NL	NL
37	F	NL	NL	⇑	IGT	Osteopenia	Osteopenia
37	M	⇓	NL	NL	SD	NL	NL
37	M	NL	NL	NL	SD	Osteopenia	NL
40	M	NL	NL	⇑	SD	Osteopenia	Osteopenia
41	F	⇓	NL	⇑	SD	Osteopenia	NL
41	M	⇑	NL	NL	IGT	Osteoporosis	Osteoporosis
42	F	NL	NL	⇑	SD	NL	Osteopenia
43	M	NL	ND	⇑	IGT	NL	NL
45	M	NL	ND	⇑	IGT	Osteoporosis	Osteopenia
46	F	NL	NL	NL	SD	Osteopenia	Osteopenia
51	F	NL	NL	NL	CD	Osteopenia	Osteopenia
52	F	⇓	NL	⇑	IGT	NL	NL

[a]Normal blood calcium = 8.8–10.2 mg/dl.
[b]Normal urine calcium (mg/dl)/urine creatinine (mg/dl) = <0.22.
[c]Mid-molecule radioimmunoassay of PTH; normal <25 nleq/ml.
[d]CD, clinical diabetes; SD, silent diabetes; IGT, impaired glucose tolerance; NL, normal. Expert Committee Classification of oral glucose tolerance test at 2 hr: glucose <140 mg/dl = NL; 140–200 mg/dl = IGT; >200 mg/dl = SD.
[e]Based on WHO criteria; T-score for bone mineral density ≥1.0 SD but ≤2.5 SD below mean = osteopenia.
[f]Based on WHO criteria; T-score for bone mineral density ≥2.5 SD below mean = osteoporosis.

patient having mild hypercalciuria (calcium/creatinine = 0.27 (mg/mg) and calcium excretion of 3.6 mg/kg/24 hr). Additional details are shown in Table I.

Parathyroid hormone (PTH) was assayed in 19 subjects using a sensitive midmolecule PTH radioimmunoassay in the Mineral Metabolism Laboratory, Yale University School of Medicine [Carpenter et al., 1994]. The sole patient with hypercalcemia had a normal PTH level, as did the patient with hypercalciuria. However, seven subjects had elevated PTH levels (>25 nleq/ml) in the setting of normal calciums while three had PTH elevations with mildly decreased calciums (8.7, 8.2, and 8.4 mg/dl). Vitamin D metabolites were assayed in eight subjects; 25-OH levels ranged from 18.8 to 26.8 ng/ml with several low to mid-normal range determinations while 1,25-$(OH)_2$ levels were in the high- normal range. Determination of blood osteocalcin, as a marker of bone formation, was performed on 10 subjects using a standard equilibrium radioimmunoassay [Gundberg et al., 1984]. Four had abnormal results with levels below the lower limit of normal (<5 ng/ml) consistent with low bone formation or turnover.

Bone mineral density was determined at three sites (lumbar spine, left femoral neck, & left total femur) by dual-energy X-ray absorptiometry using the HOLOGIC 4500 densitometer. Results were classified according to WHO criteria [Kanis et al., 1994]; see Table I for definitions and details. Twelve of 20 subjects met criteria for either osteoporosis or osteopenia using femoral neck T-score cutoffs, while 10 met these criteria using lumbar-spine cutoffs. Three males were diagnosed with osteoporosis at two or more sites. This diagnosis was confirmed in one by a quantitative CT scan of the spine; additional work-up, including an intact PTH, 25-OH and 1,25-$(OH)_2$ vitamin D, testosterone, urinary *N*-telopeptide, deoxypyridinoline, and thyroid function tests, was normal. None of the female subjects had osteoporosis involving two or more sites.

Thyroid function tests were obtained on 20 subjects and were normal in 15. One subject had hypothyroidism in the setting of elevated antithyroid antibodies consistent with autoimmune thyroiditis. Four additional patients had moderate elevations in TSH in the setting of normal thyroxine levels, consistent with compensated or subclinical hypothyroidism. No patient had hyperthyroidism.

All subjects were asked about a history of diabetes or glucose intolerance. Two had clinically been diagnosed with adult onset diabetes mellitus prior to study participation. One was managed with daily insulin whereas the other had been weaned off an oral hypoglycemic agent and was being managed by dietary control only. A third subject had a prior abnormal oral glucose tolerance test but was not receiving treatment at the time of study participation. A standard 2-hr oral glucose tolerance test (OGTT) was administered to the remaining 17 study subjects who had no prior history of diabetes. Results from the OGTT were classified according to the criteria established by the Expert Committee on Diagnosis and Classification of Diabetes Mellitus [1999] and demonstrated: silent diabetes in 6/17, impaired glucose tolerance in 9/17, and normal glucose tolerance in 2/17. Thus only two members of the entire cohort of 20 had no clinical or laboratory evidence of abnormal glucose metabolism. Preliminary data from this cohort show that insulin resistance, as manifested by elevated fasting plasma insulin levels, is not the sole cause of abnormal glucose metabolism in adults with WS.

Among our 10 female study participants, total hysterectomy had been performed in four. Three of these patients were receiving estrogen replacement therapy. Two non-hysterectomized subjects were taking birth control pills and none had entered spontaneous menopause (ages ranging from 30 to 43 years), though two were developing irregular menses. None of our female subjects had been pregnant. Two of the men had undergone vasectomy procedures.

Musculoskeletal

On physical examination, four of the 20 subjects had scoliosis, six had lordosis, and two had both. Nine subjects had stiffness or contractures of the metacarpophalangeal and/or interphalangeal joints of the hands while four had increased range of motion of these joints. Eleven subjects had decreased elbow extension or supination, possibly secondary to radioulnar synostosis, though this was not confirmed radiographically. Almost all subjects had decreased range of motion of the hamstrings and/or heelcords. In half the subjects, progressive contractures were reported. One subject had recurrent subluxation of the patellae.

Integument

Grey hair was reported and confirmed on physical exam in 19/20 subjects; the average age of onset was reported to be 29 years (range 16–41 years). Thinning of hair was reported in 10 subjects with an average age of onset of 35 years. On physical exam 10/20 subjects had soft skin, 3/20 had dry skin, and 1/20 had a wrinkled appearance to the skin. Although not systematically assessed, we noted non-pitting edema, possibly lipedema, predominantly involving the lower extremities in six study subjects. This was found in both males and females, often accompanied by almost complete hair loss of the involved extremities.

CNS

Eighteen of the 20 subjects had magnetic resonance imaging (using a GE 1.5 T scanner) with a T1 weighted high resolution ($1.2\ mm^3$) research protocol for volumetric assessments, and a standard T2 weighted series (5 mm thick axial slices) to assess for pathology. Participants were typically given a mild sedative or anxiolytic to assist them in staying still and cooperating with the procedure; two, however, moved to such an extent that their data were not analyzable. A variety of abnormalities were found during clinical reading of the films, including marked dilatation of numerous Virchow-Robbin's spaces (3/16), Chiari malformation Type I (2/16), white matter hyperintensities (2/16), and mild cortical atrophy (1/16, with one additional subject having questionable cortical atrophy). Otherwise the scans were qualitatively unremarkable from the perspective of a careful clinical reading by an experienced neuroradiologist.

Further analyses were done using quantitative procedures with the high resolution T1 weighted scans. Quantitative assessment of the brain volume found brain size reduction of about one standard deviation compared to normative data. As with normative samples, male brain volumes were about 1 SD larger than females, and both differed by an equal amount from their gender normed reference group. An additional comparison to an IQ and gender-matched group of 21 persons with WS younger than 30 years of age (mean age $= 17.1 \pm 5.6$) revealed no significant difference ($P = 0.58$) in overall brain size (1128 ± 162 cc for the aged sample vs. 1152 ± 101 cc for the younger WS sample). Independent analyses of the left and right hemisphere volume revealed no disproportionate size abnormality by hemisphere.

Neurological examination revealed increased upper extremity deep tendon reflexes in almost half of the subjects while lower extremity deep tendon reflexes were increased in 13/19. Clonus was also present in half and was bilaterally symmetric in most. One subject had abnormal plantar reflexes while two had equivocal Babinski reflexes. A fine resting tremor was observed in eight subjects; in all of these plus an additional seven, mild to moderate intention tremor was present. Among the subjects assessed for tandem gait, all performed this task with difficulty; this skill was rated as normal in none, fair to good in 10, and poor in 4. Synkenesis was present in one male. No subject had a history of seizures.

Cognitive

Full scale IQ was determined for each subject and the average full scale IQ was 68 for the group. Distribution of IQ was as follows: borderline intelligence (FSIQ 70–80) in three, mild mental retardation (FSIQ 50–69) in 14, and moderate mental retardation (FSIQ < 50) in three. There were no gender trends associated with IQ. Only a single subject had a significantly higher verbal IQ than performance IQ while most had comparable scores. In 17/20 subjects prior IQ testing was available for our review. Although there are significant limitations in making comparisons between tests, given differing assessment tools and varying time intervals, FSIQ was stable in nine, increased more than seven points in five, and decreased more than seven points in three.

The Dementia Questionnaire for Persons with Mental Retardation (DMR) was completed by the parent or caregiver of 16 study subjects [Evenhuis, 1996]. One subject's score was consistent with the presence of dementia, affecting both cognitive and social domains; this diagnosis was later confirmed on clinical assessment.

Psychiatric

Nineteen of 20 subjects were described by their parent and/or caregiver as having clinically significant problems with anxiety and/or depression. Eighteen subjects were directly interviewed and assessed by an expert child psychiatrist using semi-structured diagnostic interviews [such as the Anxiety Disorder Interview Scale (ADIS) and the Schedule for Affective Disorders and Schizophrenia (SADS)] as well as open-ended interviews. As diagnosed by the psychiatrist, 13 subjects had moderate to severe levels of anxiety, while three more had mild or subclinical anxiety. The most common subtype of anxiety was that of specific phobia and the second most common was that of generalized anxiety disorder (e.g., anticipatory and performance anxiety). An adaptation of the Kiddie-SADS-parent version was administered to parents/guardians, with highly similar findings. Simple phobias were diagnosed in half of the subjects based on a combination of subject and parent/guardian interviews. Additional diagnoses were: depression ($N = 2$); manic-depression ($N = 1$); panic disorder ($N = 1$); obsessive-compulsive disorder ($N = 1$); and sexual impulse disorder ($N = 1$). A few subjects met DSMIV criteria for several of these diagnoses.

Eleven of the subjects have been, or continue to be, pharmacologically treated for control of psychiatric symptoms. The most commonly prescribed medications were members of the SSRI class ($N = 9$), serzone ($N = 2$), Haldol ($N = 2$), and benzodiazepines ($N = 2$). Several subjects used multiple medications. Four of the subjects had required psychiatric hospitalization to treat acute psychiatric problems.

Social/Vocational Status

The adults participating in this study had a variety of living arrangements; eight continued to live with their parents, five resided in group homes, five lived in supervised apartments, and two were in retirement communities. Only one subject held (part-time) competitive employment. Six held supervised paid positions, seven worked in sheltered workshops, and six were not employed. Among those employed the average hours worked each week was 23 (range 6–35 hr).

We completed the Vineland Adaptive Behavior Scales [Sparrow et al., 1984] on 18 subjects. This semi-structured interview, completed by the participants' parent or caregiver, measures an individual's typical performance on day-to-day activities needed for self-care and getting along with others. The overall adaptive behavior standard score on the Vineland was 55 (normal mean $= 100 \pm 15$) showing that individuals

with WS have significant difficulties in their adaptive behavior skills, that are out of proportion to their cognitive deficits. Among the subscales comprising the Vineland, the mean for communication was 46, for daily living 61, and for socialization 65.

Cancer

Only one patient had been diagnosed with cancer. A 43-year-old female was diagnosed with endometrial cancer, which was treated with hysterectomy.

DISCUSSION

This cohort of WS adults extends the reported ages of previous series on WS adults [Morris et al., 1990; Lopez-Rangel et al., 1992] by focusing specifically on adults over the age of 30 years. We found that many adults showed ongoing medical problems most commonly involving the endocrine, cardiovascular, and gastrointestinal systems. An increased frequency of psychiatric problems, necessitating involvement with mental health professionals, was also found. Other studies on persons with intellectual disabilities have found an increased frequency of medical and mental health problems compared to controls [as reviewed in Jansen et al., 2004]. Although some of our findings are not necessarily restricted to WS, others do appear to be syndrome specific. Salient problems in each organ system are discussed below in the context of relevant medical literature. The results from this study, combined with our experience evaluating 25 additional WS adults in our genetics clinic, form the basis of the healthcare monitoring guidelines we propose for adults with WS (see Table II).

Discussion of General Findings

In our series 65% of WS adults have a BMI >25, indicating they are overweight or obese. Several other reports indicate that WS adults can become overweight or obese [Morris et al., 1990; Davies et al., 1997]. This finding is in sharp contrast to the growth parameters of infants and young children with WS, which are often at or below the 3rd centile. Given that the majority of our subjects were overweight or obese, it is possible that excess weight gain is an inherent part of the natural history of WS. However, data from the most recent NHANES III [Flegal et al., 2002] survey shows that two-thirds of American adults in the general population have a BMI >25. Thus, the prevalence of high BMI's in WS adults may simply reflect the widespread problem of obesity in the United States, but we cannot exclude the possibility that this is a consequence of the genetic deletion responsible for WS combined with lifestyle and/or medication choices. Interestingly, nine of our 10 obese or overweight WS subjects who underwent total body fat estimation by DEXA had a higher percent body fat, adjusting for BMI, age and gender compared to a convenience sample of healthy adults [Gallagher et al., 2000]. Unfortunately, our sample size is too small to permit rigorous statistical analysis but the data suggest an especially high percent of body fat among overweight and obese adults with WS. Independent of the cause of the adiposity, excess weight gain in persons with WS further increases their risks for a variety of medical complications, such as hypertension and diabetes.

Discussion of Visual, Audiologic, & Dental Findings

Formal ophthalmologic examinations were not performed as part of this study. Despite this our observations are similar to findings of other studies with comparable data collection methods, showing a high frequency of strabismus and poor visual acuity [Morris et al., 1990; Lopez-Rangel et al., 1992; Plissart et al., 1994]. However, the report of cataracts (type unspecified) in 20% of our study group is a finding not previously published in WS; if confirmed by a systematic ophthalmologic survey this would indicate earlier onset of cataracts compared to individuals in the general population [Klein et al., 1998; Delcourt et al., 2003] and findings more comparable to adults with Down syndrome [Van Allen et al., 1999].

Few published studies have analyzed hearing in adults with WS [Lopez-Rangel et al., 1992; Plissart et al., 1994; Johnson et al., 2001; Miani et al., 2001]. Available reports mention occasional patients with sensorineural hearing loss (SNHL), though Johnson et al. found moderate high frequency SNHL in three of the four young adults they tested aged 18–25 years. Audiologic testing performed as part of this study shows that most WS adults have a characteristic pattern of mild to moderate high frequency SNHL consistent with presbycusis. Although this pattern of hearing loss is very common in the older adult general population, it appears to be developing at an earlier than expected age in adults with WS [Codes of Federal Regulations FR, 1985]. Although not systematically evaluated in our study, sleep apnea was suspected and later confirmed in one subject. Additionally, recurrent ear-wax build-up requiring clean out was observed and/or reported in several subjects.

An almost universal problem among adults with WS is poor dental hygiene. Among adults with nonspecific mental retardation, an increased frequency of dental caries as well as periodontal disease has been reported compared to healthy controls [Gabre and Gahnberg, 1994, 1997]. Despite these observations persons with WS may be at even greater risk for dental problems, given their poor visual–spatial motor skills. Supervised brushing/flossing and more frequent dental cleanings are recommended to maintain adequate dental hygiene.

Discussion of Cardiovascular Findings

Given the high frequency of cardiovascular anomalies, ongoing cardiology follow up for adults with WS is recommended. More than half of our subjects are hypertensive, a frequency that is consistent with the published literature [Morris et al., 1990; Lopez-Rangel et al., 1992; Davies et al., 1997; Wessel et al., 1997; Broder et al., 1999]. The etiology for hypertension is likely to be mixed including generalized vasculopathy, focal vascular stenosis, and in some cases obesity. No study to date has identified a preferred class of antihypertensive medication for patients with WS; as in the general population the treatment of choice is dictated by both physician preference and patient tolerability. With the increased availability of noninvasive imaging there is growing recognition that stenosis of the descending aorta and/or isolated branch stenosis involving the renal, mesenteric, and/or celiac arteries can occur. Though none of these stenoses were clinically significant at the time of detection, the long-term natural history of these vascular abnormalities remains unknown. Intracranial vascular pathology causing stroke has been documented in a few adults with WS [Kawai et al., 1993; Wollack et al., 1996]. None of our 20 research subjects had clinical or radiographic evidence of a stroke. Nonetheless, we have observed stroke in some of our other WS adults followed clinically outside of this research study.

Discussion of Gastrointestinal Findings

Gastrointestinal pathology in WS merits more attention than it has previously received as it is a frequent cause of morbidity that may be preventable with timely intervention. One prior series found chronic constipation in 50% and diverticular disease in 25% of WS adults [Morris et al., 1988] but another noted these problems occurred with a much lower frequency [Lopez-Rangel et al., 1992]. Our findings indicate

TABLE II. Recommendations for Medical Monitoring of Adults with Williams Syndrome

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 & Vitamin D intake not to exceed RDA
- ADA diet if needed (see endocrine section below)
- Encourage active lifestyle & focused exercise regimen assuming there are no cardiovascular contraindications

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

ENT/Audiologic
- Baseline audiologic evaluation @ 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 & cleanouts as needed

Dental
- Supervision of brushing & 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, & 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 & urinalysis
- Renal & 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 & 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
- 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 & TSH annually and consider thyroid hormone replacement if TSH >10

TABLE II. (*Continued*)

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 & diet
d. Manage silent diabetes with exercise, diet, & consider medication
e. Patients with clinical diabetes should be managed like adults in the general population with diabetes
Routine gynecologic care & 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 & 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 & Vocational
Tailor residential placement to maximize independence while taking into consideration the strengths & weaknesses of WS cognitive functioning
Encourage vocational opportunities, even volunteer positions
Foster social outings and networking

that these problems are common in adults with WS and are possibly even underreported. Constipation needs to be aggressively managed as it appears to be a risk factor for rectal prolapse, hemorrhoids, diverticulosis, and diverticulitis. The frequency of diverticular disease may be significantly underestimated in WS adults because of lack of routine surveillance by colonoscopy. Recurrent abdominal pain warrants a complete examination as it can have identifiable and treatable medical causes. Anxiety can also be the cause of abdominal pain in adults with WS but this should be a diagnosis of exclusion. The possibility of celiac disease in adults with WS ought to be considered as a recent study found antibody evidence of celiac disease in approximately 10% of children with WS [Giannotti et al., 2001]. We speculate that individuals with WS may be more prone to certain of these GI pathologies, especially diverticular disease, due to elastin haploinsufficiency.

Discussion of Genitourinary Findings

There are published reports of renal dysfunction and even renal failure in the WS literature [Biesecker et al., 1987; Steiger et al., 1988; Ichinose et al., 1996; Davies et al., 1997]. None of the members of our research cohort had evidence of renal disease; likewise this was an exceptionally rare finding in our genetics clinic population of WS adults. Urinary frequency is quite common, almost seeming to be the norm and most often not due to underlying identifiable pathology. One possible cause of urinary frequency includes bladder diverticuli found in four of our patients, which is consistent with previous literature reports [Morris et al., 1990; Schulman et al., 1996]. Work by others suggests that abnormal detrussor contractions contribute to voiding frequency and incontinence [Schulman et al., 1996]. Recurrent urinary tract infections have been noted in the literature [Morris et al., 1990; Lopez-Rangel et al., 1992] and were reported in four of the 10 females in our cohort.

Discussion of Endocrine Findings

The most commonly discussed endocrine abnormality in WS is hypercalcemia, with most reports focusing on infantile hypercalcemia [Jones, 1990]. Despite the attention paid to this complication, the incidence of hypercalcemia is at best imprecisely estimated at 15% [2001] and the etiology and natural history continue to be unknown. Our observation of a case with hypercalcemia, plus reports of occasional adults in the medical literature with evidence of hypercalcemia, [Morris et al., 1988, 1990] demonstrate that the risk for hypercalcemia is not restricted to infancy. Periodic monitoring of calcium status in adults with WS is thus warranted. The fact that half our subjects had elevated PTH levels is difficult to interpret based on the available data since this may represent secondary hyperparathyroidism due to inadequate dietary calcium or protein intake, or dysregulation of PTH secretion. The finding of osteoporosis/osteopenia, especially in adult males, is of interest in light of an as yet unspecified derangement in calcium homeostasis in WS. However, adults with Down syndrome as well as those with non-syndromic mental retardation also have decreased bone mineral density suggesting our results may not be syndrome specific [Tyler et al., 2000]. Despite our ignorance surrounding the exact cause of decreased bone mineral density in WS, screening, and possibly treatment, are indicated when significant bone loss is documented.

In this series of WS adults, the most common thyroid abnormality was compensated or "subclinical" hypothyroidism found in 4/20 subjects. The benefit of treating subclincal hypothyroidism remains a matter of debate; we advise that each case should be fully evaluated before treatment with supplemental thyroid hormone is started.

We observed an extremely high frequency of abnormal glucose tolerance in this cohort of WS adults, far higher than adults in the general population with similar BMIs [Lindahl et al., 1999]. The underlying mechanism predisposing to

glucose dysregulation remains unknown but must, in large part, be caused by loss of one of the genes responsible for WS. Obesity and limited physical activity may also contribute to the high incidence of abnormal glucose tolerance. Our findings extend the previous case reports of diabetes mellitus in adults with WS [Morris et al., 1988; Lopez-Rangel et al., 1992; Plissart et al., 1994; Imashuku et al., 2000; Nakaji et al., 2001] and will be elaborated on in a separate publication.

Discussion of Musculoskeletal Findings

Musculoskeletal problems were identified in the majority of our cohort, commonly consisting of postural abnormalities and contractures. Our experience concurs with the published literature [Morris et al., 1988, 1990; Kaplan et al., 1989; Lopez-Rangel et al., 1992; Bzduch, 1994] in that most adults have decreased joint range of motion typically affecting the heelcords, hamstrings, and small joints of the hands which can worsen over time. It is unclear if the etiology of these joint contractures is secondary to intrinsic joint problems or neurological abnormalities.

Discussion of Integument Findings

Soft skin is commonly reported in WS, but there has also been some concern as to whether skin ages prematurely [Ewart et al., 1993]. Though we found a wrinkled appearance to the skin of the face and hands in only one of our subjects, half did have soft skin with a few additionally having dry skin. Presumably these mild skin changes can be attributed to the ultrastructural changes in elastin. Abnormal elastin fibers with reduced amounts of amorphous elastin and decreased elastic fiber volume and diameter have been demonstrated on microscopic analysis of skin in persons with WS [Urban et al., 2000; Ghomrasseni et al., 2001]. We found that the majority of adults had premature graying of the hair starting as early as 16 years old, a finding which has been reported previously [Morris et al., 1988]. The cause of the premature graying in WS is not currently known.

Discussion of CNS Findings

Clinical MRI evaluation of the brain with both T1 and T2 weighted series revealed surprising low rates of abnormalities, and no consistent pattern of problems to suggest a common age related "neuropathology" in WS. Quantitative assessment of brain volume was similar to prior studies [Reiss et al., 2000] on WS showing overall brain size reduction of about 15%, but no difference in the magnitude of this finding between these older individuals with WS and a matched group of younger persons with WS. Thus, in this sample of WS adults, where the mean age was almost 39 years of age, we did not find any consistent CNS signs of premature aging. Before drawing firm conclusions on this issue, it will be very important to assess a representative sample of WS where the mean age is somewhat older, e.g., 50 years of age.

Care providers should be aware that the baseline neurological examination in WS is most often "abnormal" and includes findings such as hyper-reflexia, clonus, poor balance, and intention tremor. Acute onset of neurological symptoms and/or a significant change from baseline warrant further investigation.

Discussion of Cognitive, Psychiatric and Social/Vocational Findings

Our findings indicate that most adults with WS are achieving in the range of mild mental retardation on tests of cognitive abilities. This is commensurate with prior research [Howlin et al., 1998], even though our study population is significantly older. Unlike Howlin et al., we did not observe a split between verbal and nonverbal reasoning abilities. Although not rigorously studied, our data do not show a decline in IQ over time which has been debated in the literature, with some studies showing an increase in IQ over time [Udwin et al., 1996; Howlin et al., 1998] and others showing a decrease [Gosch and Pankau, 1996].

We found that individuals with WS show evidence of significant impairment in their adaptive behavior abilities, especially in communication skills. Their performance is lower than expected given their cognitive abilities. This is consistent with the data of Howlin et al. [1998] but contrary to the findings by Plissart and colleagues [Plissart et al., 1994] who found strengths in communication and weaknesses in personal self-care. Additional research is necessary to further explore adaptive behavior profiles in adults with WS but these results, as well as our personal experience, indicate that the presence of poor adaptive skills negatively impact vocation and living opportunities, above and beyond cognitive limitations.

Our psychiatric data were systematically acquired by an experienced psychiatrist and did not rely, as have earlier studies, on behavior checklists completed by parents or caregivers. Our more rigorous methods do confirm the high frequency of behavioral and emotional problems in adults with WS previously reported [Davies et al., 1998; Udwin, 1990]. The single most common disorder in adults with WS is anxiety with the strongest components being specific phobias and generalized anxiety (e.g., performance and anticipatory anxiety). The majority of our subjects had undergone some form of treatment for anxiety, generally involving counseling and/or medication. No formal study of medication efficacy has been published to date; our experience shows some benefit of serotonin selective reuptake inhibitors (SSRIs), though standard adult doses seem to be associated with an increased risk for adverse effects such as disinhibition.

Several of our study subjects were hospitalized for exacerbation of psychiatric problems. Reports of adults with WS treated for a "psychotic" disorder exist [Bradley and Udwin, 1989]. There is inadequate direct experience to know whether psychosis represents a genuine risk for adults with WS or whether such deteriorations are transient exaggerated responses to life stresses, superimposed on baseline mental retardation and anxiety disorders. We caution against hasty labeling and pharmacological treatment of psychosis in this population.

Possible Accelerated Aging in WS

One global question that our study tried to address is whether adults with WS show evidence for mild accelerated aging. Several of the physical findings, such as earlier than expected onset of grey hair, cataracts, and high frequency sensorineural hearing loss, support this possibility. Although our own longitudinal IQ data show no decline over time other studies raise this concern, at least in some areas of functioning [Gosch and Pankau, 1996]. A recent study of older adults with WS demonstrates premature decline in selected memory tasks compared to adults with unspecified mental retardation [Devenny et al., 2004]. Two of our patients, one evaluated in this study and another followed clinically, have been diagnosed with dementia. Whether such declines are an inherent part of WS or result in large part from multiple medical problems such as hypertension and diabetes remains to be sorted out. No study, including this one, formally assessed lifespan in Williams syndrome and although we know of 60 and 70 year old adults with WS [Fryns et al., 1991; personal observations], we are concerned that the many medical problems found in our study can impact life span necessitating the close medical monitoring detailed in Table II.

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