Medical, Cognitive, and Psychiatric Characteristics in a Large Israeli Cohort of Individuals with Williams Syndrome

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ABSTRACT: **Background:** Williams syndrome (WS) is a neurogenetic syndrome characterized by a variety of medical conditions and cognitive deficits along with distinct psychiatric and behavioral characteristics. To the best of our knowledge, no studies to date have comprehensively reported the prevalence of medical, cognitive deficits, and psychiatric disorders in one cohort of people with WS in one study.

Objectives: To detail the prevalence of the various clinical features of WS in a large nationwide Israeli cohort. To examine potential risk factors for attention deficit hyperactivity disorder (ADHD) in WS.

Methods: We investigated the effects of cardiovascular anomalies, intellectual quotient (IQ), and phonophobia (fear of sounds) on the likelihood of ADHD. The study included 80 participants with WS (mean age 7.76 years). Relevant medical information from medical records was obtained retrospectively. In addition, IQ testing and psychiatric assessments using structured tools were conducted. The association between ADHD and cardiovascular anomalies, IQ, and phonophobia was analyzed using a logistic regression.

Results: Supravalvular aortic stenosis and supravalvular pulmonary stenosis are the prevalent cardiovascular anomaly in WS. Phonophobia and ADHD are the most prevalent psychiatric diagnoses in people with WS. Phonophobia was significantly associated with the risk for ADHD in WS participants.

Conclusions: Our findings regarding the type and prevalence of medical, cognitive, and psychiatric characteristics in WS correspond to results in previous publications. We also showed a potential link between phonophobia and ADHD that merits further research.

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KEY WORDS: attention deficit hyperactivity disorder (ADHD), cardiovascular anomaly, intellectual disability, phonophobia, Williams syndrome (WS)

Williams syndrome (WS) is a neurogenetic disorder, which occurs in about 1 in 20,000 live births. It is associated with a variety of medical and developmental problems along with distinct facial features and specific personality and psychiatric features [1]. The syndrome is caused by a microdeletion of about 2 million DNA base pairs from region q11.23 of chromosome 7. This segment contains 24 genes including the ELN gene. The deletion of the elastin gene is presumed to be the main cause of arterial stenosis in WS [1].

MEDICAL CHARACTERISTICS

Previous studies have shown that 50–75% of people with WS have a cardiovascular anomaly caused by arterial stenosis, most commonly supravalvular aortic stenosis (SVAS) and supravalvular pulmonary stenosis (SVPS) [2,3]. Although most people with WS do not develop severe stenosis, some will require surgery in infancy to prevent the development of heart failure, and up to 50% of those with arterial stenosis will develop hypertension during their lifetime [2]. Endocrine disorders are also common in WS, the most common being hypercalcemia, found in 15% of the population, especially in infants. Hypercalcemia is often associated with hypercalciuria, arterial calcification, and nephrocalcinosis [2,4]. Adults with WS may also develop diabetes or a pre-diabetic state [2,4]. Subclinical hypothyroidism, caused by a small thyroid gland, has also been reported. It is usually managed without medical treatment [5]. Structural defects involving the genitourinary system in people with WS, such as ectopic kidney, horseshoe kidney, and bladder diverticula, are found to occur in 20–35% of patients [6]. Many people with WS cope with hypotonia, especially in early childhood. They may also have hyperflexibility of their joints, which may affect their normal motor development by causing hyper-reflexed thighs, bent knees, and spinal kyphosis to maintain a balanced posture [3,4,7]. Other orthopedic symptoms include the development of lordosis and scoliosis. While lordosis is more common in WS, some individuals with scoliosis may need surgical intervention [3,4,7]. It has been shown that esophageal reflux occurs in 25% of people with WS at all ages [3]. People with WS also tend to develop intestinal diverticula at a young age, probably as a result of the lack of elastin [8]. Half have chronic constipation and some have chronic abdominal pain, which is linked mainly to the anxiety that is prevalent in WS [3,7].

PSYCHIATRIC CHARACTERISTICS

Psychiatric disorders are common in people with WS, including attention deficit hyperactivity disorder (ADHD) and anxiety disorders, especially specific phobias. According to a recent Israeli survey, 21% of adolescents are diagnosed with ADHD [9]. In those with WS, it is three times as prevalent and occurs in 65–84% of WS individuals [8,10-12]. Previous studies have shown clinically significant improvement of ADHD symptoms in people with WS when treated with methylphenidate [13]. One study from our group also showed that following methylphenidate treatment, 75% of participants with WS exhibited a clinically significant improvement, but 61% of those medicated experienced unhappiness or sadness and became quiet and withdrawn [14]. Previous studies have shown that the rate of specific phobias in WS range from 43–54% [7,8,12,14]. Common specific phobias in WS include phonophobia, fear of injections and blood tests, as well as fear of medical procedures in general. One study showed that the rates of specific phobias are higher in WS (45%) than in other idiopathic developmental disorders (23%) [14]. The most common specific phobia in WS is phonophobia, with the most common startling noises being electrical machines, balloons popping, fireworks, and thunder [11,15]. There is a report on rare cases of phonophobia secondary to stroke induced by methylphenidate [17].

COGNITION DEFICITS

Studies of intellectual quotient (IQ) in people with WS show a range of IQ scores from 40 to 100, with average scores of 50–60 representing a mild to moderate intellectual disability [16,18]. Previous studies show that IQ scores of individuals with WS remain relatively stable along development [16,18]. Some studies identify a difference between verbal and performance IQ in WS, with mean verbal IQ being greater than mean performance IQ (mean verbal IQ of 63 compared to mean performance IQ of 55, respectively) [16]. The cognitive profile in WS is characterized by areas of strength, including auditory memory, some language abilities, high object and facial expression identification ability, and areas of weakness such as spatial memory, mathematics and, spatial-motor skills such as navigation [8,18].

THE ASSOCIATION BETWEEN CARDIOVASCULAR ANOMALIES AND COGNITIVE DEFICITS AND ADHD

There is some evidence to suggest that cardiovascular anomalies can be associated with cognitive deficits and ADHD. Studies on children with innate cardiovascular anomalies who underwent thorough correction procedures showed that they are more prone to develop motor and cognitive impairments in addition to ADHD [19,20]. A review of 65 studies with children with innate cardiovascular anomalies found a gap of 1–2 standard deviations in scales that measured motor and cognitive abilities [19]. A study with 109 children with innate cardiovascular anomalies showed that their risk of developing ADHD was five times higher than in the general population [20]. However, to the best of our knowledge, there are no studies that have investigated the effect of the severity of cardiovascular anomalies on the development of those impairments in people with WS.

WS is a multi-systemic syndrome that can be associated with a variety of possible conditions. Surprisingly, to date, we have not found any study that has comprehensively reported the variety and prevalence of medical symptoms together with the cognitive and psychiatric manifestations of the syndrome in one single cohort.

The aim of this study was to characterize the various clinical features (medical, psychiatric, and cognitive) of WS in a large nationwide Israeli sample. We also examined the association between ADHD and cardiovascular anomalies, IQ, and phonophobia. Specifically, we hypothesized that the severity of cardiovascular anomalies, lower IQ, and the presence of phonophobia would be associated with ADHD.

PATIENTS AND METHODS

This study was approved by the Rabin Medical Center Helsinki Ethics Committee. All participants and/or their legal guardian were briefed on the purpose and method of the study and gave their signed informed consent.

We conducted a retrospective analysis of participants with WS who received comprehensive treatment from the department of child psychiatry at the Safra Pediatric Hospital, Sheba Medical Center, Tel Hashomer, Israel.

Our clinic coordinates the management of Israelis with WS who are referred from all over the country from genetic institutes and from the WS Parent Association. The clinic provides WS individuals with multidisciplinary medical care according to their specific needs, which can include cardiovascular, endocrinological, neurological, nephrological, gastrointestinal, and orthopedic. All patients with cardiovascular anomalies seen in the clinic undergo a cardiovascular assessment, which includes physical examination, electrocardiography, and echocardiography (conducted by a cardiovascular specialist). Only participants with a diagnosis of WS and a positive fluorescent in situ hybridization (FISH) test were included in the study.

DATA COLLECTION

Data were collected retrospectively from participant files and clinic databases. The information obtained included general demographic information, medical diagnoses, and procedures and treatments. Medical records included specialist consultant reports, reports of surgical procedures, and results of radiological imaging (including echocardiogram and abdominal ultrasound).

For this research study, a pediatric cardiologist designed a rating scale severity to evaluate cardiovascular anomaly. Severity was determined as follows:

- Level 1: Mild supravalvular aortic or pulmonary stenosis +/- mild mitral valve prolapse or aortic coarctation
- Level 2: Moderate supravalvular aortic or pulmonary stenosis +/- mild mitral valve prolapse or aortic coarctation
- Level 3: Severe supravalvular aortic or pulmonary stenosis +/- mild mitral valve prolapse or aortic coarctation
- Level 4: Supravalvular aortic and pulmonary stenosis +/- mild mitral valve prolapse or aortic coarctation
- Level 5: Supravalvular aortic or pulmonary stenosis + severe aortic coarctation

Participants in the study underwent psychiatric assessment, which was conducted using the Hebrew version of the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS) [21,22]. Psychiatric assessments were conducted for individuals 5 years of age and older.

IQ was evaluated using the age-appropriate Hebrew version of the Wechsler Intelligence Scale for Children (WISC-III) [23] and the Wechsler Adult Intelligence Scale (WAIS-III) [24].

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA). Rates of medical symptoms, psychiatric disorders, and cognitive factors are presented as absolute numbers and percentages. We conducted a binary regression analysis to examine the relationship between ADHD and cardiovascular anomalies, IQ, and phonophobia using logistic regression. The results are presented as odds ratios (OR) and 95% confidence interval (95%CI). We also conducted a chi-square test to examine the link between methylphenidate and phonophobia. A *P* value of 0.05 was considered as the significance threshold.

RESULTS

We obtained data on 80 participants with WS, which was confirmed by a FISH test. Our sample included 33 males and 47 females; 73 were Jewish and 7 were of Arabic descent. The mean age of the sample was 7.76 ± 7.25 years, range 0–34 years (We collected data in infants concerning medical conditions).

MEDICAL CHARACTERISTICS

The frequencies of medical conditions are shown in Table 1. We found that 72.2% of participants had cardiovascular anomalies, 35.0% had a level 1 severity cardiovascular anomaly (as defined by our rating scale), 5.0% had level 2 severity anomaly, none had level 3 severity anomaly, 27.5% had level 4 severity anomaly, and 3.8% had level 5 severity cardiovascular anomaly. The most common cardiovascular anomaly was SVPS, which was reported in 51.3% of the participants, followed by SVAS in 45%. A corrective surgical procedure was necessary for 16.2% of participants due to the severity of their cardiovascular anomaly.

Table 1. Prevalence of medical characteristics in individuals with Williams syndrome

Characteristics	n (number of participants in the sample)*	%
Neurological		
Hypotonia	49 (80)	61.3
Clumsiness	27 (80)	33.8
Microcephaly	19 (80)	23.8
Spina bifida	4 (80)	5.0
Epilepsy	4 (80)	5.0
Cardiovascular		
Supravalvular pulmonary stenosis	41 (80)	51.3
Supravalvular aortic stenosis	36 (80)	45.0
Ventricular septal defect	18 (80)	22.5
Mitral valve prolapse	6 (80)	7.5
Patent ductus arteriosus	5 (80)	6.3
Atrial septal defect	4 (80)	5.0
Coarctation of aorta	3 (80)	3.8
Renal artery stenosis	3 (80)	3.8
Congenital heart anomaly corrective surgery	6 (37)	16.2
Gastrointestinal		
Constipation	11 (80)	13.8
Gastroesophageal reflux disease	5 (80)	6.3
Rectal Prolapse	2 (80)	2.5
Celiac disease	2 (80)	2.5
Nephrological		
Dysplastic kidney	2 (80)	2.5
Vesicourether reflux	6 (80)	7.5
Hydronephrosis	6 (80)	7.5
Nephrocalcinosis	2 (80)	2.5
Ectopic kidney	7 (80)	8.8
Endocrine		
Short stature	46 (80)	57.5
Hypothyroidism	25 (80)	31.3
Early puberty	17 (80)	21.3
Hypercalcemia	16 (80)	20.0
Obesity	6 (80)	7.5
Cryptochidism	5 (33)	15.2
Micropenis	4 (33)	12.1
Musculoskeletal		
Scoliosis	19 (80)	23.8
Kyphosis	10 (80)	12.5
Torticollis	7 (80)	8.8
Joint hyperflexibility	10 (80)	12.5
Flat feet	7 (80)	8.8
Clinodactyly	4 (80)	5.0
Proximal radioulnar synostosis	4 (80)	5.0
Hamstring strain	3 (80)	3.8
Achilles tenotomy	3 (80)	3.8
Muscular dystrophy	4 (79)	5.1
Opthalmological		
Strabismus	33 (80)	41.3
Myopia	14 (80)	17.5
Astigmatism	3 (80)	3.8
Auditory		
Hyperacusis	44 (80)	55.0

*In some of the medical characteristics we did not obtain information about all 80 participants; therefore, we include (in parentheses) the number of participants in the sample for each characteristics

PSYCHIATRIC CHARACTERISTICS

Psychiatric assessments were conducted in 58 patients. Rates of psychiatric disorders are shown in Table 2. ADHD and phonophobia were the most prevalent diagnoses. The most prevalent frightening or bothering sounds in our sample were sounds of drills 13.8 %, balloon bursting 12.5%, thunder 12.5%, and

Table 2. Prevalence of psychiatric characteristics in 58 individuals with Williams syndrome

Characteristics	N out of 58 patients with WS	%
ADHD		
Combined type	15	25.8
Inattentive type	23	39.6
Hyperactive Type	2	3.4
ADHD NOS	3	5.1
ADHD any	43	74.1
Any anxiety disorder	47	81.0
Specific phobia		
Noises	19	32.7
Animals	2	3.4
Blood	8	13.7
Doctors	2	3.4
Environment	1	1.7
Social phobia	0	0
Any phobia disorder	30	51.7
Separation anxiety	8	13.7
Generalized anxiety disorder	6	10.3
Obsessive compulsive disorder	4	6.8
Any somatoform disorder	3	5.1
Any mood disorder	5	8.6
Major depressive disorder	3	5.1
Bipolar affective disorder	0	0
Cyclothymic disorder	1	1.7
Suicidal threats	1	1.7
Any PDD	2	3.4
Any psychotic disorder	0	0
Eating disorder	3	5.1
Any tic disorder	2	3.4
Any DSM-4 disorder	53	91.3

ADHD = attention deficit hyperactivity disorder, PDD = pervasive developmental disorder, DSM = Diagnostic Statistical Manual, NOS= non-specific, WS = Williams syndrome

electrical machines 11.3%. To assess whether there was an effect of methylphenidate treatment on the presence of phonophobia, we conducted a chi-square test and did not find difference in the rates of phonophobia between WS individuals treated with methylphenidate (n=27) and those not treated with methylphenidate (n=31) 33% vs. 35% respectively, $P = 0.63$.

COGNITION AND DEVELOPMENTAL CHARACTERISTICS

Cognitive assessments were conducted in 46 patients. Only 39 patient had both cognitive and psychiatric evaluations. Mean ± standard deviations (SD) of IQ levels and developmental milestones are shown in Table 3.

ADHD RISK FACTORS

Logistic regression analysis was used to identify the relationship between ADHD and cardiovascular anomalies, IQ, and phonophobia. According to our analysis IQ (OR 1.04, 95%CI 0.96–1.12, $P = 0.29$) and cardiovascular anomaly severity (OR 0.6, 95%CI 0.33–1.11, $P = 0.1$) were not associated with ADHD. We found phonophobia to be significantly associated with ADHD (OR 7.61, 95%CI 0.96–60.23, $P < 0.05$.

Table 3. IQ and developmental milestones scores in individuals with Williams syndrome

	N	Mean	Standard deviation	Range
Verbal IQ	43	72.6	14.7	44–106
Performance IQ	43	65.1	12.0	45–99
Full IQ	46	65.6	14.3	40–103
Age started walking, months	65	25.2	11.8	12–42
Age started speaking first words, months	56	24.4	12.9	6–84
Age started toilet training, months	52	40.8	15.3	18–72

IQ= intellectual quotient

DISCUSSION

The primary goal of our study was to describe the frequency of various clinical features (medical, psychiatric, and cognitive) in WS in a large nationwide Israeli sample. Similar to findings in previous studies, we found that SVAS and SVPS are the most common cardiovascular anomalies in WS. We also found that most of our participants (68.8%) had no cardiovascular anomaly or a level 1–2 severity and only 16.3% of them went through a surgical cardiac corrective intervention. These results strengthen previous studies, which reported that the severity of cardiovascular anomalies in WS is mild to moderate [2].

Short stature and hypercalcemia were the most common endocrine symptoms, and the prevalence of hypercalcemia (20%) was somewhat higher than found in previous studies (15%) [2,4]. In the genitourinary system, structural renal defects such as ectopic or dysplastic kidney were the most common according to our results, but in lower rates than those reported in previous studies [6]. In line with previous studies, scoliosis was the most common orthopedic disease in our sample [3,4,7]. The most common neurological symptom was hypotonia, which according to previous studies is replaced with age by hyperflexion and clonus [3,4,7]. We were not able to evaluate this symptom in our study due to the young average age of our sample.

In the current study, ADHD (74.1%) and phobic disorders (51.7%) were the most prevalent psychiatric diagnosis in WS individuals, which replicates findings from previous studies [7,8,11,13]. The most common subtype of ADHD was found to be the inattentive type (39.6%), similar to that of the general population [10,11]. The most common phobia found in our study was phonophobia, which has already been described as one of the trademarks of WS [11]. Our results also showed that WS individuals most commonly reported a startle response to

noises of electric tools including drills and mixers, balloon bursting, and thunder in line with previous reports [11]. We did not find a link between methylphenidate treatment and rates of phonophobia and, to the best of our knowledge, there are no publications on this potential risk other than a report on rare cases of phonophobia secondary to stroke induced by methylphenidate [17].

We found similar IQ levels to those described in previous studies [12,16]. Specifically, the results showed that mean verbal IQ score was higher than the mean performance IQ score. Further analysis was conducted to examine the correlation between ADHD and other factors, previously suggested to be related to the development of ADHD, including severity of cardiovascular anomalies, IQ level, and phonophobia. We found that phonophobia was significantly linked to ADHD. This association may be explained by the high distractibility that phonophobia causes, which may thus disrupt attention span. This finding can be explained by previous brain imaging studies, which indicate that individuals with ADHD exhibited greater functional connectivity between auditory and prefrontal cortical regions relative to non-ADHD controls [25]. It may imply a bottom-up process in which auditory stimulation disturbs executive functions that may disrupt people with ADHD from successfully using attentional controls [25]. Therefore, in people with WS and phonophobia, greater auditory stimulation is bound to disrupt attention to executive functions. However, it is unlikely that distractibility from phonophobia is the only cause of attention deficit, and other factors, including developmental disability, genetic pathways and environmental factors, should also be studied in this context.

Severity of cardiovascular anomalies and IQ scores were not associated with ADHD in our results. It is possible that we did not find a significant correlation between the severity of the cardiovascular anomalies in our participants with WS and the development of ADHD as in our sample most of the participants had relatively mild cardiovascular anomaly severity scores (level 3–5) and only a minority of them needed surgical intervention.

STRENGTHS AND LIMITATIONS

This study details clinical information from a large cohort of participants with WS. Information was obtained by medical specialists with experience in working with this population. As with all retrospective clinical studies, there is potential inaccuracy when making diagnoses, although this was limited using standardized measures such as echocardiography, IQ testing, and structured psychiatric assessments. Regarding psychiatric diagnoses, not all information was available for all participants. The mean age of the sample was 7.76 ± 7.25 years, range 0–34 years). Thus, it is possible that some patients have not developed the symptoms, particularly ADHD, yet. In addition, some would argue that the precision of the early IQ tests is more fragile. Since only 58 of the 80 patients had psychiatric evaluation and only 39 had cognitive evaluation, the power of our sample size is limited in detecting correlations between psychiatric and cognitive characteristics to medical characteristics. There is a need for further research investigating the role that genetic and environmental factors play in the development of ADHD in people with WS, as well as further investigation into the link between medical and psychiatric co-morbidities in WS.

CONCLUSIONS

To the best of our knowledge, this is the first study to detail the frequency of the various medical, psychiatric and cognitive features of WS in a large Israeli sample of individuals with WS. In our sample, we found that ADHD and phonophobia were the most common psychiatric disorders in WS. Phonophobia was significantly associated with the development of ADHD. This result raises the need for further research regarding the link between the deleted region in WS and ADHD.

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Capsule

Bacteria restricted via C3-mediated autophagy

The complement system has several important host-defense functions. Complement component C3, for example, can enhance phagocytosis, contribute to the bactericidal membrane attack complex, and initiate adaptive immune responses against invading microorganisms. **Sorbara** and colleagues uncovered another mechanism by which C3 can control pathogens. They observed interactions between the autophagy protein ATG16L1 and C3. In opsonized intracellular bacteria such as *Listeria*, this resulted in increased targeting to the autophagy system (xenophagy) and, in turn, greater autophagy-dependent growth restriction. Certain intracellular bacteria, such as *Shigella* and *Salmonella*, were able to escape C3-mediated targeting via the omptin proteases IcsP and PgtE, which cleave to complement components including C3. Mouse models reveaedl that C3-mediated autophagy-dependent restriction may be important in protecting host mucosal tissues during the early stages of *Listeria* infection.

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Capsule

Cross-specificity of protective human antibodies against *Klebsiella pneumoniae* Lipopolysaccharide O-antigen

Humoral immune responses to microbial polysaccharide surface antigens can prevent bacterial infection but are typically strain specific and fail to mediate broad protection against different serotypes. **Rollenske** and co-authors described a panel of affinity-matured monoclonal human antibodies from peripheral blood immunoglobulin M-positive (IgM+) and IgA+ memory B cells and clonally related intestinal plasmablasts, directed against the lipopolysaccharide O-antigen of *Klebsiella pneumoniae*, an opportunistic pathogen and major cause of antibiotic-resistant nosocomial infections. The antibodies showed distinct patterns of in vivo cross-specificity and protection against different clinically relevant *K. pneumoniae* serotypes. However, cross-specificity was not limited to *K. pneumoniae*, as *K. pneumoniae*-specific antibodies recognized diverse intestinal microbes and neutralized not only *K. pneumoniae* LPS but also non-*K. pneumoniae* lipopolysaccharides. These data suggest that the recognition of minimal glycan epitopes abundantly expressed on microbial surfaces might serve as an efficient humoral immunological mechanism to control invading pathogens and the large diversity of the human microbiota with a limited set of cross-specific antibodies.

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