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.

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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.

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

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

Chen Dror MD1, Amanda Sinai MD2 and Doron Gothelf MD1

1Department of Child Psychiatry, Safra Children’s Hospital, Sheba Medical Center, Tel Hashomer, Israel
2Department of Psychiatry, Sheba Medical Center, Tel Hashomer, Israel

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.

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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 and the Wechsler Adult Intelligence Scale (W AIS-III) [24].

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>
<thead>
<tr>
<th>Characteristics</th>
<th>n (number of participants in the sample)*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td>49 (80)</td>
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<td>Clumsiness</td>
<td>27 (80)</td>
<td>33.8</td>
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<td>Microcephaly</td>
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<td>23.8</td>
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<tr>
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<td>4 (80)</td>
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<tr>
<td>Epilepsy</td>
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<td>5.0</td>
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<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supravalvular pulmonary stenosis</td>
<td>41 (80)</td>
<td>51.3</td>
</tr>
<tr>
<td>Supravalvular aortic stenosis</td>
<td>36 (80)</td>
<td>45.0</td>
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<tr>
<td>Ventricular septal defect</td>
<td>18 (80)</td>
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</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>6 (80)</td>
<td>7.5</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
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<td>6.3</td>
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<tr>
<td>Atrial septal defect</td>
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<td>5.0</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>3 (80)</td>
<td>3.8</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
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<td>3.8</td>
</tr>
<tr>
<td>Congenital heart anomaly corrective surgery</td>
<td>6 (37)</td>
<td>16.2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (80)</td>
<td>13.8</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5 (80)</td>
<td>6.3</td>
</tr>
<tr>
<td>Rectal Prolapse</td>
<td>2 (80)</td>
<td>2.5</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>2 (80)</td>
<td>2.5</td>
</tr>
<tr>
<td>Nephrological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysplastic kidney</td>
<td>2 (80)</td>
<td>2.5</td>
</tr>
<tr>
<td>Vesicourether reflux</td>
<td>6 (80)</td>
<td>7.5</td>
</tr>
<tr>
<td>Hydrenephrosis</td>
<td>6 (80)</td>
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<tr>
<td>Nephrocalcinosis</td>
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<td>2.5</td>
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<tr>
<td>Ectopic kidney</td>
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<td>8.8</td>
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<tr>
<td>Endocrine</td>
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<td></td>
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<tr>
<td>Short stature</td>
<td>46 (80)</td>
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<tr>
<td>Musculoskeletal</td>
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<td></td>
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<td>Kyphosis</td>
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<td>12.5</td>
</tr>
<tr>
<td>Torticollis</td>
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<td>8.8</td>
</tr>
<tr>
<td>Joint hyperflexibility</td>
<td>10 (80)</td>
<td>12.5</td>
</tr>
<tr>
<td>Flat feet</td>
<td>7 (80)</td>
<td>8.8</td>
</tr>
<tr>
<td>Clinodactyly</td>
<td>4 (80)</td>
<td>5.0</td>
</tr>
<tr>
<td>Proximal radioulnar synostosis</td>
<td>4 (80)</td>
<td>5.0</td>
</tr>
<tr>
<td>Hamstringing strain</td>
<td>3 (80)</td>
<td>3.8</td>
</tr>
<tr>
<td>Achilles tenotomy</td>
<td>3 (80)</td>
<td>3.8</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td>4 (79)</td>
<td>5.1</td>
</tr>
<tr>
<td>Ophthalmological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strabismus</td>
<td>33 (80)</td>
<td>41.3</td>
</tr>
<tr>
<td>Myopia</td>
<td>14 (80)</td>
<td>17.5</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>3 (80)</td>
<td>3.8</td>
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<tr>
<td>Auditory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperacusis</td>
<td>44 (80)</td>
<td>55.0</td>
</tr>
</tbody>
</table>

*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 characteristic

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
ADHD Combined type
Inattentive type
Hyperactive Type
ADHD NOS
ADHD any
Any anxiety disorder
Specific phobia
Noises
Animals
Blood
Doctors
Environment
Social phobia
Any phobia disorder
Separation anxiety
Generalized anxiety disorder
Obsessive compulsive disorder
Any somatoform disorder
Any mood disorder
Major depressive disorder
Bipolar affective disorder
Cyclothymic disorder
Suicidal threats
Any PDD
Any psychotic disorder
Eating disorder
Any tic disorder
Any DSM-4 disorder

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

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 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 6.0, 95%CI 0.33–11.11, 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).
In addition, some would argue that the precision of the early years, range 0–34 years). Thus, it is possible that some patients have not developed the symptoms, particularly ADHD, yet. 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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The authors would like to thank all the participants who took part in this study. We also thank Prof. Loni Bleden from the Department of Cardiology, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel, for his consultation on the cardiovascular anomalies severity scale used in this study and Odil Giladi MD for her contribution to data collection for this paper.

Correspondence
Dr. C. Dror
Dept. of Child Psychiatry, Safra Children’s Hospital, Sheba Medical Center, Tel Hashomer 5265601, Israel
Phone: (972-3) 530-2663
Fax: (972-3) 530-2593
email: chen dri@clalit.org.il

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