The 4-Year Course of Tic Disorders in Boys With Attention-Deficit/Hyperactivity Disorder

Thomas Spencer, MD; Joseph Biederman, MD; Barbara Coffey, MD; Daniel Geller, MD; Timothy Wilens, MD; Stephen Faraone, PhD

Background: Despite long-standing clinical concerns, relatively little is known about the comorbidity between attention-deficit/hyperactivity disorder (ADHD) and tic disorders. Therefore, we examined tic disorders in an ongoing prospective follow-up study of male subjects with ADHD, a sample unselected for any comorbid disorder.

Methods: One hundred twenty-eight male children and adolescents with ADHD and 110 male controls were comprehensively evaluated at baseline and 4 years later. We characterized tic disorders along with a wide range of neuropsychiatric correlates, including other comorbid disorders and indices of psychosocial function in multiple domains (school, cognitive, social, and family).

Results: Compared with controls, subjects with ADHD showed more tic disorders at baseline and more new onset were reported at follow-up. Attention-deficit/hyperactivity disorder and tic disorders appeared to be independent in course: in contrast to low rates of ADHD remission, tic disorders mostly remitted. The age-adjusted rate of ADHD remission was 20% and that of tic remission, 65%. Tic disorders had little effect on the psychosocial functioning of subjects with ADHD.

Conclusions: These findings suggest that comorbidity with a tic disorder has a limited effect on ADHD outcome. However, because of the relatively small sample of subjects with tic disorders, our conclusions should be considered preliminary until confirmed in larger studies of medicated and unmedicated children with ADHD with and without tic disorders.

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SUBJECTS AND METHODS

Methods and an overview of results have been extensively described in previous reports.

SUBJECTS

The sample consisted of 238 male subjects representing 91.4% of the subjects with ADHD and 91.6% of the normal controls seen at baseline. Seventy-five (54%) of 128 subjects with ADHD were ascertained from referrals to a pediatric psychiatric clinic and 58 (45%) of 128 were ascertained from referrals to a pediatric clinic. Eligible subjects were white, non-Hispanic males aged 6 to 17 years with IQs greater than 80. We excluded adopted children and stepchildren, and children with low socioeconomic status, major sensorimotor handicaps, mental retardation, psychosis, or autism. Three hundred ninety-two probands with ADHD were referred. Of these, 252 (64%) were excluded because (1) they did not meet research criteria for ADHD on structured interview, (2) they met exclusion criteria, or (3) they refused participation.

ASSESSMENTS

Assessments at baseline and 4-year follow-up employed identical methods. Follow-up assessments were made for the interval period and were made blind to prior assessments. All psychiatric assessments relied on the Kiddie Schedule for Affective Disorders and Schizophrenia, Epidemiological version (DSM-III-R) and were based on interviews with the mothers and direct interviews of offspring aged 12 years or older. Based on 173 interviews, the median ρ coefficient of agreement between raters and senior clinicians was 0.86. For the diagnoses of tics and TS, perfect reliability was established (κ = 1.0). We estimated IQ from subtests of the Wechsler Intelligence Scales–Revised and academic achievement from the Wide Range Achievement Test. Measures of family functioning were obtained using the 4-factor Hollingshead scale (1 = highest, 4 = lowest). The social competency scales of the Child Behavior Check List (t score) (mean, 50; SD, 10; higher values are better) measured adaptive functioning in activities, social functioning, and school functioning. The Social Adjustment Inventory for Children and Adolescents (12, best; 48, worst) was used to examine interpersonal functioning. Measures of family functioning were obtained using the Moos Family Environment Scale along 3 dimensions: cohesion (1, worst; 68, best), expressiveness (15, worst; 73, best), and conflict (32, best; 81, worst).

STATISTICAL ANALYSES

Categorical data were analyzed by χ² analysis. Parametric testing of continuous data were analyzed by 1-way analysis of variance, nonparametric data by the Wilcoxon rank sum test. Continuous and binary dependent variables were analyzed using regular and logistic regressions when correcting for age differences. The Kaplan-Meier method was used for survival analysis to estimate lifetime prevalence rates and to generate survival curves, which were compared with the Cox proportional hazards model. The software used for analyses was STATA: Release 5. To protect against type II errors, we set a low threshold for statistical significance of 5%. All statistical tests were 2 tailed.

RESULTS

The overall rate of tic disorders was significantly greater in the children with ADHD vs controls (+3/128 [34%] vs 7/110 [6%], χ² = 26, P < .001). The rate of tic disorders in subjects with ADHD did not differ by referral source (26/70 [37%] vs 17/58 [29%], χ² = 0.9, P = .35; psychiatric vs pediatric ascertainment, respectively). Among children who did not have a tic disorder reported at baseline, those with ADHD had a greater probability of having a tic disorder reported only at follow-up (21/106 [20%] vs 3/106 [3%], χ² = 15, P < .001). In addition, the probability of a tic disorder being reported only at follow-up was greatest in the ADHD group that was youngest at baseline (12/36 [33%] aged 6-8 years, 5/38 [13%] aged 9-12 years, 4/32 [13%] aged 13 years
<table>
<thead>
<tr>
<th>Characteristics of Sample and Functional Outcome</th>
<th>Mean ± SD or No. (%)</th>
<th>ADHD + Tics Baseline (n = 22)</th>
<th>ADHD + Tics Follow-up (n = 21)</th>
<th>ADHD (n = 85)</th>
<th>Controls (n = 110)</th>
<th>Test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline age of probands, y</strong></td>
<td>10.0 ± 2.5</td>
<td>9.3 ± 3.3</td>
<td>11.0 ± 3.0</td>
<td>11.6 ± 3.6</td>
<td>F2,125 = 3.04</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td>2.2 ± 1.0</td>
<td>1.5 ± 0.9</td>
<td>1.8 ± 1.0</td>
<td>1.5 ± 0.7</td>
<td>F2,125 = 2.2</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td><strong>Intact families</strong></td>
<td>14 (64)</td>
<td>17 (81)</td>
<td>62 (73)</td>
<td>90 (82)</td>
<td>x2 = 1.6</td>
<td>.44</td>
<td></td>
</tr>
<tr>
<td><strong>Total No. of DSM-III-R ADHD symptoms</strong></td>
<td>11.0 ± 2.3</td>
<td>12.1 ± 2.0</td>
<td>11.4 ± 1.9</td>
<td>1.7 ± 1.9</td>
<td>F2,125 = 1.94</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td><em>Inattentive</em></td>
<td>5.0 ± 1.1</td>
<td>5.3 ± 0.9</td>
<td>5.3 ± 0.9</td>
<td>0.9 ± 1.3</td>
<td>F2,125 = 0.58</td>
<td>.56</td>
<td></td>
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<tr>
<td><em>Hyperactive/Impulsive</em></td>
<td>6.0 ± 1.7</td>
<td>6.8 ± 1.5</td>
<td>6.1 ± 1.5</td>
<td>0.8 ± 1.1</td>
<td>F2,125 = 2.03</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td><strong>Age at onset of ADHD, y</strong></td>
<td>3.0 ± 2.0</td>
<td>2.3 ± 1.6</td>
<td>2.7 ± 2.2</td>
<td>NA</td>
<td>F2,125 = 0.59</td>
<td>.56</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of ADHD, y</strong></td>
<td>10.6 ± 3.0</td>
<td>10.5 ± 3.9</td>
<td>11.6 ± 3.9</td>
<td>NA</td>
<td>F2,125 = 1.2</td>
<td>.32</td>
<td></td>
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<tr>
<td><strong>Impairment of ADHD</strong></td>
<td>2.7 ± 0.5</td>
<td>2.9 ± 0.4</td>
<td>2.6 ± 0.5</td>
<td>NA</td>
<td>F2,125 = 1.59</td>
<td>.21</td>
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<tr>
<td><strong>Additional comorbid disorders</strong></td>
<td></td>
<td></td>
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<tr>
<td>Conduct</td>
<td>6 (27)</td>
<td>7 (33)</td>
<td>23 (27)</td>
<td>6 (5)</td>
<td>x2 = 0.34</td>
<td>.85</td>
<td></td>
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<tr>
<td>Oppositional-defiant</td>
<td>15 (68)</td>
<td>17 (81)</td>
<td>61 (72)</td>
<td>18 (16)</td>
<td>x2 = 0.98</td>
<td>.61</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>11 (50)</td>
<td>10 (48)</td>
<td>37 (44)</td>
<td>7 (6)</td>
<td>x2 = 0.35</td>
<td>.84</td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>4 (18)</td>
<td>5 (24)</td>
<td>6 (7)</td>
<td>0 (0)</td>
<td>x2 = 5.6</td>
<td>.06</td>
<td></td>
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<tr>
<td>Multiple anxiety, ≥2</td>
<td>9 (41)</td>
<td>8 (38)</td>
<td>28 (33)</td>
<td>10 (9)</td>
<td>x2 = 0.58</td>
<td>.75</td>
<td></td>
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<tr>
<td>Obsessive-compulsive</td>
<td>4 (18)</td>
<td>3 (14)</td>
<td>7 (8)</td>
<td>1 (1)</td>
<td>x2 = 2.06</td>
<td>.36</td>
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<tr>
<td><strong>Functional outcome</strong></td>
<td></td>
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<tr>
<td><strong>Cognitive functioning</strong></td>
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<tr>
<td>Full IQ</td>
<td>106 ± 16</td>
<td>107 ± 14</td>
<td>111 ± 13</td>
<td>119 ± 10</td>
<td>F2,124 = 0.17</td>
<td>.19</td>
<td></td>
</tr>
<tr>
<td>Learning disorders, %‡</td>
<td>8 (38)</td>
<td>5 (26)</td>
<td>29 (31)</td>
<td>12 (11)</td>
<td>x2 = 0.68</td>
<td>.71</td>
<td></td>
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<tr>
<td>School functioning</td>
<td></td>
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<tr>
<td>Repeated grade</td>
<td>8 (36)</td>
<td>6 (29)</td>
<td>26 (31)</td>
<td>12 (11)</td>
<td>x2 = 0.36</td>
<td>.84</td>
<td></td>
</tr>
<tr>
<td>Extra help</td>
<td>12 (55)</td>
<td>11 (52)</td>
<td>49 (58)</td>
<td>28 (25)</td>
<td>x2 = 0.22</td>
<td>.90</td>
<td></td>
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<tr>
<td>Special class</td>
<td>9 (41)</td>
<td>8 (38)</td>
<td>24 (28)</td>
<td>1 (1)</td>
<td>x2 = 1.7</td>
<td>.42</td>
<td></td>
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<tr>
<td><strong>Psychosocial functioning</strong></td>
<td></td>
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<tr>
<td>Past GAF</td>
<td>51.9 ± 7.7</td>
<td>49.9 ± 7.8</td>
<td>54.3 ± 7.8</td>
<td>67 ± 7.7</td>
<td>F2,125 = 2.99</td>
<td>.05</td>
<td></td>
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<tr>
<td>Current GAF</td>
<td>55.4 ± 7.6</td>
<td>53.0 ± 6.8</td>
<td>57.2 ± 7.4</td>
<td>69 ± 6.0</td>
<td>F2,125 = 2.63</td>
<td>.06</td>
<td></td>
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<tr>
<td>Interpersonal (SAICA)</td>
<td>20 ± 11</td>
<td>19 ± 10</td>
<td>18 ± 12</td>
<td>12 ± 10</td>
<td>F2,125 = 0.17</td>
<td>.85</td>
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<tr>
<td>Child Behavior Checklist (social)</td>
<td>52.8 ± 23</td>
<td>51.3 ± 23</td>
<td>57.6 ± 25</td>
<td>57 ± 14</td>
<td>F2,125 = 0.64</td>
<td>.53</td>
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<td>Moos FES</td>
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<tr>
<td>Cohesion</td>
<td>53 ± 17</td>
<td>52 ± 19</td>
<td>47 ± 19</td>
<td>58 ± 14</td>
<td>F2,125 = 0.84</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>Expressive</td>
<td>55 ± 12</td>
<td>57 ± 12</td>
<td>50 ± 15</td>
<td>54 ± 13</td>
<td>F2,125 = 1.95</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Conflict</td>
<td>52 ± 11</td>
<td>55 ± 9</td>
<td>56 ± 12</td>
<td>48 ± 12</td>
<td>F2,125 = 1.06</td>
<td>.35</td>
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</tbody>
</table>

*ADHD indicates attention-deficit/hyperactivity disorder; NA, not applicable; GAF, Global Assessment of Functioning scale; SAICA, Social Adjustment Inventory for Children and Adolescents; and FES, family environment scale.

†Analyses were performed among ADHD subgroups only (ADHD + tic disorder baseline, ADHD + tic disorder follow-up, and ADHD without tic disorder).

‡Not all subjects were assessed for learning disorders. The denominators were ADHD + tic disorder baseline, n = 21; ADHD + tic disorder follow-up, n = 19; ADHD, n = 81; and controls, n = 106.

or older; x2 = 6.3, P < .05. The number of cases of tic disorders with TS was 12 (55%) of 22 at baseline and 6 (29%) of 21 at follow-up. Statistical comparisons were made between 3 groups of ADHD patients: (1) those who had a tic disorder reported at baseline (ADHD and tic disorder at baseline; n = 22), (2) those whose tic disorder was reported only at follow-up (ADHD and tic disorder at follow-up; n = 21), and (3) those without a report of tic disorder at baseline or follow-up (ADHD; n = 85). Other than for comparisons of rates of tic disorders, findings in controls without ADHD (n = 110) are presented for reference only.

**CLINICAL CHARACTERISTICS OF ADHD AND TIC DISORDERS**

There were no significant differences between the 3 ADHD groups in age, percentage of intact families, or socioeconomic status. Subjects with ADHD with and without tic disorders had a similar mean number of ADHD symptoms, age at onset, and duration of ADHD. On average, ADHD impairment was rated between moderate to severe (mean, 2.7; mild = 1, moderate = 2, severe = 3) in all groups (Table).

The onset of tic disorders was overwhelmingly prepubertal in both ADHD groups with comorbid tic disorders (onset of tic disorder at age ≤ 12 years: 21 (95%) of 22 vs 18 (86%) of 21, x2 = 1.1, P > .10, mean age of onset: 6.1 ± 3.0 vs 8.0 ± 4.6 years, F1,40 = 2.4, P > 0.1, in ADHD and tic disorder at baseline and ADHD and tic disorder at follow-up, respectively). Nine (43%) of 21 of the subjects with ADHD and tic disorder at follow-up reported that the onset of the tic disorder was earlier than their age at baseline. Most ADHD cases with comorbid tic satisfied criteria for chronic tic disorder, defined as having a tic for more than 1 year (91% vs 86%, x2 = 0.3, P > .10, baseline vs follow-up, respectively). In fact, the average duration of tic disorders was 4.9 ± 3.8 years, representing approximately one third of the lifetime of these children. There was little difference in the average impairment attributed to tic symptoms (mean severity, 1.6 vs 1.2; F1,40 = 3.25, P = .08) in sub-
Subjects with ADHD and tic disorder at baseline and ADHD and tic disorder at follow-up, respectively.

ONSET AND REMISSION OF TIC DISORDERS AND ADHD

The average age at onset of tic disorders in probands with ADHD was significantly later than the average age at onset of ADHD (7.1 ± 4.0 vs 2.6 ± 1.8 years, respectively; t₀₁ = 6.9, P < .001; Figure 1, left). In all but 3 cases, ADHD preceded the onset of tic disorders. A Cox proportional hazards model showed that the age at onset of ADHD was similar in children with ADHD with and without a lifetime history of tic disorders (z = 0.43, P > .10). In contrast to an age-adjusted rate of 20% (unadjusted, 19 of 128) of remission of ADHD, the rate of remission of tic disorders was 65% (unadjusted, 24 of 43) (Figure 1, right). In subjects with both tic disorders and ADHD, their tic disorder was more likely to remit than their ADHD (McNemar χ²₁ = 5.8, P < .02). The average age at offset of tic disorders of subjects with ADHD was significantly younger than that at offset of ADHD (12.0 ± 3.6 vs 13.3 ± 3.3 years, respectively; t₀₁ = 3.1, P < .01; Figure 1, right), and offset of tic symptoms was independent of remission of ADHD (z = 0.83, P > .10).

COMORBIDITY AND FUNCTIONAL OUTCOME

No statistically significant differences were detected between subjects with ADHD with and without comorbid tic disorders in any of the multiple outcome measures assessed: psychopathological, cognitive, interpersonal, family, and school functioning (Table). These results were confirmed after reanalyzing the data using the combined sample of probands with ADHD who developed tics at either baseline or follow-up assessments, controlling for age. With the exception of more impaired Global Assessment of Functioning scale scores (t₁₂₅ = 2.5, P < .02; t₁₂₅ = 2.1, P < .04), higher rates of bipolar disorder (z = 2.2, P < .03), and less impaired Moos Family Environment Scale expression scores (t₁₀ₐ = 2.0, P < .05) in subjects with ADHD and tic disorders vs ADHD alone, respectively, no other meaningful differences were detected.

While 114 (89%) of 128 probands with ADHD were exposed to medication at some point during their lifetime (lifetime exposure), only 56 (44%) of 126 were medicated during the 4-year follow-up period of the study (recent exposure). These recently exposed, medicated subjects were treated with stimulants at a mean methylphenidate-equivalent daily dose of 0.8 ± 0.5 mg/kg. Subjects with ADHD without tic disorders were nonsignificantly more likely to be treated with stimulants compared with subjects with ADHD with tic disorders (40 [48%] of 84 vs 16 [38%] of 42, respectively; χ²₁ = 1.0, P = .3). Among children who did not have tic disorder at baseline, interval stimulant treatment (recent exposure) was most common in the ADHD group that was youngest (baseline) (25/36 [69%] aged 6-8 years, 14/37 [38%] aged 9-12 years, 10/31 [32%] aged 13 years or older; χ²₁ = 16, P < .001). However, the rates of new onset of tics were similar (or lower) at each age for subjects with ADHD who were treated with stimulants (tic disorder rates were 32% vs 36% for subjects aged 6-8 years, χ²₁ = 0.43, P = .8; 7% vs 13% for subjects aged 9-12 years, χ²₁ = 0.3, P = .6; 0% vs 19% for subjects aged 13 years or older, χ²₁ [2.2] = 0.1, P > .10; for those treated with stimulants vs those who were not treated, respectively). The rate of onset of tic disorders did not differ by either the presence or absence of lifetime exposure to stimulants (age adjusted, 50% vs 31%; unadjusted, 39 of 114 vs 4 of 14, respectively; z = 0.39, P > .10) or recent exposure to stimulants (age adjusted 32% vs 51%; unadjusted, 16 of 56 vs 26 of 70, respectively, z = 0.54, P > .10) (Figure 2, left). Only 1 stimulant-treated subject with ADHD with a comorbid tic disorder at baseline progressed to TS during the follow-up period. In contrast, although 11 (92%) of the 12 subjects with ADHD with TS at baseline were exposed to stimulants, 9 (75%) had their tic status downgraded to no tics (5 subjects) or to that of a non-TS tic disorder (4 subjects) at follow-up.

COMMENT

In a large, controlled, longitudinal, and naturalistic study of male children and adolescents with ADHD, we found more tic disorders in subjects with ADHD when compared with a control sample of subjects without ADHD. Attention-deficit/hyperactivity disorder and tic disorders had distinct courses, suggesting that the 2 disor-
Figure 2. Top, Age at onset of tic disorders in probands with attention-deficit/hyperactivity disorder (ADHD) who were exposed or not exposed to stimulants during the 4-year follow-up period of the study (n = 56 and n = 70, respectively). Bottom, Age at remission of tic disorders in ADHD probands who were exposed or not exposed to stimulants during the 4-year follow-up period of the study (n = 16, n = 26, respectively).

Of the many comparisons, very few suggested that tic disorders contributed to impairment in children with ADHD—the exceptions were more impaired global functioning scores and higher rates of bipolar disorder. Similar associations between mania and TS have been reported in adults.44-46 Considering its severity, the confirmation of an association between tics and mania may lead to refinements in the treatment of complex patients with tics. Families of children with ADHD and tic disorder showed less impairment in our measure of expressiveness than other families with children with ADHD. This finding was unexpected and may be due to chance. Nevertheless, this finding was consistent with our other results in suggesting that the presence of tics was not associated with worse psychosocial function.

Our results suggest that the treatment of ADHD with stimulants has a limited effect on the course of tics. Because this was a naturalistic study, physicians may have chosen not to use stimulants in children with current or past tic disorders. Although our data show that this did not occur, we must be cautious in drawing conclusions about the putative link between tic exacerbation and stimulants. Recent studies, including short-term, placebo-controlled studies with long-term extensions22,24 and a controlled discontinuation study,27 are beginning to provide more definitive and reassuring data on this issue. However, these studies were not designed to address rates of onset or the course of tic disorders in an ADHD sample unselected for tics. In this regard, our study may be viewed as complementary to these data, providing an indication of the natural course of untreated and treated (or partially treated) tics in an unselected ADHD population.

The findings presented in this report should be evaluated in light of their methodological limitations. The diagnoses of tic disorders and TS were derived from structured diagnostic interviews with the mothers and children aged 12 years or older, not by direct examinations of children. Although this approach may have underestimated the true rate of tics in our study sample, this would not have confounded group comparisons. Moreover, considering the waxing and waning profile of tic disorders and TS, the ability of children to inhibit tics, and the limited ability of children to accurately report a prior history, parental interviews may be quite informative.48,49

Because information on the onset and offset of disorders was retrospective, it may have been vulnerable to recall bias, but should not have confounded group comparisons. As noted, 9 (43%) of 21 of the subjects with ADHD + tic disorder at follow-up reported that the onset of the tic disorder was earlier than their age at baseline. It is likely that mild tics were not reported at the baseline assessment. But, because these worsened over time, they were reported at follow-up and, at that time, their mild manifestations prior to baseline were recalled. Although the average severity of tic disorders in our study was mild to moderate, the average duration of tic disorders was 4 years. In a recent study that investigated the role of tic severity in prevalence bias, 30% of subjects with tic disorders were unaware of tics noted by examiners and only 19% had sought medical care.30 The authors concluded that most cases of TS and chronic motor tics were mild and that tic disorders were much more prevalent than generally appreciated.30

Owing to sample restrictions, our results cannot be generalized to patients with tic disorders who do not have...
ADHD, community samples, females, minorities, or children meeting exclusion criteria.

Because assessments of tic disorders were not independent of that of ADHD at cross-sectional assessments, it is possible that ratings of one disorder were biased by ratings of the other. Such effects are unlikely because: (1) Structured interviews were created to systematize the assessment process in a manner that reduces such biases. Indeed, it is common practice for one rater to assess research participants for several disorders. (2) At the time of assessment we had no a priori hypotheses about the relationship between tic disorders and ADHD.

Despite these limitations, our findings from a large sample of male children and adolescents with ADHD suggest that while tic disorders are overrepresented in ADHD, they have a limited effect on the course of ADHD.

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REFERENCES


