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Predictors of Persistent ADHD: An 11-year Follow-up Study

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Abstract

Objective—Despite the existence of several follow-up studies of children with ADHD followed up into adulthood, there is limited information on whether patterns of persistence and remission in ADHD can be predicted over the long-term. The main aim of this study was to evaluate predictors of persistence of ADHD in a large sample of boys with and without ADHD followed prospectively for 11 years into young adulthood.

Method—Subjects were Caucasian, non-Hispanic boys with (N=110) and without (N=105) ADHD who were 6 to 17 years old at the baseline assessment (mean age 11 years) and 15 to 31 years old at the follow-up assessment (mean age 22 years). Subjects were comprehensively and blindly assessed with structured diagnostic interviews and assessments of cognitive, social, school, and family functioning.

Results—At the 11-year follow-up, 78% of children with ADHD continued to have a full (35%) or a partial persistence (subsyndromal (22%), impaired functioning (15%), or remitted but treated (6%)). Predictors of persistence were severe impairment of ADHD, psychiatric comorbidity, and exposure to maternal psychopathology at baseline.

Conclusions—These findings prospectively confirm that persistence of ADHD over the long term is predictable from psychosocial adversity and psychiatric comorbidity ascertained 11 years earlier.

Keywords

ADHD; persistence; predictors; longitudinal; young adult

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Mr. Carter Petty reports no potential conflicts of interest.

Ms. Allison Clarke reports no potential conflicts of interest.

Ms. Alexandra Lomedico reports no potential conflicts of interest.

In the past year, Dr. Stephen Faraone has received consulting fees and has been on Advisory Boards for Eli Lilly, Ortho-McNeil and Shire Development and has received research support from Eli Lilly, Pfizer, Shire and the National Institutes of Health. In previous years, Dr. Faraone has received consulting fees or has been on Advisory Boards or has been a speaker for the following sources: Shire, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. In previous years he has received research support from Eli Lilly, Shire, Pfizer and the National Institutes of Health.

1. Introduction

Follow-up studies have documented the persistence of attention deficit hyperactivity disorder (ADHD) into adolescence and adulthood (Faraone et al., 2006). The magnitude of this persistence has been inconsistent across studies, ranging from 85% (Barkley et al., 2002; Biederman et al., 1996b) to an almost complete remission by early adulthood (Gittelman et al., 1985; Mannuzza et al., 1988; Mannuzza et al., 1993). Although the reasons for these discrepant results are not entirely clear, one possible explanation is that they could be due to the various methods used to determine diagnostic status (Faraone et al., 2006).

In our previous four-year longitudinal follow-up study of boys with ADHD followed into mid to late adolescent years (Biederman et al., 1996b; Biederman et al., 2000), we showed that patterns of persistence and remission were highly dependent on the definition of remission used, ranging from 60% for syndromatic remission, to 30% for symptomatic remission and only 10% for functional remission (Biederman et al., 2000). These results were recently confirmed in our 11-year follow-up of this sample onto young adult years in which we also found high levels of syndromatic remission but modest levels of symptomatic and functional remission (Biederman et al., 2010). In that study only 20% of the sample attained functional remission without the aid of psychopharmacologic treatment and had an absence of major psychopathology in the past year while the remaining 80% maintained some form of persistence of psychopathology and dysfunction or required continued treatment.

Although these studies clearly documented that ADHD persists in many cases, they provided little information regarding the predictors of persistence. With the exception of a few studies that examined predictors of persistence, there has been a paucity of research on the subject with a narrow focus on largely conduct disorder and symptoms. For example, several studies found that aggression or conduct problems in childhood (Gittelman et al., 1985; Loney et al., 1981; Taylor et al., 1991) predicted persistence of ADHD into adolescence and young adulthood. Hart et al. (1995) reported that the persistence of ADHD at a 4-year follow-up was predicted by hyperactive/impulsive symptoms and by comorbid conduct disorder. However, whether a wider range of risk factors will be predictive of a persistence course onto adult years have not been adequately investigated.

We found a positive association between the risk for ADHD and the number of Rutter's adversity indicators (Biederman et al., 1995c) as well as indices of exposure to parental conflict and parental psychiatric illness, which suggests that adversity may increase the risk for ADHD persisting over time. Also some reports suggested that psychiatric comorbidity was linked to the persistence of ADHD (Gittelman et al., 1985; Hart et al., 1995; Lara et al., 2009). Consistent with this literature, our group identified psychosocial adversity (Biederman et al., 1995c) and patterns of psychiatric comorbidity (Biederman et al., 1992) as important risk factors for persistence of ADHD into adolescence. However, whether these risks factors predict outcome in adulthood is unknown.

A better understanding of predictors of persistence in ADHD over the long term has major clinical, scientific, and public health relevance. Clinically, it may help design appropriate treatment strategies to hasten remission; scientifically, it can help identify more homogeneous subgroups with a higher likelihood of persistent course; from the public health perspective, this knowledge can help focus scarce societal resources toward ADHD children at higher risk for persistent illness.

The main aim of this study was to comprehensively evaluate predictors of persistence of ADHD over the long term attending to issues of adversity, comorbidity, and characteristics of ADHD. To this end we used data from an 11-year longitudinal follow-up family study of

a large sample of comprehensively assessed referred children and adolescents with and without ADHD ascertained from pediatric and psychiatric sources. Based on the literature, we hypothesized that persistence of ADHD would be predicted by comorbidity with conduct, mood, and anxiety disorders, as well as family conflict and exposure to maternal psychopathology.

2. Methods

2.1 Subjects

Detailed study methodology has been previously reported (Biederman et al., 1996a; Biederman et al., 2006). Briefly, subjects were derived from a longitudinal case-control family study of referred youth with and without ADHD. At baseline, we ascertained male Caucasian subjects aged 6–17 years with (N=140) and without (N=120) DSM-III-R ADHD from pediatric and psychiatric clinics. Previously, this sample was followed-up one year and four years after the baseline assessment (Biederman et al., 1996a). Psychiatric assessments relied on the Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic 4th Version (K-SADS-E) (Orvaschel & Puig-Antich, 1987). Diagnoses were based on independent interviews with the mothers and direct interviews with subjects older than twelve years of age. Parents and adult offspring provided written informed consent to participate, and parents also provided consent for offspring under the age of 18. Children and adolescents provided written assent to participate. The human research committee at Massachusetts General Hospital approved this study.

2.2 Follow-up Assessment Procedures

The present study reports on the 11-year follow up of this sample (mean follow-up 11 years; range: 9–14 years), where 112 ADHD and 105 control probands were successfully re-ascertained. Psychiatric assessments at the 11-year follow-up relied on the DSM-IV based K-SADS-E-IV (Epidemiologic Version) assessing DSM-IV disorders (Orvaschel, 1994) for subjects < 18 years of age and the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997) (supplemented with modules from the K-SADS-E to assess childhood diagnoses) for subjects 18 years of age and older. We conducted direct interviews with subjects and indirect interviews about subjects with their mothers (i.e., mothers completed the interview about their offspring). Of the 217 subjects interviewed, the proportion that provided direct only, indirect only and both types of reports were 22%, 17%, and 62%, respectively. We combined data from direct and indirect interviews by considering a diagnostic criterion positive if it was endorsed in either interview.

First-degree relatives of these probands included mothers (N=217), fathers (N=216), and siblings (N=243). Parents received direct interviews and siblings received an indirect interview if they were younger than 12 years of age, and both an indirect and a direct interview if between 12 and 17 years of age, and a direct interview if 18 years of age and older.

The interviewers were blind to the subject's baseline ascertainment group, the ascertainment site, and all prior assessments. The interviewers had undergraduate degrees in psychology and were extensively trained and supervised. First, they underwent several weeks of classroom style training, learning interview mechanics, diagnostic criteria and coding algorithms. Then, they observed interviews by experienced raters and clinicians. They subsequently conducted at least six practice (non-study) interviews and at least three study interviews while being observed by senior interviewers. The principal investigator (JB) supervised the interviewers throughout the study. We computed kappa coefficients of agreement by having experienced, board certified child and adult psychiatrists and licensed

clinical psychologists diagnose subjects from audio taped interviews. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was .98. Kappa coefficients for individual diagnoses included: ADHD (0.88), conduct disorder (1.0), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (.95), substance use disorder (1.0), and tics/Tourette's (0.89).

A committee of board-certified child and adult psychiatrists who were blind to the subject's ADHD status, referral source, and all other data resolved diagnostic uncertainties. Uncertainties arose in a minority of comorbid disorders and never for ADHD. Diagnoses presented for review were considered positive only when the committee determined that diagnostic criteria were met to a clinically meaningful degree. We estimated the reliability of the diagnostic review process by computing kappa coefficients of agreement for clinician reviewers. For these diagnoses, the median reliability between individual clinicians and the review committee assigned diagnoses was 0.87. Kappa coefficients for individual diagnoses included: ADHD (1.0), conduct disorder (1.0), major depression (1.0), bipolar (0.78), separation anxiety (0.89), agoraphobia (0.80), panic (0.77), substance use disorder (1.0), and tics/Tourette's (0.68).

As a measure of overall functioning, we used the Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000), a summary score assigned by the interviewers based on information gathered during the diagnostic structured interview. Socioeconomic status (SES) was measured using the 5-point Hollingshead scale (Hollingshead, 1975). Low socioeconomic status was defined as subjects with a 3 or 4 on this scale at baseline (no subjects had a 5, the lowest SES). Additionally, questions regarding family intactness (parents married living together versus divorced/separated), academic functioning (tutoring, repeated grades, placement in a special class), and treatment history were asked during the interview.

Cognitive function was assessed with the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974). Following Sattler (Sattler, 1988), Full Scale IQ was estimated using the vocabulary and block design subtests. The Child Behavior Checklist (CBCL) (Achenbach, 1991) provided dimensional measures of child syndromes.

Exposure to maternal psychopathology was defined as the mother having at least two psychiatric disorders (any disorders assessed by the SCID) during the child's lifetime (up until the baseline assessment). Family conflict was defined using the Moos Family Environment Scale (Moos & Moos, 1974). We combined the three measures of family relationships (cohesion, expressiveness, and conflict) to generate a binary indicator of familial conflict. Details of this procedure have been described previously (Biederman et al., 1995c).

2.3 Statistical Analysis

Consistent with our previous work (Biederman et al., 2000), we defined the following mutually exclusive categories of persistence: a) subjects meeting full DSM-IV criteria for ADHD ("Syndromatic Persistence"), b) subjects meeting subthreshold DSM-IV criteria (more than half of the symptoms required for a full diagnosis, "Symptomatic Persistence"), c) subjects not meeting criteria (a) or (b) who were functionally impaired with a GAF score ≤ 60 ("Functional Persistence"), and d) subjects not meeting criteria (a), (b) or (c) who were receiving pharmacotherapy for ADHD ("Medicated") in the month prior to the subject's 11-year follow-up assessment.

To predict persistent ADHD, comparisons of baseline data were made between subjects with persistent ADHD, partially remitted ADHD, and fully remitted ADHD using logistic, linear,

and negative binomial regression, depending on the distribution of the outcome. The presence of cohort effects (e.g., differences due to age at enrollment) could be misinterpreted as developmental effects. To address this, we included age at follow-up as a covariate in all statistical models. All tests were two-tailed and alpha was set at 0.05.

3. Results

Of the 140 ADHD and 120 control subjects recruited at baseline, 112 (80%) and 105 (88%), respectively, were re-assessed at the 11-year follow-up. The rate of successful follow-up did not differ between groups ($p=0.11$). The average follow-up time was 11.2 years ($SD=0.9$ years); ages at follow-up ranged from 15 to 31 years (mean=22.2, $SD=3.7$, 90% were 18 years of age or older). There were no significant differences between those successfully followed up and those lost to follow-up on age, GAF score, family intactness, ascertainment source, or psychiatric outcomes. At the 11-year follow-up, 2 of the 112 ADHD subjects could not be analyzed due to missing diagnostic data. Of the remaining 110 ADHD subjects, 39 (35%) had Syndromatic Persistence, 24 (22%) had Symptomatic Persistence, 16 (15%) had Functional Persistence, 7 (6%) were not symptomatic, syndromatic, or functionally impaired but were medicated for ADHD, and 24 (22%) were fully remitted. Therefore, 78% (86/110) of ADHD subjects showed some evidence of persistence. Using only ADHD subjects who had reached adulthood (at least 18 years of age), 76% (76/100) met one of our definitions of persistence.

3.1 Sociodemographic Characteristics

Comparisons were made between non-ADHD subjects (Controls, $N=105$), ADHD subjects with syndromatic persistence, symptomatic persistence, functional persistence, or medicated (Persistent ADHD, $N=86$), and ADHD subjects who fully remitted (Remittent ADHD, $N=24$). Because the Persistent ADHD group was somewhat younger in age compared to the other two groups, all subsequent analyses were adjusted by age. The Controls had a significantly lower rate of being recruited from the MGH ascertainment source compared to the Persistent ADHD group. Therefore, all analyses involving Controls controlled for ascertainment source. The groups did not significantly differ on baseline family socioeconomic status or rate of intactness of the family (Table 1).

3.2 Characteristics of ADHD

The Persistent ADHD group had a significantly higher rate of ADHD-associated moderate/severe impairment at baseline compared to the Remittent ADHD group (Table 2). No other characteristics of ADHD were significantly associated with persistent or remittent ADHD.

3.3 Comorbid Psychopathology

As shown in Figure 1, Persistent ADHD was associated with a significantly higher rate of oppositional defiant disorder (ODD), conduct disorder (CD), and multiple (≥ 2) anxiety disorders at baseline compared to the Remittent ADHD group. Both ADHD groups had significantly higher rates of ODD and major depressive disorder at baseline compared to Controls. However, only the Persistent ADHD group had significantly higher rates of bipolar disorder compared to the Controls.

Examination of baseline CBCL findings revealed that the Persistent ADHD group had significantly higher T-scores at baseline on the Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior subscales of the CBCL compared to the Remittent ADHD group (Figure 2). Both ADHD groups had significantly higher Anxious/Depressed, Social Problems, Attention, Delinquent, and Aggressive T-scores at baseline compared to the Controls. However, only the Persistent ADHD group had

significantly higher Withdrawn, Somatization, and Thought Problems T-scores at baseline compared to the Controls.

3.4 Functional Correlates

Both ADHD groups had significantly higher rates of repeated grade, placement in a special class, tutoring, and learning disabilities at baseline compared to Controls (Figure 3A). The Persistent ADHD group had a significantly higher rate of exposure to maternal psychopathology compared to the Controls (Figure 3B). Both ADHD groups had significantly (all $p < 0.05$) lower full scale IQ (Controls = 118.8 ± 10.3 ; Remittent ADHD = 111.3 ± 12.3 , Persistent ADHD = 109.8 ± 13.8), arithmetic (Controls = 12.5 ± 2.8 ; Remittent ADHD = 10.9 ± 3.2 , Persistent ADHD = 10.8 ± 3.3), and digit span (Controls = 10.7 ± 2.8 ; Remittent ADHD = 9.1 ± 2.7 , Persistent ADHD = 9.2 ± 3.0) at baseline compared to the Controls. Finally, the Persistent ADHD group had a significantly ($p < 0.001$) lower digit symbol score at baseline compared to the Controls (Controls = 11.8 ± 2.7 ; Remittent ADHD = 11.0 ± 3.2 , Persistent ADHD = 9.8 ± 3.6).

4. Discussion

Using a prospective longitudinal design, comprehensive measures, and blind assessments, our 11-year follow-up found that impairment caused by ADHD, exposure to maternal psychopathology, and psychiatric comorbidity with oppositional defiant, conduct, bipolar, and anxiety disorders at baseline were significant predictors of a persistent course of ADHD independent of age at follow-up assessment. The number or type of ADHD symptoms at baseline did not differentiate patients with persistent and remittent ADHD. These findings confirm and extend previous work documenting that ADHD is a highly persistent disorder (Barkley et al., 1990; Gittelman et al., 1985; Hart et al., 1995; Lambert et al., 1987; Weiss et al., 1985) and that patterns of persistence and remission can be predicted over the long term into young adult life.

Consistent with our prior work into adolescence (Biederman et al., 1996b) is the finding that psychiatric comorbidity predicted a persistent course of ADHD over the long term. Persistent ADHD probands differed from remitting probands in their higher rates of comorbid disruptive behavior (conduct and oppositional defiant disorder), mood (bipolar disorder), and anxiety disorders. Prior work (Gittelman et al., 1985; Loney et al., 1981; Taylor et al., 1991) showed conduct/aggressive symptoms predicted persistence of ADHD. Hart et al. (1995) also reported that the persistence of ADHD at a 4-year follow-up was predicted by comorbid conduct disorder. Most recently, in an 8-year prospective follow-up of children with ADHD, Molina et al. (2009) showed that conduct problems were significantly associated with later adolescent functioning, including persistent ADHD symptoms. We have replicated these findings and extended them to include mood and anxiety disorders as predictors of persistence. The high level of psychiatric comorbidity in persistent cases of ADHD is consistent with findings reported in adults with ADHD (Biederman et al., 1995b; Biederman et al., 1994). Thus, our results indicate that psychiatric comorbidity in ADHD probands predicts not only more impaired outcome (Biederman et al., 2010) but also persistence of the disorder over time. These results highlight the importance of early recognition of psychiatric comorbid disorders for prevention and early intervention strategies in children with ADHD. Because the predictive value of baseline psychopathology was also seen for CBCL scale scores, our findings regarding psychiatric comorbidity cannot be attributed to reverse halo effects or other potential interviewer biases.

Our finding that impairment of ADHD at baseline predicted persistence is consistent with Lara and colleagues' (2009) retrospective findings that high ADHD impairment in childhood predicted adult persistence. It is also consistent with Molina et al.'s (2009)

longitudinal findings that severity of ADHD symptoms predicted later adolescent functioning, including ADHD symptoms at follow-up. Consistent with our previous work (Biederman et al., 1995a; Seidman et al., 1995), we also found that exposure to maternal psychopathology was a predictor of persistence of ADHD. Taken together, these findings stress the importance of familial factors, either genetic or psychosocial, as risks for persistence of ADHD. Our previous findings from this 11-year follow-up showed that persistence of ADHD was associated with a family history of mood disorders (Biederman et al., 2010). This is partially consistent with findings by Lara et al. (2009), who found that persistence of ADHD was associated with paternal (but not maternal) anxiety or mood disorders. Recent genetic findings suggest that DRD4 (Biederman et al., 2009) and DAT1 (Franke et al., 2009) may influence the persistence of ADHD.

Our treatment history findings revealed no significant associations between persistence or remission and intensity of treatment. This indicates that treatment at baseline did not account for the patterns of persistence and remission observed. This is consistent with the longitudinal findings of Molina et al. (2009) and retrospective findings of Lara et al. (2009).

The question of whether a given child with ADHD will have a persistent illness is of great clinical importance. Although there were some differences in the profile of ADHD symptoms between persistent and non-persistent cases, these differences were not dramatic. In contrast, impairment, adversity, and comorbidity predicted persistence or late remission. Children who have none of these risk factors may have a relatively good prognosis. Further work needs to address whether the predictive validity of these domains extends into later adulthood.

Our results must be interpreted in the context of methodological limitation. Because of the many variables examined in our analyses, some of our findings may reflect type I errors due to the multiple tests performed. Although we included both psychiatrically and pediatrically referred samples, we do not know to what degree our findings will generalize to non-referred children with ADHD in the community. In addition, the current study included only Caucasian male probands. Thus, we do not know whether our findings can be generalized to female or non-white subjects. In addition, although raters were blind to the diagnosis of the probands, parents were not.

Despite these limitations, in a large sample of children with ADHD grown up, ascertained from pediatric and psychiatric facilities, we have shown that, persistence of ADHD was predicted by impairment of ADHD, adversity, and comorbidity with antisocial, mood, and anxiety disorders. These findings should help parents and families in forecasting the course of the disorders and help develop appropriate intervention programs aimed at reducing the risk for a persistent course.

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Figure 1.
Comorbid disorders at baseline.
A=vs. Controls, B=vs. Remittent ADHD; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Figure 2.

CBCL at baseline.

A=vs. Controls, B=vs. Remittent ADHD; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Figure 3.
School functioning and psychosocial adversity at baseline.
A=vs. Controls, B=vs. Remittent ADHD; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table 1

Sociodemographic characteristics at baseline.

	Controls (N=105)	Remittent ADHD (N=24)	Persistent ADHD (N=86)	Test Statistic	P-VALUE
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		
Age (years)	11.5 $\pm$ 3.7	12.1 $\pm$ 3.0	10.2 $\pm$ 2.9 ^{ab**}	F _(2,212) =5.28	0.006
Socioeconomic status	1.4 $\pm$ 0.7	1.8 $\pm$ 1.0	1.7 $\pm$ 0.9	$\chi^2_{(2)}$ =4.79	0.09
	N (%)	N (%)	N (%)		
Intact family	87 (83)	18 (75)	61 (71)	$\chi^2_{(2)}$ =3.90	0.14
Ascertainment status (psychiatric)	30 (29)	11 (46)	47 (55) ^{****}	$\chi^2_{(2)}$ =13.57	0.001

Table 2

ADHD characteristics at baseline

	Remittent ADHD (N=24)	Persistent ADHD (N=86)	Test Statistic	P-VALUE
	Mean $\pm$ SD	Mean $\pm$ SD		
Age of onset	2.8 $\pm$ 2.5	2.6 $\pm$ 1.9	$t_{(107)}=-0.19$	0.85
Symptoms				
Total symptoms	10.7 $\pm$ 2.0	11.7 $\pm$ 1.9	$z=1.24$	0.22
Inattentive symptoms	5.1 $\pm$ 0.9	5.4 $\pm$ 0.9	$z=0.52$	0.60
Hyperactive-impulsive symptoms	5.6 $\pm$ 1.8	6.3 $\pm$ 1.5	$z=1.21$	0.23
	N (%)	N (%)		
Impairment				
Moderate/severe impairment	19 (79)	84 (98)	$z=2.37$	0.02
Severe impairment	8 (33)	54 (63)	$z=2.10$	0.04
Treatment				
Counseling	3 (12)	5 (6)	$z=-0.93$	0.35
Medication	7 (29)	23 (27)	$z=0.21$	0.83
Counseling + Medication	11 (46)	49 (57)	$z=0.48$	0.63
Age of treatment onset (mean $\pm$ SD)	2.8 $\pm$ 2.5	2.6 $\pm$ 1.9	$t_{(73)}=-0.06$	0.95