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ORIGINAL ARTICLE

Anxiety and methylphenidate in attention deficit hyperactivity disorder: a double-blind placebo-drug trial

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Abstract To examine the relationship between attention and anxiety and the response to methylphenidate in children with attention deficit hyperactivity disorder (ADHD), a total of 57 boys, between the ages of 7–12 years, were assessed for their attention and level of anxiety. Methylphenidate was administered for a week in a randomized double-blind drug/placebo–drug cross-over design. The levels of anxiety were evenly distributed between the inattentive and hyperactive/impulsive types. Anxiety was significantly correlated with the attention as reported by both teachers and parents. The response to methylphenidate was inversely correlated with the reported anxiety level only in boys with the hyperactive/impulsive and combined types. The higher the level of anxiety, the lower level of response to methylphenidate was observed. In the assessment and treatment of children with ADHD, the level of anxiety should be evaluated and taken into account while planning and monitoring treatment regiment.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral condition that causes significant impairment in childhood. It is often associated with a variety of other neurobehavioral deficits (Pliszka 1998; Hechtman et al. 2004).

Epidemiological studies show that up to one-third of the children diagnosed with ADHD would also manifest associated anxiety disorder (Pliszka 1998; Biederman et al. 1991; Angold et al. 1999; March et al. 2000; Pliszka 1992; Spencer et al. 1999; Spencer 2006). The possible effects of anxiety on ADHD have been discussed (March et al. 2000; Livingstone et al. 1992). An increased prevalence of moderate anxiety but not necessarily at the level warranting a clinical diagnosis of a disorder was also reported in children with ADHD (Gray 1987; Kellogg et al. 1999). However, the specific type of ADHD has not always been accounted for (Bedard and Tannock 2008; Tannock et al. 1995). A few reports have suggested that children with attention deficit without hyperactivity are more prone to show anxiety as compared to hyperactive/impulsive children (Lahey et al. 1988; Eiraldi et al. 1997). Others, however, have found no clear relationship between the ADHD subtypes and the prevalence of anxiety (Volk et al. 2005). The relationship between childhood anxiety and information processing has been previously discussed (Daleiden and Vasey 1997). The increased level of distractibility observed among children with anxiety as reported in this review as well as the differential activation of cognitive processes and attentional brain areas as related

to anxiety, evident in functional neuroimaging studies (Etkin et al. 2004), is of particular relevance. Once primary anxiety disorder is diagnosed, treatment approach should be appropriately tailored and the diagnosis of ADHD as well as the subsequent treatment carefully considered. However, a proportion of the children with ADHD present with a lower anxiety threshold yet fail to meet the diagnosis of a full-blown anxiety disorder. The consensus statements of both the American Academy of Pediatrics (Brown et al. 2005) and the American Academy of Child and Adolescence Psychiatry (AACAP 2007) advocate for the use of stimulants as the first-line pharmacological treatment.

The results of studies addressing the response of anxious children with ADHD to methylphenidate are mixed (March et al. 2000; Tannock et al. 1995; Adler et al. 2007; Abikoff et al. 2005; Pliszka 1989). These studies, like the approach adopted in the present study, also relate to the full spectrum of anxiety rather than to the categorical definition of a disorder. However, the criteria employed for the assessment of anxiety differ between studies.

A recent study focusing on the measures of attention in children with ADHD reported a worsening of the global ADHD score following the administration of methylphenidate in children with associated anxiety (Goez et al. 2007). Lack of methylphenidate benefit related to the neurocognitive aspects as well as an early decline in the behavioral effect of the medication in children with ADHD and anxiety was described (Tannock et al. 1995). Conversely other studies reported no significant effect of anxiety on the behavioral response to methylphenidate, as perceived by children with ADHD and their parents (Eiraldi et al. 1997; Abikoff et al. 2005; Diamond et al. 1999). Differences in results are possibly accounted for by differences in methodology. While the study by Tannock et al. (1995) compared two groups of children with and without anxiety, other studies, for example by Abikoff et al. (2005), compared anxiety among a selected group of children who following stimulants administration showed ADHD and anxiety and were randomized to treatment with stimulants and treatment with stimulants and fluvoxamine to reduced anxiety. These previous studies included children with a diagnosed anxiety disorder and treated ADHD as a unitary diagnosis. The present study, employing non-restrictive criteria of anxiety, thus allowing for a spectrum of severity, and a double-blind design aimed to focus specifically on anxiety as a modifier of the behavioral as well as the cognitive response elicited by methylphenidate in children with ADHD.

We hypothesized that children with ADHD and anxiety would differ from their peers with ADHD without anxiety, in measures of reported attention. We also hypothesized that increased anxiety would be related to a less than optimal response to methylphenidate both in the class observations and test of attention, and this effect would be related to the type of ADHD.

Methods

Subjects

Consecutively referred boys between the ages of 7–12 years (*M* 9.5 years, 1.5 SD) diagnosed with ADHD according to (DSM-IV) criteria (American Psychiatric Association 1994) were included. Since the proportion of boys with ADHD is about four times more than that of girls and controlling for gender would have required a much larger sample size, we included only boys in our investigation. Children with other chronic psychiatric and neurological disorders, for example, obsessive compulsive disorders, Tourette syndrome, seizure disorder, severe learning disability, (defined by special education enrollment), a definitive primary diagnosis of an anxiety disorder (DSM-IV) or sensory impairment, were not included in the study. Only children who were drug naïve with no other intervention and who were found as suitable candidates for methylphenidate treatment were included in the study. We recruited only children who met the following inclusion criteria: The attention disorder was associated with a significant effect on their daily life, and the scores on one of the attention subscales of both parent and teacher questionnaires were 1.5 SD or above the mean as suggested in clinical guidelines. Following the initial evaluation of 78 boys, employing the above criteria, fifty-seven were found suitable to participate in the study. Out of the 57 boys, 47 % had ADHD-inattentive type and 53 % had ADHD of the hyperactive/impulsive and combined type (DSM-IV). The children were from families representing all socioeconomic strata. All parents and children gave their consent to participate in the study, and the study was approved by the Helsinki Committee of the Bnai Zion Medical Center.

Procedure

Each child and his parents underwent a comprehensive interview related to past medical history including psychiatric aspects. A developmental and emotional/behavioral history of the child and parents was obtained, and parents and teachers were required to complete a set of questionnaires. A complete physical and neurological examination was undertaken, including evaluations of hearing, vision, attention, and emotional state. Following the diagnosis of ADHD, the child and parents were offered a double-blind placebo-drug, cross-over trial (a week long

each) with methylphenidate and all gave their signed consent. The procedure is according to the standard clinical practice at our center for each child who is a candidate for treatment with methylphenidate (Tirosh et al. 1993). Following each week of treatment using a table of random numbers, either drug (0.3 mg/kg/IR methylphenidate, once daily, ranging 6–12 mg.) or placebo (prepared as look—alike capsules by the hospital pharmacy), administered in a balanced order, the children were interviewed and reassessed for their attention and the teachers' questionnaires were obtained.

Instruments

The Conners Parents Rating Scale (CPRS) (Goyette et al. 1978) was completed by the parents prior to the first assessment. The sex and age adjusted scale is divided into six subscales: Conduct, Learning, Psychosomatic, Hyperactive/impulsive, Anxiety, and Hyperactivity index. The raw score of each scale was converted into T score. A score of 1.5 SD or above was considered significant (Carter and Syed-Sabir 2008). The anxiety subscale of the CPRS was found to be well correlated with other measures of anxiety in children with a chronic disorder (Vila et al. 1999). This subscale was previously shown to be most significantly different between children with ADHD who were treated with MPH when compared to dexamphetamine (Efron et al. 1997).

The Conners Teacher Rating Scale (CTRS) (Goyette et al. 1978) was provided by the teachers prior to the first assessment. This age- and sex-adjusted scale is divided into four subscales: Conduct, Hyperactive/impulsive, Inattentive, and Hyperactivity index. The raw score of each scale was converted into T score, and a score of 1.5 SD or above was considered significant. The anxiety subscale of the ANSER-P system (Levine 1992) has been previously validated for children with ADHD (Schmidt et al. 2000) and has recently been revalidated among Israeli children with ADHD and learning disabilities (Or et al. 2010). This 13-item scale includes items such as "has difficulty falling asleep or staying asleep at night, or is a restless sleeper," "is a worrier", "is fearful of being alone", "often has headaches." This scale was administered to cover externalizing symptoms not addressed by the Conners' anxiety subscale. Anxiety was determined if a score above the group mean of 5.1 was obtained.

The Matching Familiar Figure Test (MFFT) (Kagan 1965) consists of 12 stimuli pictures. Two age- and sex-adjusted T scores were derived: 1. Error rate (the number of error made out of 60 total possible incorrect responses) and 2. Mean latency (the mean time elapsed from the time of exposure to the first response). This test qualifies the degree of reflection/impulsivity typical to cognitive styles of children with attention deficit.

Statistical analysis

For the analysis of anxiety prevalence in the two ADHD types, using the parent's questionnaires, Fisher's exact test was employed. The level of anxiety between the groups was compared using the t test for independent samples. Pearson correlation was employed for the analysis of the association between the anxiety score and the response to methylphenidate as measured with the teacher's questionnaire and the attention test. The difference between the drug and placebo scores was adjusted for the baseline score obtained at the initial assessment. The attention test scores obtained in the different phases of the study were also analyzed using the ANOVA for repeated measures. The Bonferroni correction for multiple comparisons was employed. Cohen's d was used to estimate effect size. A sample of 45 participants is required, with an anticipated effect size (ES) of 0.3, statistical power of 0.95, and an alpha of 0.05.

Results

The scores of the CTRS subscales and age distribution were not different between the two ADHD types at the initial assessment (Table 1). The degree of anxiety as measured by both parents' questionnaires was also evenly distributed among the children of the different ADHD types at the initial assessment (Table 2). Employing a cut-off score of both measures of anxiety revealed no significant differences in the proportion of children with anxiety in the different ADHD subtypes (Table 2). A significant correlation between the level of anxiety as reported by the parents and both poor learning—attention scores as reported by parents ($r = 0.43$, $P < 0.05$) and inattentive—passive as reported by teachers ($r = 0.43$, $P < 0.05$) was

Table 1 The mean (SD) of the age and CTRS subscales as related to the ADHD group

	ADHD type	
	AD	HI + combined
Age	9.4 (1.5)	9.6 (1.4)
CTRS-A	66.5 (12.6)	67.8 (13.4)
CTRS-B	65.0 (11.5)	70.0 (10.2)
CTRS-C	63.5 (8.4)	62.0 (9.3)
CTRS-D	70.5 (8.9)	71.4 (7.8)

There were no statistically significant differences between the two groups

ADHD attention deficit hyperactivity disorder, *AD* inattentive, *HI* hyperactive/impulsive, *CTRS* Conners Teacher Rating Scale, *A* conduct, *B* hyperactivity, *C* inattentive passive, *D* hyperactivity index

Table 2 Level and rates of anxiety as measured by the two parents' questionnaires in the two ADHD types and the respective percentage of anxious children

Anxiety	ADHD type	
	AD Mean (SD)	HI + combined Mean (SD)
CPRS	54.3 (10.9)	51.9 (10.7)
Score ≥ 1.5 SD	6.0 (22 %)	3.0 (10 %)
ANSER	4.7 (2.5)	5.4 (3.1)
Score > 5	11 (44 %)	12 (44.4 %)

ADHD attention deficit hyperactivity disorder, *CPRS* Conners Parents Rating Scale, *AD* inattentive, *HI* hyperactive/impulsive, *ANSER* aggregate neurobehavioral student health and educational review

Table 3 The CTRS subscales' mean (SD) a related to the study phase

	Hyperactivity	Inattentive passive	HA index
Baseline (BL)	67.6 (11.0)[a]	62.7 (8.8)[b]	62.7 (8.8)[c]
Placebo (P)	65.2 (9.9)[a]	60.5 (9.5)[b]	60.5 (9.5)[c]
MPH	55.2 (9.9)[a]	55.4 (8.8)[b]	55.4 (8.8)[c]

ANOVA for repeated measures

CTRS Conners Teacher Rating Scale, *HA* hyperactivity, *MPH* methylphenidate

[a] BL > *P* > MPH, $F = 20.0$, $P < 0.001$

[b] BL = *P* > MPH, $F = 12.8$, $P < 0.001$

[c] BL = *P* > MPH, $F = 21.0$, $P < 0.001$

found exclusively among children with ADHD-inattentive type.

A significant response to methylphenidate as compared to placebo for all the children was found in both teachers' scales of hyperactivity/impulsivity and inattention (however, with a low effect size (0.15 for both) (Table 3). No significant correlation between the level of anxiety and the response to methylphenidate as compared to placebo was evident in the whole cohort. However, in the children with hyperactive/impulsive and combined subtypes, increased anxiety scores were associated with a decreased response to methylphenidate as compared to placebo. Thus, there was a significant negative correlation between the level of anxiety as measured with the Conners anxiety subscale and the teachers' scores of the hyperactivity index, in response to MPH among children with ADHD of the hyperactive and combined type ($r = -0.48$, $P < 0.001$). Following Bonferroni correction for multiple comparisons, this result remained significant.

Methylphenidate administration was associated with a significant decrease in error rate in the attention test in the whole cohort. (F 4.66, $P < 0.05$, ES 0.35). The analysis of the correlation obtained at each stage, between the level of reported anxiety and the attention test latency as well as error score for the whole group, revealed no methylphenidate effect. Yet, once the type of ADHD was controlled for, the correlation was found significant for the attention test latency in children with ADHD-inattentive type only ($r = 0.4$, $P < 0.05$). Anxious children with ADHD of the inattentive type decreased their response time while being on methylphenidate as compared to placebo. No similar significant effect of methylphenidate on error rate was noted.

Discussion

Our first hypothesis related to the correlation between level of anxiety and attention as observed by parents and teachers has been substantiated. It should be noted that although anxiety was reported by parents and thus a within observer bias could have been expected, this correlation held true for teachers observations also. In both measures, the factor related to attention and not hyperactivity/impulsivity was noted to be correlated with anxiety. This finding is in line with previous observations suggesting a specific relationship between anxiety and ADHD-inattentive type (Lahey et al. 1988; Eiraldi et al. 1997; Biederman et al. 2001). Others, however, found no relationship between anxiety and ADHD type in clinical subjects (Power et al. 2004; Ghanizadeh 2008). Similarly, no difference between the rate of anxiety in the two ADHD types was found in the present research. These discrepant results might stem from different populations under study (clinical versus population samples) and different definitions of anxiety. It appears that the employment of anxiety as a continuum rather than as a categorical variable and focusing on children with symptoms of anxiety but not a defined anxiety disorder contributes to the variance between the studies results.

Not in line with our second hypothesis, a reduced observed response to methylphenidate in anxious boys with ADHD hyperactive/impulsive and combined type suggests that at least some of the symptomatology in these children could possibly be attributed to anxiety rather than attention deficit. Therefore, the possible role of anxiety as contributing to both suboptimal response of attention as well as hyperactivity/impulsivity to stimulants in children with this type of ADHD should be entertained. (Spencer 2006). This finding is in contradiction to previous findings relating reduced response to methylphenidate predominantly among children with internalizing symptoms more typical of the inattentive type (Abikoff et al. 2005; Pliszka 1989; Diamond et al. 1999; DuPaul et al. 1994). A different methodology including diagnostic definition, instruments and population source as well as the differentiation of the type of ADHD might contribute to this discrepancy.

Notwithstanding, the findings of a proportionate true comorbidity of anxiety (rather than an overlapping artifact) in children with ADHD (Milberger et al. 1995) the possible misdiagnosis of anxiety symptomatology as attention related has been emphasized (Spencer 2006; Adler et al. 2007).

The effect of methylphenidate on the latency score of children with ADHD-inattentive type as related to their anxiety suggests acceleration while on the drug. This effect was not associated with an increase in error rate. This finding is in contrast to previous findings of lack of effect of methylphenidate on executive functions in children with ADHD and anxiety as compared to the improvement observed in non-anxious peers (Tannock et al. 1995). A recent study compared the results of the global score of the test of attention while on methylphenidate, demonstrating a significant disadvantage to children with anxiety when compared to their peers with ADHD only. However, no reference to the type of ADHD was reported (Goez et al. 2007). It appears therefore that a favorable change in latency among children with ADHD and anxiety is specifically related to ADHD-inattentive type.

The two findings of the relationship between level of anxiety and behavioral as well as cognitive response to methylphenidate in children with ADHD-inattentive type and not in children with the hyperactive/impulsive and combined types are complementary.

The results of the present study should be interpreted with caution. Since only boys were included, the results might not be valid for girls. The children were clinic referrals and therefore might not be representative of the population of children with ADHD at large. Furthermore, children with diagnosed severe anxiety as a primary diagnosis were not included in the study. The instruments employed were those commonly used in clinical practice for children with suspected ADHD and not designed specifically for children with an anxiety disorder. However, the use of these instruments contributes to the clinical applicability of our results. The present investigation extended over a 2-week trial only, and it is not inconceivable that a longer follow-up would have revealed a different effect of methylphenidate on attention as related to anxiety.

In conclusion, our study suggests that in children with ADHD inattention as reported by parents and teachers is related to the level of reported anxiety. Furthermore, cognitive and behavioral responses to methylphenidate are influenced to a degree by the level of anxiety in the individual. This relationship appears to be of particular relevance in children with ADHD of the hyperactive/impulsive and combined type. This group possibly derives less benefit from methylphenidate treatment as compared to their peers with ADHD-inattentive type with associated anxiety. Consequently, physicians following children treated with stimulants should take into account the anxiety status of their patients and tailor their treatment accordingly. Addressing the anxiety with a non-medical intervention along side the use of stimulants or alternatively examining the benefits of non-stimulant medication should be entertained. Future studies investigating drug effects in children with ADHD should relate to the type of the disorder in their analysis.

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