RESEARCH ARTICLE

Efficacy of Methylphenidate in ADHD Children across the Normal and the Gifted Intellectual Spectrum

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Abstract

Objective: This study evaluates whether attention-deficit/hyperactivity disorder (ADHD) children with a borderline intelligence quotient (IQ) (70≤FSIQ<80), normal IQ (80≤FSIQ<120) and high IQ (FSIQ≥120) respond differently to psychostimulant treatment. **Method:** 502 children, aged 6 to 12 years, with an IQ range from 70 to 150 participated in a two-week, double-blind, placebo-controlled, crossover methylphenidate (MPH) trial. **Results:** In addition to differences in socioeconomic background and parental education, higher IQ children were found to present with less severe symptoms. No significant differences were found with regards to treatment response. **Conclusion:** ADHD children within the normal and high levels of intellectual functioning all respond equally to psychostimulant treatment, and that proper medication management is necessary for all children with the disorder.

Key words: *ADHD, IQ, methylphenidate response*

Résumé

Objectif: Cette étude évalue si les enfants souffrant du trouble du déficit de l'attention avec ou sans hyperactivité (TDAH) et ayant un quotient intellectuel (QI) limite (70≤QI global<80), normal (80≤QI global<120) et élevé (QI global≥120) répondent différemment à un traitement par psychostimulant. **Méthode:** Cinq cent deux enfants de 6 à 12 ans, dont le QI variait entre 70 et 150, ont participé à un essai à double insu, contre placebo, croisé, sur deux semaines de méthylphénidate (MPH). **Résultats:** Outre les différences de statut socioéconomique et de niveau d'instruction des parents, il a été observé que les enfants ayant un QI élevé présentaient des symptômes moins graves. Aucunes différences significatives n'ont été constatées en ce qui concerne la réponse au traitement. **Conclusion:** Les enfants souffrant du TDAH qui se trouvent aux niveaux normaux et élevés du fonctionnement intellectuel répondent tous également au traitement par psychostimulant, et une bonne gestion de la pharmacothérapie est nécessaire pour tous les enfants souffrant de ce trouble.

Mots clés: *TDAH, QI, réponse au méthylphénidate*

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric behavioral disorder that presents with the core deficits of inattention, impulsivity and hyperactivity and often leads to significant impairments in school and overall functioning. The use of stimulant drugs, such as methylphenidate (MPH) is only efficacious in 70% of ADHD patients (Spencer et al., 1996). It is therefore important to differentiate between responders and non-responders to stimulants.

There are conflicting reports in the present literature as to the effects of intellectual functioning on stimulant treatment

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Submitted: August 31, 2011; Accepted: May 25, 2012

Clinical Trials Registry: Clinical and Pharmacogenetic Study of Attention-Deficit/ Hyperactivity Disorder.
Trial Registration: ClinicalTrials.gov NCT00483106

response in children who function within the normal intellectual spectrum. The relationship of intelligence to responder status has been reviewed to be inexistent or at most minimal (Gray & Kagan, 2000). Some studies have failed to demonstrate significant intelligence quotient (IQ) differences between responders and non-responders to MPH (Mayes, Crites, Bixler, Humphrey, & Mattison, 1994; Zeiner, Bryhn, Bjercke, Truyen, & Strand, 1999). However, the small sample sizes and absence of parental evaluation of outcome in Mayes et al.'s study and lack of objective laboratory ratings in Zeiner et al.'s study may limit their findings.

On the other hand, an equally important body of literature has demonstrated a significant positive influence of IQ on the response to MPH. Results reported by the Multimodal Treatment Study of Children with ADHD (MTA) (n = 579, IQ mean = 101, SD = 14.7) have shown in a subgroup a positive relationship between child IQ and MPH response (Owens et al., 2003). Several other studies have also reported that higher IQs are associated with better responses to MPH (Buitelaar, Van der Gaag, Swaab-Barneveld, & Kuiper, 1995; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). Nonetheless the findings of these studies may be limited by their small sample sizes (n<70) and by their exclusive use of parent and teacher ratings of behavior to evaluate treatment response. In a study conducted with a group of 336 children, in which 89% had IQs between 80 and 120, Thomson & Varley reported that higher IQ levels positively predicted the response to MPH. However full scale IQ (FSIQ) from the Weschler Intelligence Scale for Children-Revised (WISC-R) was available for only 155 children (Thomson & Varley, 1998).

In contrast to the above findings, lower IQ has also been found to predict a better response to MPH (Taylor, Schachar, Thorley, Wieselberg, & Everitt, 1987), but the small sample size (n=39) and the absence of objective laboratory rating scales may limit the generalizability and validity of their results.

As for the children functioning in the extremes of the intellectual spectrum, a small but consistent body of literature has demonstrated the reduced efficacy of MPH among children with an intellectual quotient (IQ) of less than 70 compared to those whose IQ is greater than 70 (Aman, Buican, & Arnold, 2003; Aman, Marks, Turbott, Wilsher, & Merry, 1991). In contrast, with regards to ADHD children functioning in the higher intellectual spectrum of giftedness (IQ above 120) (Antshel, 2008), most studies do not have a large enough high IQ sample size (often <10) to examine specifically how gifted children respond to MPH compared to lower IQ children. At present the scarcity of reliable literature does not point to a conclusion on the efficacy of psychostimulants in children with higher intellectual abilities.

No clear consensus has been reached on IQ as a predictor of the response to MPH in children with normal and high intellectual abilities. However determining whether IQ can influence stimulant treatment outcome in ADHD patients is important, as it may significantly impact clinical decision-making.

We conducted a two-week, double-blind, placebo-controlled, crossover, randomized MPH trial with a large sample size of 502 children using parent, teacher as well as laboratory evaluations of outcome. The aim of our study was to compare the responses to MPH treatment of children functioning in the high, normal and borderline levels of the intellectual spectrum.

Methods

Participants

Participants were recruited from the Severe Disruptive Behavior Disorder Program and from the outpatient clinics at the Douglas Mental Health University Institute, a psychiatric teaching hospital in Montreal, Canada.

The present study consisted of 502 children 6 to 12 years old (mean = 9.05; SD = 1.86). It included 393 boys and 109 girls. 46.1% of the subjects came from a family with an income of more than $40,000 CAD per year, 11.9% between $30,000 and $40,000 CAD, 14.4% between $20,000 and $30,000 CAD and 27.7% less than $20,000 CAD. The fathers of the participants received on average 12.44 years of education (range 3 to 27 years, SD = 3.4) and, the mothers received on average 13.06 years (range 5 to 27 years, SD = 3.16).

The children were diagnosed as ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 2000) by two experienced child psychiatrists. The diagnosis was based on clinical interviews with a psychiatrist, school reports, the Conners Global Index Teacher version (CGI-T) (Conners, Sitarenios, Parker, & Epstein, 1998b) and the Conners Global Index Parent version (CGI-P) (Conners, Sitarenios, Parker, & Epstein, 1998a). Within the sample, 51.7% of the children had a combined subtype of ADHD, 38.0% had the inattentive subtype, and 10.3% had the hyperactive subtype.

Exclusion criteria included an IQ of less than 70, a history of Tourette's syndrome, pervasive developmental disorder, psychosis, and previous intolerance or allergic reaction to MPH. 38.9% of children in our sample had been on some medication in the past, but all medications were stopped for two weeks before the start of our clinical trial.

Baseline IQ scores were obtained from the full scale IQ (FSIQ) of the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) (Wechsler, 1991) from 1999 to 2004 and the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) from 2004 to 2011 (Wechsler, 2003).The correlation between WISC-IV and WISC-III FSIQ in normal children has been found to be reliably high (r = 0.89) (Strauss, Sherman, & Spreen, 2006). FSIQs ranged from 70 to 150 (mean = 96.31; SD = 13.34). According to their FSIQ, the children were classified into three groups: borderline IQ (70 ≤FSIQ<80; n = 45; mean = 74.98; SD = 3.20), average IQ (80 ≤FSIQ<120; n = 430; mean = 96.68; SD = 9.98), and superior IQ (FSIQ ≥120; n = 27; mean = 126.07; SD = 6.98).

The participant's mothers reported whether they smoked tobacco or consumed alcohol during their pregnancy.

Other baseline measures included: the Child Behavior Checklist (CBCL) (Achenbach & Edelbrock, 1983), a 113-item questionnaire for parents that measures internalizing and externalizing behavior; the Conners' Global Index for Parents (CGI-P) and the Conners' Global Index for Teachers (CGI-T) , filled out, respectively, by parents and teachers. Both CGI-T and CGI-P were used to determine the frequency of 10 types of ecologically relevant behavior.

The parents of the children signed informed consent, and the subjects agreed to participate in the trial.

Stimulant Trial

The core of this study consisted of a two-week, double-blind, placebo-controlled, crossover, randomized MPH trial. The Research and Ethics Board of the Douglas Institute approved the trial. After an initial week of baseline assessments, all subjects received either placebo or 0.5 mg/kg of body weight of MPH divided into two equal doses administered daily in the morning and at noon for one week. The participants were then crossed over in the second week. A research psychologist who had no contact with the patients completed the randomization. All capsules, MPH and placebo, were prepared by a clinical pharmacist who was not otherwise involved in the study. No important adverse events or side effects were noted.

Assessments of Outcome

During the medication trial weeks, after observing each child for five days at school, teachers were asked to evaluate the participants' behavior at school by completing the CGI-T. Parents were asked to evaluate behavior at home by completing the CGI-P on the Sunday after giving the medication to the children during the weekend. The subtracted difference between the CGI-T and CGI-P scores of the medication and of the placebo weeks was used as an outcome measure. Scoring change on the restless-impulsive (RI) and on the emotional lability (EL) subscales of both CGI-T and CGI-P were also examined. In addition the children were assessed in the laboratory on the third of day of each week with the Restricted Academic Situation Scale (RASS), a measure that assesses off task, fidgeting, vocalizing, playing with objects and being out of seat behavior while doing math problems (Barkley, 1990). The RASS was given before and 45 minutes after the administration of the medication. Detailed explanations of our clinical diagnosis and stimulant trial procedures can be found in (Grizenko, Paci, & Joober, 2010).

Statistical Analysis

IQ groups were compared using cross-tabulations and calculated significance using χ^2 tests for categorical variables. For continuous variables, analysis of variance (ANOVA) and independent samples T-tests were used.

Results

ANOVA analysis of the demographic characteristics of our sample yielded significant differences between the three IQ groups with regards to their income groups (p<0.001), the fathers' education durations (p<0.001) as well as the mothers' education durations (p<0.001) (see Table 1). Subsequent independent samples T analysis between the groups all proved to be significant. Generally higher IQ subjects came from families with a higher income and had parents with more education than subjects of lower IQ. No difference was found with regards to in utero tobacco and alcohol exposure between the three groups.

Baseline CBCL total T score differed markedly upon ANOVA analysis between the IQ groups (p=0.010) (see Table 2). Subjects from the superior IQ group display less behavior problems compared to average IQ (p=0.014) and borderline IQ children (p=0.002).Subsequent detailed ANOVA analysis of CBCL subscales scores revealed significant differences between the groups with regards to social problems (p=0.001), attention problems (p=0.003) and delinquent behavior (p=0.025).

Independent Samples

T-tests demonstrated that average IQ children display less social (p=0.001) and attention (p=0.006) problems than their borderline IQ counterparts, and that superior IQ children scored less than borderline IQ children on the subscales of externalizing behavior (p=0.048), social problems (p=0.001), thought problems (p=0.010) and attention problems (p=0.002). Superior IQ subjects differed from the average IQ subjects on only the subscale of delinquent behavior, with the average IQ subjects displaying more problems (p=0.009).On the baseline CGI-P test, parents of superior IQ subjects rated their children's symptoms as being less severe compared to subjects with a borderline IQ (p=0.031). Baseline CGI-T scores did not differ significantly between the IQ groups (p=0.558).

ANOVA analysis of the improvements in CGI-P, CGI-T and RASS scores following medication did not show significant differences between the IQ groups (see Table 3). Subsequent independent samples T-tests showed a trend but no statistically significant difference in change on the CGI-P total and RI scores between the superior IQ and borderline IQ subjects, with the high IQ children generally showing

Table 1. Demographics of ADHD subjects according to IQ level

	Borderline (Bord.) IQ	Average (Av.) IQ	Superior (Sup.) IQ	Statistics	Degrees of freedom (*df*)	*P*[a]
IQ range	70 ≤ FSIQ < 80	80 ≤ FSIQ < 120	FSIQ ≥ 120			
N (%)	45 (9.0)	430 (85.7)	27 (5.4)			
Age (SD)	8.85 (2.03)	9.07 (1.85)	9.22 (1.67)	F = 0.39	2	0.675
Bord. vs Av. IQ				t = -0.754	473	0.451
Av. vs Sup. IQ				t = -0.406	455	0.685
Bord. vs Sup. IQ				t = -0.797	70	0.428
Male/female (%)	35/10 (77.8/22.2)	334/96 (77.7/22.3)	24/3 (88.9/11.1)	χ^2 = 1.887	2	0.389
Bord. vs Av. IQ				χ^2 = 0.000	1	0.987
Av. vs Sup. IQ				χ^2 = 1.883	1	0.170
Bord. vs Sup. IQ				χ^2 = 1.408	1	0.235
Income group[b] (SD)	3.86 (1.67)	4.62 (1.56)	5.46 (1.02)	F = 8.60	2	0.000
Bord. vs Av. IQ				t = -3.007	443	0.003
Av. vs Sup. IQ				t = -2.596	424	0.010
Bord. vs Sup. IQ				t = -4.256	65	0.000
Father's years of education (SD)	10.76 (3)	12.51 (3.29)	15.22 (3.28)	F = 12.68	2	0.000
Bord. vs Av. IQ				t = -2.944	346	0.003
Av. vs Sup. IQ				t = -3.808	336	0.000
Bord. vs Sup. IQ				t = -5.271	54	0.000
Mother's years of education (SD)	11.45 (2.791)	13.23 (3.14)	14.6 (3.37)	F = 8.74	2	0.000
Bord. vs Av. IQ				t = -3.438	414	0.001
Av. vs Sup. IQ				t = -2.111	399	0.035
Bord. vs Sup. IQ				t = -4.086	63	0.000

χ^2 for Chi-square, *F* for Anova, *t* for *T*-test

[a] Significance set at p = 0.05

[b] Income groups set at 1 for < Can$ 6 000, 2 for Can$ 6-10 000, 3 for Can$ 10-20 000, 4 for Can$ 20-30 000, 5 for Can$ 30-40 000, 6 for > Can$ 40 000.

less improvement than borderline IQ children (p=0.085 and p=0.071).

Discussion

The major result of this study is that there was no statistically significant difference in the response to MPH for children in the borderline, average and superior IQ levels.

The results of this study suggest that ADHD children, depending on their cognitive ability, differ in their socio-economic background as well as the amount of education received by their parents. Not surprisingly, higher IQ children tend to have more educated parents than children with lower IQ, and these parents in turn tend to earn more for the family.

Higher IQ children generally presented with a less severe symptomatology than children of lower IQs. Borderline IQ children had the greatest level of attention, social and externalizing problems at baseline. Our results are in line with previous findings of a negative phenotypic correlation between IQ and ADHD symptoms scores (Simonoff, Pickles, Wood, Gringras, & Chadwick, 2007). At present the mechanism of this relationship has not been elucidated, although Simonoff et al. found no evidence that inappropriate expectations by raters or confounding associations with other psychiatric problems could account for it.

With regards to MPH treatment, ADHD children with different IQs do equally well by improving on parent, teacher and laboratory ratings. However some degree of variation was observed. When mean scoring changes are examined, superior IQ children (mean = 1.91; SD = 11.57) show less improvement on the CGI-P total score when compared to average (mean = 4.56; SD = 14.41) and borderline IQ subjects (mean = 8.13; SD = 14.16), but all three groups of children seem to improve equally on teacher ratings of the CGI. In addition, a trend was found when examining the improvements of superior IQ children compared to borderline counterparts on CGI-P total and RI scores (p=0.085 and p=0.071). The rather large standard deviations might explain the lack of significance. The discrepancy between the parent and teacher ratings of improvement suggests that the improvements due to medication in children with a superior IQ are minimized by their parents who may not notice important changes in their child's behavior at home. In this

Table 2. Baseline clinical characteristics according to IQ level

	Borderline (Bord.) IQ	Average (Av.) IQ	Superior (Sup.) IQ	Statistics	Degrees of freedom (*df*)	P^a
IQ range	70 ≤ FSIQ < 80	80 ≤ FSIQ < 120	FSIQ ≥ 120			
ADHD subtype: inattentive/ hyperactive/combined (%)	14/6/25 (31.1/13.3/55.6)	164/42/223 (38.2/9,8/52)	12/4/11 (44.4/14.8/40.7)	$\chi^2 = 2.661$	4	0.616
Bord. vs Av. IQ				$\chi^2 = 1.154$	2	0.562
Av. vs Sup. IQ				$\chi^2 = 1.515$	2	0.469
Bord. vs Sup. IQ				$\chi^2 = 1.598$	2	0.450
CBCL[b] total T score (SD)	70.58 (6.95)	68.46 (8.69)	64.15 (10.44)	$F = 4.69$	2	0.010
Bord. vs Av. IQ				$t = 1.578$	462	0.115
Av. vs Sup. IQ				$t = 2.468$	444	0.014
Bord. vs Sup. IQ				$t = 3.138$	70	0.002
CGI-P[b] total baseline score (SD)	75.31 (11.24)	72.27 (11.35)	69.28 (9.65)	$F = 2.29$	2	0.103
Bord. vs Av. IQ				$t = 1.597$	427	0.111
Av. vs Sup. IQ				$t = 1.286$	413	0.199
Bord. vs Sup. IQ				$t = 2.209$	62	0.031
CGI-T[b] total baseline score (SD)	71.34 (13.78)	69 (12.59)	69.19 (13.79)	$F = 0.58$	2	0.558
Bord. vs Av. IQ				$t = 1.086$	438	0.278
Av. vs Sup. IQ				$t = -0.074$	426	0.941
Bord. vs Sup. IQ				$t = 0.613$	62	0.542

χ^2 for Chi-square, *F* for Anova, *t* for *T*-test

[a]Significance set at p = 0.05

[b]CBCL: Child Behavior Checklist; CGI-P: Conners Global Index - Parent version; CGI-T: Conners Global Index - Teacher version

sense parental ratings seem to be more sensitive to changes in the hyperactivity of their child rather than to subtle improvements in attention deficits. On the other hand, medication effects are noticed by teachers who see obvious improvements in their performances at school as well as in their general behavior. Furthermore, it is important to note that children with borderline IQ, according to parents on the CBCL and CGI-P, tend to be seen as having more behavioral and attentional problems than the others. This may also explain why the change in the CGI-P score with medication was greater for children in the borderline intelligence group. What is important though is that the teachers, who saw all children equally problematic on the CGI-T at baseline reported a CGI-T change score on medication as very similar across IQ levels. Therefore, the magnitude of amelioration may be affected by the perceived initial severity of symptomatology.

A limitation of our study lies in the lack of different MPH doses in our medication trial. Different doses of the medication may have allowed us to see different improvement effects in the children. It is also important to point out that our sample is clinically referred and not population-based. Even though our sample is one of the largest in the literature to examine the effects of IQ in response to medication in a double-blind placebo-controlled MPH trial we do have relatively few children in the gifted range. Furthermore our trial did not examine the effect of long-acting psychostimulants other than methylphenidate.

Conclusion

To our knowledge, this study is the first large double-blind, placebo-controlled, crossover methylphenidate trial study to be conducted with the specific focus of looking at responses among children with different intellectual functioning levels in the normal and gifted range. The results of this study point to the conclusion that ADHD children, despite individual variations in intellectual ability, all respond in a similar fashion to methylphenidate. Therefore a proper medication treatment plan is warranted for all ADHD children.

Acknowledgements/Conflicts of Interest

The authors would like to thank Johanne Bellingham, Sandra Robinson, Jacqueline Richard, Phuong-Thao Nguyen and Marie-Ève Fortier for their devoted help with data collection. This study was supported by grants from The Canadian Institutes of Health Research (CIHR) and the Fonds de la recherche en santé du Québec (FRSQ). The authors have no conflict of interest to declare.

Table 3. Response to medication according to IQ level

	Borderline (Bord.) IQ	Average (Av.) IQ	Superior (Sup.) IQ	Statistics	Degrees of freedom (*df*)	P^a
IQ range	70 ≤ FSIQ < 80	80 ≤ FSIQ < 120	FSIQ ≥ 120			
Change in CGI-Pbtotal score (SD)	8.13 (14.16)	4.56 (14.41)	1.91 (11.57)	$F = 1.563$	2	0.211
Bord. vs Av. IQ				$t = 1.474$	417	0.141
Av. vs Sup. IQ				$t = 0.848$	400	0.397
Bord. vs Sup. IQ				$t = 1.754$	59	0.085
Change in CGI-P restless-impulsive score (SD)	8.36 (13.40)	5.40 (14.26)	1.95 (12.43)	$F = 1.506$	2	0.223
Bord. vs Av. IQ				$t = 1.241$	417	0.215
Av. vs Sup. IQ				$t = 1.109$	400	0.268
Bord. vs Sup. IQ				$t = 1.838$	59	0.071
Change in CGI-P emotional lability score (SD)	5.26 (17.12)	1.78 (15.15)	1.86 (11.71)	F = 0.927	2	0.396
Bord. vs Av. IQ				$t = 1.346$	417	0.179
Av. vs Sup. IQ				$t = 0.024$	400	0.981
Bord. vs Sup. IQ				$t = 0.825$	59	0.412
Change in CGI-T[b] total score (SD)	8.57 (13.80)	9.85 (13.18)	9.82 (12.40)	F = 1.59	2	0.853
Bord. vs Av. IQ				$t = 0.562$	402	0.575
Av. vs Sup. IQ				$t = 0.011$	387	0.991
Bord. vs Sup. IQ				$t = 0.349$	57	0.728
Change in CGI-T restless-impulsive score (SD)	8.11 (12.62)	9.35 (12.23)	8.82 (10.76)	$F = 0.185$	2	0.831
Bord. vs Av. IQ				$t = 0.585$	402	0.559
Av. vs Sup. IQ				$t = 0.198$	38	0.843
Bord. vs Sup. IQ				$t = 0.220$	57	0.826
Change in CGI-T emotional lability score (SD)	6.22 (15.10)	7.78 (13.59)	7.91 (14.24)	$F = 0.221$	2	0.802
Bord. vs Av. IQ				$t = 0.660$	402	0.510
Av. vs Sup. IQ				$t = 0.043$	387	0.965
Bord. vs Sup. IQ				$t = 0.425$	57	0.672
Change in RASS[b] (SD)	27.14 (40.07)	27.07 (30.72)	29.47 (23.32)	F = 0.75	2	0.928
Bord. vs Av. IQ				$t = -0.014$	464	0.989
Av. vs Sup. IQ				$t = 0.399$	448	0.690
Bord. vs Sup. IQ				$t = 0.274$	68	0.785

χ^2 for Chi-square, *F* for Anova, *t* for T-test

[a] Significance set at p = 0.05

[b] CGI-P: Conners Global Index – Parent version; CGI-T: Conners Global Index – Teacher version; RASS: Restricted Academic Situation Scale

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