DYSKINESIA IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

PhD thesis outline

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1. Introduction

1.1. Attention-deficit/hyperactivity disorder (ADHD)

ADHD is one of the most common psychiatric disorders in childhood: its prevalence is 8-12% in childhood and it persists into adulthood in 30-60% of cases. The disorder has several negative consequences in different areas of life: underachievement in learning/work, problems in interactions with parents/spouse and friends. Comorbid psychiatric diagnoses also commonly occur. ADHD is a multicausal syndrome, in 80% genetic factors and also environmental factors play a role in its development. The best theories to explain the central nervous system background of the disorder are those assuming the dysfunction of frontostriatal brain areas and dopamine and noradrenaline neurotransmitters.

1.2. Treatment of ADHD

The treatment of ADHD includes evidence based non-pharmacological and pharmacological interventions as well. Pharmacotherapy comprises stimulants and atomoxetine. One of the most commonly prescribed stimulants is methylphenidate, which is safe and effective treatment.

1.3. Dyskinesia and methylphenidate treatment for ADHD

In the past few decades, and especially in recent years, an emerging number of case studies concerning the association

between stimulant (mostly methylphenidate) treatment and dyskinesias have been reported. These cases can be divided into two groups. 1) late-onset dyskinesia, where it arises many weeks after the first administration of the stimulant, and diminishes only months after the withdrawal of the therapy; 2) early-onset dyskinesia, where both the emergence and the cessation occurs on the same day of (or in some days following) the first administration of the stimulant.

Regarding the background of the studies presented in my doctoral dissertation it is important, that prior to these studies my supervisor had met a case in her clinical work, where a 6½-year-old boy treated with methylphenidate for ADHD developed early-onset dyskinesia – this was published in her case study. Reviewing the literature, we have not found any systematic studies which had focused on this phenomenon.

2. Objective of the study

The objective of my doctoral dissertation is to examine the possible connection between methylphenidate treatment and occurrence of dyskinesia symptoms in children diagnosed with ADHD.

The aim of the first study was to compare the level of dyskinesia symptoms in children with ADHD diagnosis treated

with methylphenidate, and in a healthy control group of children. Furthermore, the purpose of the study was to see that in case there is a significant relationship between methylphenidate treatment and dyskinesia, is this relationship affected by covariates such as gender, age, dosage and duration of methylphenidate treatment. In addition, we also wanted to investigate if a single dose of methylphenidate would worsen dyskinesia symptoms in children already receiving methylphenidate treatment for ADHD prior to and during our examination.

Since this study compared two groups: children with ADHD diagnosis, already receiving methylphenidate treatment, and healthy children, the results do not show what the higher level of dyskinesia in the ADHD group (see below) is due to. It can be suggested that 1) it is developed due to the treatment, 2) the more frequent occurrence of dyskinesia is a characteristic of ADHD as a neurodevelopmental disorder itself, through a shared central nervous system involvement.

To explore this issue, a second study was designed with three groups.

Besides the healthy control group, we involved two ADHD groups: one receiving methylphenidate treatment prior to and

during the study, and a new group with ADHD diagnosis but with no previous methylphenidate treatment.

We studied children in the latter group when the first dose of methylphenidate was administered to them. Therefore, our aim was also to examine the effect of the administration of a first therapeutic dose of methylphenidate on dyskinesia.

3. Methods

3.1. First study

Participants

Study participants in the clinical group were recruited from the Vadaskert Foundation, Child and Adolescent Psychiatric Hospital and Outpatient Clinic. Inclusion criteria were children and adolescents aged 6–18, diagnoses of ADHD, and treatment with methylphenidate.

Participants in the control group were recruited from the local community through convenience sampling. Exclusion criteria were any past or present mental and neurological disorders.

The study was approved by the Regional Ethics Committee of Szent Imre and Szent János Hospitals. Participation was voluntary for study participants. The parents of each child and children older than 14 years included into this study provided

written informed consent or ascent after being informed of the nature of the study. Anonymity of data was guaranteed.

Measures

The presence or the absence of psychiatric diagnoses, including ADHD, were measured by the Hungarian, adapted version of the MINI Neuropsychiatric Interview Kid (M.I.N.I. Kid). The M.I.N.I. Kid is a short, structured diagnostic interview.

Dyskinesia symptoms of subjects were measured by using the Abnormal Involuntary Movement Scale (AIMS). The raters scored the observed involuntary movements during a baseline and a dyskinesia triggering provocation situation. Children were measured with AIMS on two occasions: before administration of medication (T1) and one hour after (T2).

Statistics

Besides descriptive statistics (analysis of variance, Chi-square test/Fischer's exact), the relationship between dyskinesia and potential predictors was investigated by the Generalized Linear Integrated Mixed Model (GLIMMIX) approach.

3.2. Second study

Participants

Children in the clinical group were recruited from the Vadaskert Foundation, Child and Adolescent Psychiatric

Hospital and Outpatient Clinic. The clinical group comprised of two sub-groups: 1) children with ADHD diagnosis with methylphenidate treatment prior to and during the study (hereafter: treated ADHD group), (b) children with ADHD without previous methylphenidate treatment (hereafter: treatment-naive ADHD group). Inclusion criteria for the treated ADHD group were children aged 6 to 18 years, a diagnosis of ADHD and treatment with methylphenidate that had started before and was ongoing during the study. Inclusion criteria for the treatment-naive ADHD group were children aged 6 to 18 years, a diagnosis of ADHD and no previous methylphenidate treatment. Furthermore, we studied these children when the first dose of methylphenidate was administered to them according to the instructions of their child psychiatrist (thus regardless of our study) as part of their treatment.

Healthy control children were recruited on a voluntary basis from primary schools in Budapest and Szekszárd. Inclusion criteria were children aged 6 to 18 years, no ADHD diagnosis and no previous or ongoing psychiatric or psychological treatment.

The study was approved by the Medical Research Council Scientific and Research Committee. The study was conducted between 2012-2014. The participation was voluntary for study

participants. Parents and children received both oral and written information about the study. Parents and children older than 14 years gave their written consent.

Measures

The M.I.N.I. Kid and the AIMS were used for measurements in this study as well. The assessment of dyskinesia with AIMS was also conducted before administration of medication (T1) and one hour after (T2) in all three groups (with no administration of medication in the control group, obviously).

Statistics

For the description of the study sample, we examined the differences between the study groups applying an ANOVA, or an independent

samples t-test with robust version when necessary and chi-square test. Relationship between the AIMS total scores in T1 and T2 and the study groups was investigated by the Generalized Linear Model (GLM). To analyze the effect of the administration of a single dose of methylphenidate, we applied the generalized linear mixed models (GLMM).

4. Results

4.1. First study

Altogether 37 children were eligible for inclusion in the ADHD group with 86.5% being male (n=32) and a mean age of 10.8 years SD = 2.4). Altogether 34 children were eligible for the control group, 38.2% (n=13) were male with a mean age of 9.8 years (SD= 3.5). The difference in gender ratio in the two groups reached statistical significance ($\chi 2 = 17.8$; df = 1; $p < 0.001$), but there was no significant difference between the mean age (t = 1.470; p = n.s.) of children with ADHD and controls.

In the analysis of the effect of provocation (baseline vs provocation) and diagnostic group (ADHD vs. control) on the total AIMS score before the administration of methylphenidate (baseline), age, gender, and body weight are included as covariates. As indexed by the total score on the AIMS, the ADHD group had significantly higher severity at baseline (M=1.43; S=2.57) than the control group (M=0.62; S=1.18; F = 4.51; p = .038). In addition, provocation was also associated with a significantly higher mean value on the AIMS total score (ADHD group: M=3.22; S=4.32; control group: M=1.50; S=1.52; F = 30.97; p < .001), whereas the interaction between

diagnostic group and provocation did not reach statistical significance.

The effects of provocation and administration of methylphenidate (before vs. after) on the total score of AIMS in the ADHD group was assessed using age, gender, and weight as covariates. The total score of AIMS in the ADHD group was as follows: 1) Baseline, before administration of methylphenidate: M=1.43; S=2.57; 2) Provocation, before administration of methylphenidate: M=3.22; S=4.32; 3) Baseline, after administration of methylphenidate: M=1.06; S=1.76; 4)Provocation, after administration of methylphenidate: M=2.56; S=2.51. The administration of methylphenidate did not have a significant effect on the AIMS total score, but provocation - similarly to baseline, before the administration of methylphenidate - had an effect on the AIMS total score ($F = 35.91$; $p < .001$). There was no significant methylphenidate–provocation interaction observed. Regarding potentially important covariates, neither gender nor body weight had significant effect on these results, whereas age did ($F = 6.21$; $p = .018$).

4.2. Second study

The control group included 55 children, 49.1% boys (n=27) whose mean age was 9.99 years (standard deviation = 2.1). The treatment-naive ADHD group included 63 children, 82.5% boys (n=52) whose mean age was 10.28 years (standard deviation = 2.8). In the treated ADHD group 40 children were included, 85.0% boys (n = 34) whose mean age was 11.25 years (standard deviation = 2.2). The three study groups differed significantly in age ($F(2.150) = 3.927$, $p = .023$), with the control group being significantly younger than the treated ADHD group ($p = .039$). The study groups also differed in gender ($\chi^2(2.156) = 18.645$; $p < .001$).

We did not find any significant differences between the treatment-naive ADHD group and the treated ADHD group in the type of ADHD, the number of ADHD symptoms, the dose per weight rate and comorbid psychiatric diagnoses.

Figure 1 presents the AIMS total scores at T1 and T2 in the three study groups.

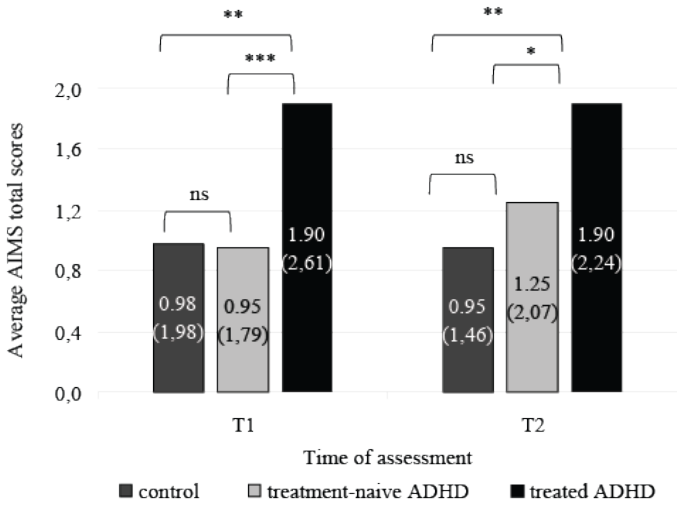

Figure 1. AIMS total scores at T1 and T2 in the three study groups. Mean (standard deviation).) (Keresztény et al, 2016, with the permission of the publisher)

5. Conclusions

My doctorial dissertation's central thread is the examination of dyskinesia symptoms in children with ADHD diagnosis treated with methylphenidate, by presenting the results of two studies built on each other. Below, I am going to discuss the main results of these studies in more detail.

5.1. First study

According to our study, a single, therapeutic dose of methylphenidate does not trigger dyskinesia symptoms or worsen already existing ones in children and adolescents receiving regular methylphenidate treatment for ADHD. Our main finding is that there is significantly more dyskinesia in the ADHD group than in the control group. This finding is even more pronounced if we use the data of the provocation test during the administration of the AIMS; provocation compared to no provocation situation was associated with a significantly higher mean value on the AIMS total score.

Dyskinesia measures using provocation methods are not part of the routine diagnostic tools in case of children with ADHD in child and adolescent psychiatry

Dyskinesia scores have not changed significantly after the administration of methylphenidate; in fact, interestingly the AIMS total scores were numerically lower after the administration of methylphenidate than before the administration. The administration of a single therapeutic dose of methylphenidate did not worsen subclinical dyskinesia in

children receiving chronic treatment with methylphenidate either.

Limitations:

- Whereas we measured the AIMS score of the children in the ADHD group twice (before and 90-120 minutes after the administration of methylphenidate), we measured it only once in the control group (due to logistical difficulties, no measurement was conducted 90-120 minutes later).
- The control group was recruited via convenience sampling.
- The two groups significantly differed in gender ratio; however, we could not identify effects of gender on our results. In addition, to

account for a potential bias, gender was included as a covariate in all statistical analyses.

- This sample did not include treatment-naive children with ADHD. Thus, based on this study we could not speculate if increased dyskinesia is an effect of repeated exposure to methylphenidate or an increased sensitivity related to ADHD or an interaction of these two factors.

The second study undertook to answer these questions.

5.2. Second study

To our knowledge, this study is the first to investigate the level of dyskinesia by comparing a stimulant-treated and a treatment-naive ADHD group of children. Our results show that the treatment-naive ADHD group did not differ significantly from the healthy control group regarding dyskinesia scores either before or after the first methylphenidate administration. However, the ADHD group treated prior to and during the study had a significantly higher dyskinesia score than either the treatment-naive ADHD group or the control group both before and after methylphenidate administration.

These results corroborate the assumption that the dyskinesia is not due to the disorder, but it may be associated with the treatment. These results also call attention to the fact that clinicians should pay special care to the possible development of dyskinesia during ADHD

treatment with methylphenidate.

When we investigated the AIMS total scores before and after methylphenidate administration, our results suggested, that a single therapeutic dose of methylphenidate would not enhance the level of dyskinesia neither in children who were undergoing methylphenidate treatment, nor in the treatment naive group of children with ADHD.

Our study highlights the importance that clinicians should take special care for the possible development of dyskinesia during the treatment of their ADHD patients with methylphenidate, which is of special importance because dyskinesias can be seen by others, and
these phenomena can be a sign of the treatment for people in the environment of the child. Therefore, treating dyskinesia when needed can prevent the stigmatization of these children.

The limitation of the study should be considered: 1) it is a cross-sectional study, 2) differences in age and gender between the control group and the ADHD groups; however, there were no significant differences between the two ADHD groups in this regard. These variables were included as covariates in our analyses.

6. Bibliography of the candidate's publications:

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