Study Protocol

Official title:

The Relationship Between CES1 Genotype and Methylphenidate Response in Children With ADHD - INDICES Work Package 6

Date of approval from human subject protection review board:

22nd March 2012

Short summary:

This is a prospective observational study of a cohort of children diagnosed with Attention Deficit Hyperactive Disorder (ADHD) and followed with weekly assessments during the first 12 weeks of Methylphenidate (MPH) treatment. The study was extended to include a three-year follow-up which is described in the additional protocol “Predictors of long-term outcome in a clinical cohort of children with attention-deficit hyperactivity disorder (ADHD)”.

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The relationship between CES1 genotype and methylphenidate response in children with ADHD – INDICES workpackage 6
Protocol version 3

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INDICES: (Individualised drug therapy based on pharmacogenomics: Focus on carboxylesterase1)
SUMMARY.
We wish to examine the relationship of Carboxylesterase 1(CES1) genotype with the response to Methylphenidate (MPH) in children with attention deficit hyperactivity disorder (ADHD). This will allow us to develop guidelines for individualized CES1 genotype-based MPH treatment in patients with ADHD.

The INDICES project combines pharmacology, genetics and metabolomics with clinical psychiatry and cardiology. It consists of 7 workpackages with focus upon carboxylesterase 1 (CES1), an enzyme with a major role in the metabolism of a variety of essential drugs including methylphenidate (MPH) and trandolapril (TA) for treatment of ADHD and cardiovascular disease (CVD), respectively.
The overall aim is to develop and implement guidelines for individualized treatments with MPH and TA and obtain a better drug response and reduce the risk of adverse reactions.

Background (Workpackage 6):
MPH is first-line treatment for ADHD, which affects 3-5% of children and adolescents. In most cases it persists into adulthood[1]. In Denmark the consumption of MPH has increased by a factor of 10 during the last 10 years[2]
Comorbidity is common, affecting more than 80% of patients with ADHD.
15- 20 % of patients treated with MPH are nonresponders. Adverse reactions are common, but few studies have had adverse reactions as their primary focus[3,4]. Decreased appetite is closely linked to stimulant treatment, and sleep problems occurs in approximately 70% in the initial stages of treatment. Increased blood pressure and heart rate, associated with stimulant treatment, affects a minority of treated individuals (5%). Potentially more serious cardiovascular events, however, seem to appear in stimulant treated children, with a risk, similar to the background population [5].
Discontinuation of treatment because of adverse reactions occurs in 2-10% [4]. Overall, adverse reactions in MPH treatment seem to be linked to individual underlying mechanisms, possibly related to pharmacokinetics and pharmacogenomics. Guidelines for treatment with MPH emphasize the need for individually tailored medication dosage, and further research into pharmacogenetics , but the clinical use of these tools is still highly variable [3,6,7] Several studies have found evidence for genetic variations in MPH response, especially variations in the dopamine transporter and dopamine D4 receptor. Variations in candidate genes, predict differences in ADHD treatment response and side effects of immediate release MPH [8-10]

Carboxylesterase 1(CES1) is a key enzyme in the metabolism of MPH, various other drugs, and endogenous lipids. Clinical and preclinical studies indicate that polymorphisms in the CES1 gene are responsible for individual variations in MPH treatment response and drug-drug interactions [11-13]. Recent data from a collaborative study supported by the European Commission (EU-FP7) have revealed duplication of the CES1 gene at frequencies of approximately 0.20 in Europe (Henrik Berg Rasmussen, unpublished). Gene duplication may give rise to increased rate of metabolism of CES1 dependent drugs.

Hypotheses:
Our main hypotheses: Individuals with a gene variant of CES1 resulting in rapid metabolic breakdown of MPH will experience less therapeutic effect and thus need higher dosages.
Individuals with a gene variant of CES 1 resulting in slow metabolizing of MPH will experience a better therapeutic effect and thus need lower dosages.
Our exploratory hypotheses: Dose-related side effects in MPH treatment will be associated with the metabolic rate of MPH breakdown, in line with its therapeutic effect.

Aims:
We aim to examine the influence of the CES1 genotype in children with ADHD on the effectiveness and the pharmacokinetics of MPH. Moreover, we aim to develop guidelines for individualised MPH therapy, based on CES1genotype by combining the results from INDICES Workpackage 2, a pharmacokinetic study of the correlation of CES1 genotype and copy number, with the pharmacokinetics of trandolapril and methylphenidate..
Implementation of guidelines for individualized pharmacotherapy will improve treatment efficacy and safety in this group of children.

Studypopulation:
200 drugnaïve children diagnosed with ADHD according to DSM-IV criteria in the age 7-12 years will be recruited from the three Child- and Adolescent Psychiatric Centers in the Capital Region of Copenhagen. To allow for a naturalistic setting, and because more than 80% of children and adolescents with ADHD have a comorbid psychiatric condition, we will only exclude patients with an IQ < 70, current serious medical or psychiatric illness (e.g. schizophrenia, bipolar disorder, untreated epilepsy, heart failure).

Inclusion criteria:
Age: 7-12 years (both inclusive)
Both sexes
DSM-IVADHD diagnosis (any subtype)
Clinical indication for methylphenidate treatment, based on national guidelines, confirmed by an ADHD-RS score +1.5 SD above mean adjusted for age and sex
Drug naïve to ADHD medication (Methylphenidate, Dexamphetamine, Atomoxetine)
Written informed consent by parents holding custody, and the child, to participate in the study

Exclusion criteria:
Medical conditions that contraindicate treatment with MPH: Cardiovascular or cerebrovascular disease, hyperthyroidism, phaeocromocytoma, glaucoma.
Psychiatric conditions that contraindicate treatment with MPH: Mania, psychosis, former severe depression, bipolar disorder not well controlled, suicidal conduct, anorexia nervosa

Diagnosis of mental retardation (IQ < 70)
Any ADHD medication ever (Methylphenidate, Dexamphetamine, Atomoxetine)
Current treatment with another CES1 related drug (Tamiflu, Trandolapril)
Current treatment with antipsychotics
Treatment with irreversible MAO inhibitors within the last 14 days before treatment start

Methods:
The psychometric instruments used in this study, for diagnostic assessment, are standard procedures for children in the age group, referred with a possible diagnosis of ADHD, in the Capital Region of Copenhagen. The staffs (Child- and adolescent psychiatrists and psychologists) who are conducting the assessments at the three study sites have all been trained in the psychometric instruments used in this study. We will measure interrater-reliability (by using kappa) for the K-SADS interviews.
The INDICES workpackage 6 study group includes a local child and adolescent psychiatrist, who is the responsible researcher on each of the three study sites.

Diagnostic assessment:
All children referred to the three Centers of Child and Adolescent Psychiatry in the Capital Region of Copenhagen, with a possible diagnosis of ADHD, are assessed by the following procedures:
The CBCL[14] (web-based questionnaires)
K-SADS interview[15]
Clinical assessment and diagnosis of ADHD according to Danish national guidelines, including history of development, symptoms and sociodemographics, clinical observation of symptoms, cognitive test and standard physical examination
ADHD diagnosis confirmed by K-SADS
Comorbidity diagnosed with K-SADS.
Possible cases, based on age and ADHD diagnosis, are evaluated by the local responsible researcher for inclusion in the study, and if relevant, contacted for permission and written informed consent by parent(s) holding custody, and the child, to participate in the study

Baseline ratings and measures on patients meeting inclusion criteria:
ADHD-RS [16] rated by parent
ADHD-RS rated by teacher
Investigator rated ADHD-DSM-IV-RS [17]
CGI- Severity scale [18]
Connors CPT[19] or TOVA[20](to be finally decided)
Adverse reactions-Rating Scale [21]
ASK-ME parent rated questionnaire, attitude scale (7 questions) [22]
Body weight and height
Blood pressure and pulse

DNA samples:
A sample of saliva

Patients included in the study enter a twelve week study period with dose escalation of methylphenidate, weekly telephone ratings and monthly clinical assessments of effect and adverse reactions to MPH treatment. Weekly telephone ratings are done by the PhD. student, and the following decision on pursuing further dose escalation is made in cooperation with the

child's regular psychiatrist at the study site. Monthly clinical assessments and decisions on dose escalation are done by the child's regular psychiatrist.

Weekly assessment and ratings:
(not made in week 4, 8 and 12)
By telephone: ADHD-DSM-IV-RS and Adverse Reaction-Rating Scale .
Weekly decision on pursuing further dose escalation based on the above ratings

Clinical assessment:
Every four weeks:
Measurement of blood pressure, pulse, weight and height
ADHD-DSM-IV-RS
Parent rated ADHD-RS
Adverse reactions-Rating Scale

Supplementary rating and test at week 8:
Teacher rated ADHD-RS
Blood test to measure serum concentration of Ritalin acid, and DNA

Outcome ratings after twelve weeks :
Investigator rated ADHD-DSM-IV-RS (primary outcome measure)
CGI-Severity (secondary outcome measure)
CGI-Improvement (secondary outcome measure)
CGI-Efficacy (secondary outcome measure)
Connors CPT or TOVA(secondary outcome measure)
Parent rated ADHD-RS (secondary outcome measure)
Teacher rated ADHD-RS (secondary outcome measure)
Adverse reactions-Rating Scale (secondary outcome measure)

Outcome measures:
Investigator rated ADHD-DSM-IV-RS score
Parent rated ADHD-RS score
Teacher rated ADHD-RS score
CGI-I
CGI-S
CGI-E
Connors or TOVA
MPH dose required for "Borderline normalisation" on ADHD-DSM-IV-RS: T-score 60-70
MPH dose required for normalisation on ADHD-DSM-IV-RS: T-score < 60
Occurrence (no. of weeks from treatment initiation) and type of adverse reactions
MPH dose at occurrence of adverse reaction
MPH dose at discontinuation, if that is necessary, because of adverse drug reactions or
Treatment failure (no effect of MPH on ADHD core symptoms)
Serum concentration of Ritalin acid at week 8

Body weight, height, blood pressure and pulse

Dose escalation:
MPH is initiated at a low dose: 5mg. MPH-IR three times daily (TID), and escalated weekly with 0 - 2,5 - 5mg MPH-IR TID. Maximum dose is 2mg/kg/day. MPH dose morning, midday and afternoon can be individually escalated, based on effect and adverse reactions. Decisions on dose escalation will be based on a clinical decision manual, elaborated for the study. Individual deviations in dose escalation are noted in the CRF and case records.

Dose escalation is continued on a weekly basis until one of the following:

- Normalisation on ADHD-RS defined as T-score < 60
- Borderline normalisation on ADHD-RS, if normalisation is not obtainable, defined as T-score 60-70
- Cessation of dose escalation because of adverse reactions
- Discontinuation of MPH because of either intolerable adverse reactions, or no effect of MPH on ADHD core symptoms.

On basis of this, we exploratively will categorize patients as

1) Clinically normal reponders
2) Clinically slow responders
3) Clinically rapid responders

Results:
We plan to use multivariate regression models with the change in symptom severity, measured with the ADHD-DSM-IV rating scale score as the dependent measure, whereas CES1genotype, weight adjusted MPH dosage (mg/kg/day), age, gender, occurrence of adverse reactions and ADHD subtype will serve as predictors.
We will repeat the analysis with CGI-I as the dependent measure.
This will allow us to assess whether MPH is less effective in subjects with CES1 gene variants, that are known to have a rapid metabolic breakdown of MPH, whether higher dosages of MPH, necessary to adapt to the genetic differences in these subjects, are associated with more side effects, whether subjects with CES1 gene variants that are known to have a slow metabolic breakdown of MPH, need lower dosages of MPH than expected, to have effect on ADHD core symptoms, and whether lower dosages of MPH, necessary to adapt to the genetic differences in these subjects, are associated with less side effects.
By combining our results with data from the pharmacokinetic work-package in the INDICES study, we will develop guidelines for individualised therapy of ADHD with MPH

Ethics
The clinical work package 6 focused on ADHD is covered by existing permissions from the local committees on scientific ethics (De Videnskabsetiske Komiteer for Region Hovedstaden) and the Danish Data Protection Agency (Datatilsynet). Those permissions allow the collection and examination of data as well as biological samples from psychiatric patients with ages below 18 years, for research purposes, including genetic research projects. Journal number: H-B-2009-026

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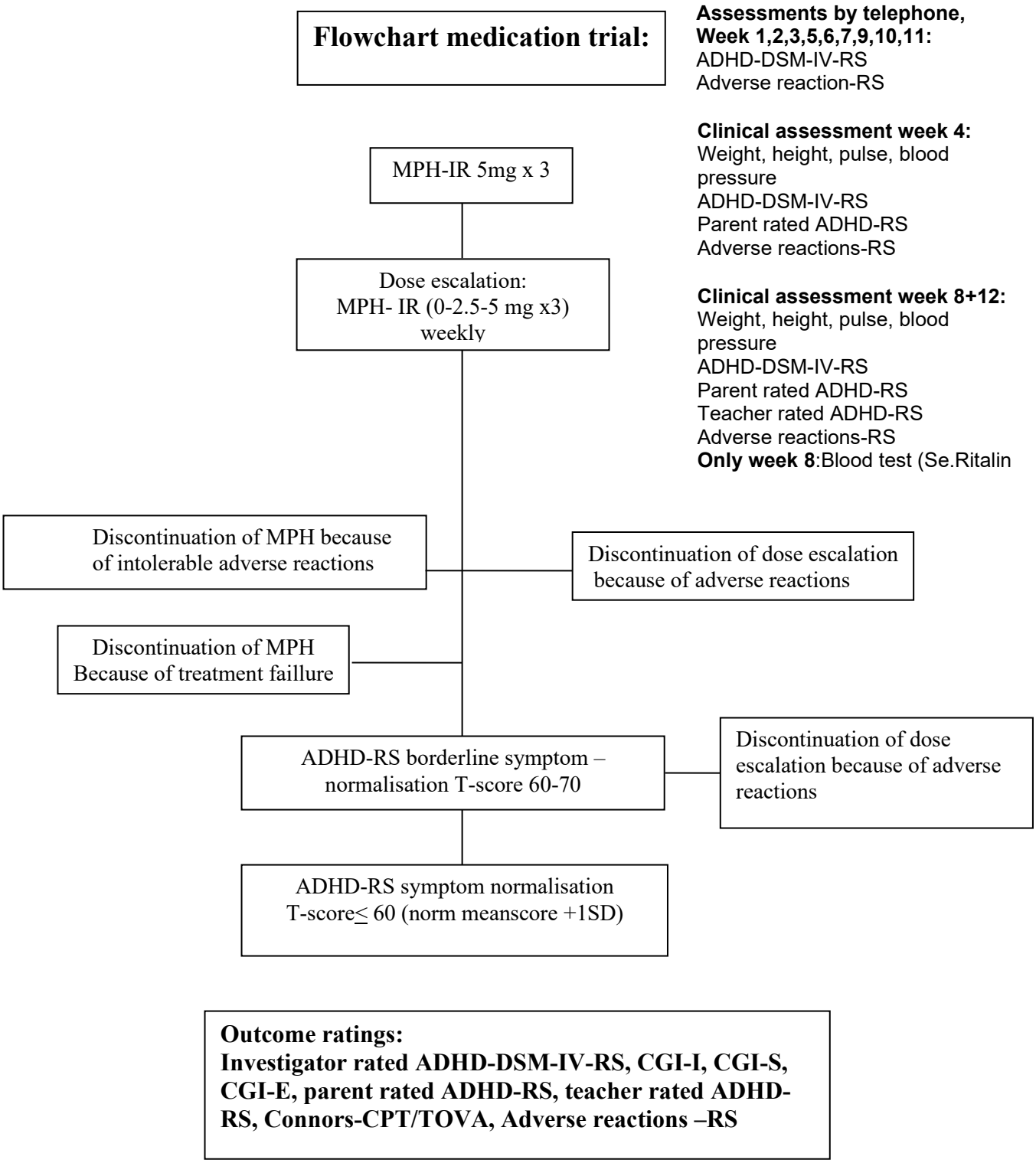
Milestones
2012: Month 1-2: planning and introduction
2012: Month 3-12: recruitment of 100 patients who will complete a 3-month study period of drugescalation
2013: Month 13-24: recruitment of 100 additional patients who will complete a 3-month study period corresponding to a total of 200
2014: Month 25-29: Finalization of entire clinical study. Data analysis. Preparation and submission of two manuscripts.
2014: Month 30-36: study visit at University of Nijmegen
2015: Month 37-39: Statistical treatment of data and elaboration of manuscripts. Advices for improved stimulant therapy developed
2015: Month 40-42: Preparation of PhD thesis. (Month 29-42: preparation of PhD thesis)

Economy:
The funding of this Research Project consists of a grant to the Parties from the Danish Strategic Research Council, and self financing.

WP6 DSF grant:		
Scientific/academic salaries, 1 PhD student in 42 months:	1.650.000 Dkr.	
Operating expenses in 42 months:	380.000 Dkr.	
Overheads 3.1%	62.930 Dkr	
Total DSF grant:		2.092.930 Dkr

WP6 Self-financing, Child and adolescent psychiatric center Glostrup:		
Scientific/academic salaries, 42 months:	288.000 Dkr.	
Technical/administrative salaries, 42 months:	90.000 Dkr.	
Overheads 3,1%	11.718 Dkr.	
Total self-financing:		389.718 Dkr.


Flowchart medication trial:
Assessments by telephone, Week 1,2,3,5,6,7,9,10,11:
ADHD-DSM-IV-RS
Adverse reaction-RS
Clinical assessment week 4:
Weight, height, pulse, blood pressure
ADHD-DSM-IV-RS
Parent rated ADHD-RS
Adverse reactions-RS
Clinical assessment week 8+12:
Weight, height, pulse, blood pressure
ADHD-DSM-IV-RS
Parent rated ADHD-RS
Teacher rated ADHD-RS
Adverse reactions-RS
Only week 8:Blood test (Se.Ritalin
MPH-IR 5mg x 3
Dose escalation: MPH- IR (0-2.5-5 mg x3) weekly
Discontinuation of MPH because of intolerable adverse reactions
Discontinuation of dose escalation because of adverse reactions
Discontinuation of MPH Because of treatment faillure
ADHD-RS borderline symptom – normalisation T-score 60-70
Discontinuation of dose escalation because of adverse reactions
ADHD-RS symptom normalisation T-score≤ 60 (norm meanscore +1SD)
Outcome ratings:
Investigator rated ADHD-DSM-IV-RS, CGI-I, CGI-S, CGI-E, parent rated ADHD-RS, teacher rated ADHD-RS, Connors-CPT/TOVA, Adverse reactions –RS

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Predictors of long-term outcome in a clinical cohort of children with attention-deficit hyperactivity disorder (ADHD)

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Attention-deficit hyperactivity disorder (ADHD) is a common developmental disorder that arises during childhood and involves difficulties in the acquisition and execution of specific intellectual, motor, or social functions. The course of severity and impairment in ADHD, have great individual variations and fluctuations over time, and has a chronic course in half of the affected individuals. Psychiatric comorbidity is common with prevalence rates between 50-80, but also, somatic comorbidity is reported with increased odds ratios compared to control groups, and ADHD is associated with significantly increased mortality rates due to especially accidents, also when controlled for conduct- and substance use disorders. Long-term cohort and register studies indicate that ADHD is associated with problems in the domains of education, employment status, suicidal behavior and risk behavior including accidents, substance use disorder and criminality. Studies of childhood predictors for adolescent and adult outcome in ADHD have identified severity of ADHD symptoms, psychiatric comorbidity, especially conduct disorder and major depressive disorder, female gender, IQ, low family income, and stressfull life events to predict a poorer outcome. Experience of poor treatment effect, side effects, and reluctance or forgetfulness in relation to medication have often been reported as reasons for discontinuation of ADHD medication[39,45]. Thus identification of predictors for successful treatment could aid in the decision of which treatment should be offered the individual patient with ADHD, in order to improve adherence and outcome. In studies of antipsychotics, early onset of antipsychotic effect, is shown to predict later clinical treatment response in psychotic disorders, also in children and adolescents(Stentebjerg-Olesen, Jeppesen et al. 2013). To our knowledge no studies have investigated time to treatment effect as a predictor for outcome in childhood ADHD.

The project makes use of systematically and prospectively collected data from a representative, consecutively recruited clinical cohort of 200 children, recently diagnosed with ADHD, who were closely monitored under standardized conditions during the first 12 weeks of Methylphenidate (MPH) treatment. We will use the existing prospective clinical data in this cohort and combine those with information's concerning risk- and psychosocial factors derived from parental reports and the Danish registries. Finally, we will follow the cohort after three years with respect to ADHD symptoms and impairment in daily life functioning. The findings, based on a systematic analysis of these associations, may aid the development of an evidence-based and individualized program for initiation and monitoring of drug- and psychosocial treatment in childhood ADHD with the main objective to improve the long-term prognosis of the disorder in the children.

Objectives

The primary aim of this study is to investigate if time to MPH treatment response is a predictor for the long-term symptomatic and functional outcome in a clinical cohort of children with ADHD. We hypothesized that response to MPH treatment after three weeks, during a 12 weeks treatment trial, independently of baseline level of symptoms, other child and family characteristics, and MPH response after 12 weeks, can

predict the outcome after three years. The secondary aim is to describe the course of ADHD symptoms and level of functional impairment three years after initiation of ADHD treatment.

The following hypotheses will be tested:

1. Early treatment response defined as ≥ 20% reduction in clinician rated ADHD symptoms between baseline and week three, will predict symptom severity and level of functioning in daily life activities three years after baseline, independently of baseline level of symptoms, and other child and family characteristics
2. Treatment response after 12 weeks, defined as ≥ 40% reduction in clinician rated ADHD symptoms between baseline and week 12, will predict symptom severity and level of functioning in daily life activities three years after baseline, independently of baseline level of symptoms, and other child and family characteristics.

Background

ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neuropsychiatric disorder characterized by disturbances of activity, impulsivity, and attention. It is the most frequent diagnosis in child- and adolescent psychiatry in Denmark (Classified as Hyperkinetic Disorder according to ICD-10[1]) and recently a population based Danish study reported a prevalence of approximately 3% in 11-12 year-old children[2], while the Danish prevalence by DSM-IV diagnostic classification[3] was reported to be approximately 6 % in 8-9 year-old children[4]. The estimated worldwide DSM-IV prevalence is approximately 5 % in school children [5]. Recent research suggests that the aetiology of ADHD combines genetic, pre- and perinatal risk factors, and other environmental and psychosocial risk factors, which probably are interrelated in a gene-environment interplay [6]. The heritability of ADHD is high [7,8], and the disorder frequently occurs simultaneously in several members of a family [9,10].

Moreover, according to clinical studies psychiatric comorbidity occurs in 70-80 % of children with ADHD[11,12], such as sleep disorder, oppositional defiant- or conduct disorder, tic disorders, anxiety- and depressive disorders, and learning and developmental disorders. Recently, a Danish nationwide registry study reported a comorbidity rate of 52% in children and adolescents according to ICD-10 criteria over a sixteen-year period [13]. The lower rate of comorbidity in this registry study could perhaps be explained by the fact that there are daily clinical routine practices and diagnostic traditions in the country.

Long-term studies indicate that ADHD often persists into adulthood[14,15] and is associated with problems in the domains of education, personal relationships, employment status, self-esteem, secondary psychiatric disorders, substance abuse, and criminality[14,16-21]. Successful treatment in childhood may improve child development, daily functioning, school attendance and learning, and thereby potentially also the prognosis and may reduce the societal costs of ADHD[20,22-27]. Thus, there is a strong need, both on the individual and the societal level, to further map out the evidence of factors that moderate the effect and the treatment compliance of children with ADHD.

Treatment

Psychosocial treatment guided by the symptoms of the child and the needs of the family is mandatory in childhood ADHD. In moderate to severe ADHD, Danish and international guidelines specify the combination of psychosocial treatment and drug treatment with methylphenidate (MPH) as the first line treatment. However, drug treatment is not indicated for all children with ADHD and the indication for continuous treatment needs regular assessment [28-30].

MPH treatment has a beneficial effect on the core symptoms of ADHD and academic performance in approximately 70% of the children with ADHD [31,32] and a significantly better general function in medicated children with ADHD has been reported[28]. Furthermore, drug treatment may have a protective effect on risk behaviors associated with ADHD, such as accidents, substance abuse, and criminality. A Swedish registry based study assessing criminality rates in adolescents(≥15 years old) and adults diagnosed with ADHD, reported a significant reduction in criminality rates during periods with ADHD medication[33,34]. The long term effects of drug treatment of ADHD are less well studied, but recent data have demonstrated a protective long-term effect on the development of substance abuse [20,35], suicidal behavior[23], self-esteem, and social- and academic functioning [26,36]. A Danish registry based study, covering a total of 20.742 patients with ADHD, has recently reported that patients medicated with MPH only, had the lowest rate of substance use disorder[37].

However, studies on adherence indicate a rather high discontinuation rate of ADHD-medication of 53 % within the first 6-12 months of treatment[38-41], and up to 80 % after 36 months[42-44]. Early non-compliance has been associated with advanced age of the child, younger parental age, severity of ADHD core symptoms and conduct disorder[38,44]. Parental experience of poor treatment effect, side effects, especially psychological effects such as mood changes and irritability, or the child's reluctance or forgetfulness in relation to medication have been frequently identified as reasons for treatment discontinuation[39,45].

The Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA)[46] measured saliva MPH concentration at four time points during a 14 months treatment period. Only 53% of the participants were adherent at every time point. In addition, non-adherence resulted in greater deterioration of function in children in the medication-only group, compared to the group receiving both pharmacological and psychosocial treatment[41]. This study emphasized the importance of a psychosocial treatment program in combination with drug treatment.

Psychosocial aspects of childhood ADHD

The importance of the psychosocial environment on the effectiveness and compliance in pharmacological treatment of ADHD has only sparsely been described. A recent British study of 570 children with ADHD recruited from child and adolescent psychiatry and pediatric services with a mean age of 10,78 years reported a parental rate of ADHD as high as 29 % [54]. The symptom load in the parents was associated with greater ADHD symptom severity in the child, comorbid Conduct Disorder, higher levels of conflict and lower levels of cohesion in the family.

Likewise, the impact of having a child with ADHD on the parents should not be underestimated. A recent register based Danish study reported a significant negative association between a diagnosis of ADHD in the first born child, and stability of parental relationship and labor market attachment[55]. In addition, ADHD symptoms in the child and behavior seem to evoke maternal hostility, regardless of maternal status of ADHD[56].

The eight year prospective follow-up study of the MTA cohort concluded that early clinical presentation and function, socio-demographic advantage, and a good initial response to any kind of treatment predicted the best long- term prognosis[57]. A recent Canadian study followed a population-based birth cohort of 1920 children from the age of 5 months to 10 years. Socio-demographic baseline data, children's mental health symptoms, and parenting practices were assessed by questionnaires at baseline and at 6 time points during the follow-up period. The strongest predictor of ADHD medication use, beside ADHD symptoms, was low maternal education, whereas immigrant status lowered the likelihood of medication use[58]. This study relied solely on parental questionnaires and no data of diagnoses, functional impairment and adherence to treatment was obtained.

An increased knowledge of these associations and predictors, based on data from the national Danish registers, could contribute to the development of more differentiated treatment programs. Moreover, it could contribute to the identification of patients and families in need of a more intensive and broad-spectrum treatment and monitoring program.

Functional impairment

Overall, ADHD has a negative effect on the quality of life of children, which is comparable to severe physical disorders. Recent data suggest that this effect is mediated by an impaired daily functional level in the areas of education and social interaction[59]. The combination of ADHD core symptoms, emotional dysregulation, comorbidity, and learning difficulties causes a marked impairment in behavioral, social, and academic functioning which is beyond what might be expected based on the ADHD core symptoms alone[59,60]. Often families specify the wish to improve the child's academic and social functioning at school and his or her interaction with friends and the family. This is the main reason for seeking treatment of ADHD, rather than ADHD core symptoms alone[61].

Materials and methods

Participants

The design is a longitudinal, naturalistic study of a clinical cohort of 200 drug-naïve children, aged 7-12 years, followed up closely with respect to the beneficial and adverse effects during the first 12 weeks of MPH treatment at the Child and Adolescent Mental Health Center – Capital Region of Denmark[62]. The recruitment was completed in August 2014 and the three months follow-up was completed in November 2014 with patient data recorded in a research database.

Methods

Recruitment and assessment

A schematic outline of the assessments over time is given below. We have examined and diagnosed 200 referred children with ADHD based on a clinical assessment, a diagnostic interview (Schedule for affective disorders and schizophrenia for school-aged children(K-SADS-PL)[63], rating scales (Child Behavior Checklist, CBCL and Teacher Report Form[64-66], Weiss Functional Impairment Rating Scale-Parent Report, WFIRS-P [67,68] , ADHD-Rating Scale, ADHD-RS [69,70], and a computerized test of attention and impulsivity (Test of Variables of Attention, TOVA [71]). Children were diagnosed according to both ICD-10 and DSM-IV criteria.

The following rating scales were used both at baseline (t1) and after 3 months (t2) of MPH treatment: Clinician rated ADHD-DSM-IV-RS[72], Clinical Global Impression (CGI)- Severity [73], CGI-Improvement, Barkleys Side Effect Rating Scale modified with questions of cardiovascular symptoms, parent and teacher rated ADHD-RS, WFIRS-P, and finally a TOVA test.

At the 36 months (t3) follow-up we will send out the following questionnaires to parents: ADHD-RS, and WFIRS-P

ADHD core symptoms: The ADHD core symptom severity was measured by parent- and teacher-rated ADHD-RS, and clinician-rated ADHD-DSM-IV-RS.

Level of psychosocial functioning: The level of daily- and social functioning was measured by the WFIRS-P, which is a parent rated questionnaire for assessment of functional impairment within six domains: Academic (learning and behavior), family, life skills, self-perception, social activities, risky activities. The WFIRS-P is a psychometric questionnaire which has been used in several studies for assessment of

treatment related changes in ADHD[74-76]. The psychometric properties of WFIRS-P are investigated in an ongoing project at the Child and Adolescent Mental Health Center – Capital Region of Denmark[77].

Data from the national registers
We will apply for permission to use the following data from several national registers to allow for a thorough analysis of risk and psychosocial factors.

Danish Medical Birth Register: Gestational age, birth weight, Apgar score, birth complications, maternal smoking during pregnancy

Danish Civil Registration System: Age of parents and siblings, ethnicity (parental country of birth)

Integrated Database for Longitudinal Labour Market Research (IDA): Education of mother and father (level and duration), employment status, income, and marital status

Danish National Hospital Register: Lifetime somatic diagnoses of the index child

Danish Psychiatric Central Register: Lifetime psychiatric diagnoses of index child, parents and siblings.

Danish Prescription Registry:
ADHD medication prescribed and purchased by the cohort in the 36 months follow-up period, in particular the frequency of dispensed prescriptions (methylphenidate (ATC code N06BA04), dexamfetamine (N06BA02) or atomoxetine (N06BA09)), as well as the date of the first and the last dispensed prescription in the follow-up period. Dosage will be defined as DDD (defined daily dosages) and depending on the distributions duration and dosage will be treated either as continuous or categorical variables in the analyses.

Analyses
The hypotheses of the study will be tested, with the following data either assessed at baseline, or collected from the national registers, or re-assessed in the follow-up study:

The predictive value of responder status in week three and week 12 for the ADHD-RS score and WFIRS-P score after three years will be tested with ANOVAs. Adjusted R2 will be used as a measure of the proportion of the variation in the outcome variables explained by potential predictors.
To select the best model of predictors for outcome after three years, multiple linear regression analyses will be carried out, with three models of predictors. Model one includes gender, age group (</≥ 10 years), comorbidity (none versus ≥ 1 comorbid diagnosis), IQ (full scale IQ > 85/ 70-85), maternal education (primary and lower secondary, upper secondary, higher), parental psychiatric disorder (none/ any maternal or parental disorder), baseline ADHD-RS total score. In model two responder status in week three will be added. In model three responder status in week 12 will be added and responder status in week three removed, to test if this is a better model of predictors.
We will perform QQ plots of the outcome variables in the multiple linear regression analyses. Paired-samples T-tests will be used to explore the development and significant changes in impairment in daily life and social functioning as measured by WFIRS-P.
To explore the relation between symptomatology (ADHD-RS) and impairment in daily life and social functioning (WFIRS-P) correlations between scores at baseline, week 12 and year three will be computed.

We will also investigate the moderating effect of pharmacological treatment of ADHD on ADHD symptom score and functional impairment in daily life, after 3 and after 36 months of follow-up in separate studies.

Innovative value and perspective of the project

From a clinical perspective, the project will provide new insights and recommendations how to individualize and improve the treatment of children with ADHD. Thus, the project will have an impact on clinical practice and services provided to this clientele.

From a scientific perspective, the project will provide new knowledge about predictors for successful treatment of ADHD, and for the long-term symptomatic and functional outcome in this disorder. The systematic and prospective collection of baseline data, data on symptoms, functional impairment, and treatment effect during the first 3 months of treatment on all children in the cohort, in combination with selected data from the registries is a unique feature of this study. In addition, attrition analyses can be performed to study the impact of baseline and risk factors on dropping out of the study at 36 months follow-up.

In a future perspective, these data combined with data from the 36 months follow-up study might constitute a unique cohort, which can be followed and linked to genetic and other biological data derived from blood samples of the participants. At this time, all participants (or there guardians, respectively) have consented already, to participate in the Gene and Environment Study[78]

Ethical considerations

The baseline and 3 months follow-up data have already been collected with a protocol that is covered by existing permissions from the local committees on scientific ethics (De Videnskabsetiske Komiteer for Region Hovedstaden) and the Danish Data Protection Agency (Datatilsynet). These permissions allow the collection and examination of data as well as biological specimens from psychiatric patients below the age of 18 years for research purposes. The parents have given informed consent to the data collection. The local committees on scientific ethics in the Capital Region of Denmark and the Danish Data Protection Agency have given permission to collect data from the national registers and the 36-month follow-up study. The latter consists of two parental questionnaires (overall duration about 20 min). The data collected in the study and from the registers will be linked anonymously.

Intellectual and scientific environment of the project

The project is conducted by the Research Unit at the Child and Adolescent Mental Health Center, Mental Health Services - Capital Region of Denmark, headed by Professor Anne-Katrine Pagsberg. The principal supervisor is Professor Frank Verhulst. Pia Jeppesen, Ph.D., senior researcher and consultant, and Professor Niels Bilenberg, Department of Child and Adolescent Psychiatry, University of Southern Denmark, Odense, will collaborate and serve as expert consultants on the study.
The project will be carried out by consultant Tine Houmann, head of the unit for preschool-children at the Child and Adolescent Mental Health Center. Collaborators in data collection and analyzes are Kristine K. Jørgensen MD, Ph.D.-student at the Center for Child and Adolescent Mental Health, Mental Health Services, the Capital Region of Denmark; and Henrik Berg Rasmussen, Ph.D, senior researcher at the Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services, the Capital Region of Denmark.

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Summary of amendments to study protocol

Protocol version	Date of approval	Revisions
Original protocol	Approval from human subject protection review board: 22nd March 2012	Original version approved by the local scientific ethics committee (Journal nr.:H-B-2009-026)
Additional protocol	Approval from human subject protection review board: N/A Latest approval for data extraction: 22nd November 2016	The additional protocol includes questionnaires and retrospective data extraction from registers and patient journals. The local scientific ethics committee deemed this addition not applicable for ethical review.